Ancillary Effects of Oral Naloxegol (Movantik)

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Version 2: 11/10/2017

Version 3: 1/17/2018

Version 4: 10/30/2018

Version 5: 11/26/2019

Summary of changes in Version 2:

1. Page 14 table 1 - Sedation scores and follow-up on POD3 were removed from table 1 (to conform to the protocol text). Evening bladder scan timing description changed, since the is no evening drug administration
2. Page 15 inclusion criteria – added revision arthroplasties and general anesthesia
3. Page 15-Removed the requirement for PCA, added a general requirement for post-op opioids
4. Page 17-The need for straight catheterization in PACU and/or on the floor when it is medically indicated (volumes exceeding 400 ml) will be recorded by the study team and subsequent bladder scan will therefore not be done. Postoperatively, all patients will be given intravenous or oral opioids for pain control. Clinicians will adjust analgesic management as necessary in an effort to adjust verbal response pain scores to less than 4.
5. Bladder scan to be done on the evening of surgery.
6. Patient clinically does not have ileus if he is passing gas (no need to record /look for bowel sounds)

Summary of changes in Version 3:

1. Page 16 Exclusion criteria- removed antihistamines, phenothiazines, antidepressants and antipsychotics

Summary of changes in Version 4:

1. Page 14 Secondary Aim Hypothesis – changed ORSDS questionnaire from being asked on first, second, and third post-operative days to just the first two post-operative days.
2. Page 15 Study Overview – wording added to maintain consistency with previous revisions for including knee surgery cases
3. Page 15 Table – bladder scanning during PACU stay omitted. Far right column in version 3 that represented nothing was removed for clarification.
4. Page 22 Secondary and exploratory analysis - ORSDS was changed to only being asked on post-operative days 1 and 2. Myles Quality of Recovery scale was changed to only be asked on either post-operative day 2 or the day of discharge.
5. Removal of requirement for bladder scanning to be done on the evening of surgery

Summary of changes in Version 5:

1. Page 21 – “POD 1 to 3” changed to “POD 1 and 2” regarding ORSDS follow up
2. Page 21 – “POD 1 and 3” changed to “POD 2” regarding Quality of Recovery follow up
3. Page 21 – Added clause regarding loss of follow up rate and the need for extra patients to reach planned power to 136 patients with 2 pilots

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INTRODUCTION

Pain is a psychological sensory experience, which is caused by various factors. Surgery results in tissue damage which leads to postoperative pain. Studies in recently developed animal models of postoperative pain have advanced our knowledge of the mechanisms of pain resulting from surgical incision and associated tissue injury. Postoperative pain results from combination of nociceptive and inflammatory components[1]. The nociceptive component results from activation of peripheral sensory neurons damaged by surgical incision, and fades gradually as tissues heal. The inflammatory component enhances pain sensitivity via release of mediators from the surgically injured tissue. Central neuronal sensitization also seems to contribute to postoperative pain and hyperalgesia. [1, 2] Due to aforementioned mechanisms, pain is present in spontaneous resting at the site of surgery plus surrounding tissues. Movement or touching of the wound site, breathing, coughing, and gastrointestinal motility can all evoke pain. Unrelieved postoperative pain leads to multiple physiological and psychological consequences, which worsen outcomes. For example, inadequate perioperative analgesia is associated with myocardial ischemia, impaired wound healing, delayed gastrointestinal motility, atelectasis, and postoperative pneumonia.[3-5] Furthermore, poorly controlled acute pain is strongly associated with development of persistent incisional pain, which can be devastating for patients. [6, 7]

A. Opioids Analgesics and side effects

Although the concept of "multimodal analgesia" of using different drugs with different mode of action to interfere with the pain pathway, such as using non-opioid adjuvants (e.g. NSAIDS, steroids, regional anesthesia) have been developed to improve postoperative pain management, opioids remain the cornerstone of treatment of postoperative pain. Opioids produce analgesia and other effects by binding to specific opioid receptors in the peripheral and central nervous system. Three types of opioid receptors and their subtypes have been discovered: mu, delta, and kappa receptors. The most commonly used opioids bind to mu receptors. The mu1 receptor is responsible for the production of opioid-induced analgesia, whereas mu2 receptors provoke respiratory depression, cardiovascular effects, and inhibition of gastrointestinal motility commonly seen with opioids.[8-10] Sole reliance on opioids is often inadequate and leads to significant side effects.[11]

Adverse events associated with opioids include an increased risk of postoperative urinary retention (POUR). It has been shown in multiple studies that systemic opioids contribute to urinary retention. Opioids inhibit the release of acetylcholine and thereby decreases the parasympathetic output to the detrusor and thus bladder contractility. This effect is directly related to the dose of opioids given and the opioid sparing multi-modal analgesia has been shown to reduce urinary retention.[12, 13] The true incidence of POUR is unclear but is estimated to vary between 5-70%.[14]

The opiates or its analogues decrease the sensation of bladder fullness by partially inhibiting the parasympathetic nerves that innervate the bladder. In addition, opiates have been shown to increase the sphincter tone of the urinary bladder via sympathetic overstimulation, resulting in increased bladder outlet resistance. The combination of decreased sensation of fullness and increased outlet resistance increase the risk of urinary retention. Studies suggest that the half-life of the opioid used has an impact on urinary function and risk of retention.

Type of opioids used and delivery methods seem to affect the POUR as well. Studies that evaluated orthopedic patients who received fentanyl (short half-life) for post-operative analgesia noted that these patients experienced significantly less risk for urinary retention than those who received morphine (intermediate half-life). Several authors have demonstrated that the risk of retention is also increased in patients using PCA compared to those receiving intermittent IV or IM opioids.

Although the cause of POUR is multifactorial and depends on type and duration of surgery as well as existence of comorbidities, systemic opioids are an important risk factor. Urinary retention requires urethral catheterization and potentially indwelling catheter, leading to patient discomfort, hemorrhage, and increased risk of UTI. Urinary catheters can provide an opportunity for gram negative bacterial infections that can lead to further urological and infectious manifestations (e.g. pyelonephritis, urosepsis, death).[15] Catheter-related UTI is responsible for 13% of 100,000 nosocomial infection related deaths each year.[16] It affects about one million Americans annually and is a significant source of morbidity and mortality. It is the most common “preventable” nosocomial infection that accounts for over $400 million spent annually in the U.S. alone.[15, 17] Bacteria causing the UTI can potentially hematogenously spread and lead to surgical site infection.[18] Bacterial seeding from UTI is a special concern after certain type of surgery,

especially those with prosthetic hardware implanted. For instance, ample evidence related UTI with deep joint infection, hemiarthroplasties and total hip arthroplasties in orthopedic procedures, which carries significant morbidity and financial costs. There is currently no effective medical treatment for POUR from opioids. Previous trials of using phenoxybenzamine to treat POUR have shown mixed results.[19, 20] Naloxone had been tried in the past its reversal of analgesia has limited its usefulness in the clinical setting.[21] Furthermore, naloxone's short half-life of 1-1.5 hours is outlasted by the opioids' effects on the bladder. There is a need for an effective treatment to for urinary retention without mitigating the analgesic effects of opioids.[22]

Postoperative ileus (POI) is common after surgery (incidence of 4.5%), and is a transient loss of peristalsis from inflammatory response and release of endogenous opioids from surgical stress.[23-25] POI contributes to patient discomfort, morbidity, and is the one of the major reasons for prolonged hospital stay and overall health care costs.[25, 26] Opioid receptors, belonging to the G-protein coupled receptor family, are found throughout the enteric nervous system. The actions of opioids on the GI tract are mainly mediated by mu-receptors which lead to: inhibition of release of excitatory acetylcholine, non-peristalsis contractions, decreased water/electrolyte secretion, and increased tone of pyloric and intestinal sphincters.[27-30] The result is an exacerbated postoperative ileus and prolongs the return of bowel function. The true incidence of POI is unknown and varies between the type of surgery but is estimated between 3-15%.[31] Currently there is no promising treatment for POI. Several peripheral opioid antagonists have been developed to treated opioid related POI but with limited application. [32, 33]

Patients in the postoperative period will experience many unavoidable physiologic derangements as a result of anesthesia and surgery. Most studies have examined the effect of anesthetic practices on major clinical outcomes, such as recovery time, cardiovascular complications, stroke, length of hospital stay, and mortality. These endpoints are clinically relevant but do not necessarily reflect the overall state of recovery after anesthesia. Quality of Recovery (QoR), first developed in 2000 by Myles et al., is a psychometric has become an important clinical outcome in anesthesia research because it describes the global quality of life from the patients' perspective after surgery and anesthesia. It indicates the impact of adverse events on such as pain and immobility on the patient's recovery and also indirectly reflects quality of health care. The original quality of recovery 9 (QoR - 9) score was later evolved into a more extensive QoR-40

that has improved reliability and validity. The most recent validated version is a 15-item QoR scale as discussed by Stark et. al.[32] It incorporates five dimensions of health, including patient support, comfort, emotions, physical independence, and pain, and has been proven useful in multiple setting and languages. Quality of recovery will undoubtedly have influence patients' satisfaction of their care, which in the current economic constraints of the healthcare system, and the fact that Centers of Medicare & Medicaid Services are linking hospital reimbursement based on patient's satisfaction, quality of recovery has real financial implications. Opioid analgesia, although an indispensable part of postoperative pain management, is often needed to satisfy the high expectation of pain relief of patients. Overuse of opioids is associated with numerous side effects, (e.g. nausea and vomiting, delay return of bowel function, sleep disturbance, pruritus) which has negative impact on quality of recovery.

B. Opioid-related side effects - composite

In addition to urinary retention and postoperative ileus, other common side effects associated with opioids are nausea/vomiting, pruritus, and respiratory depression. Postoperative nausea and vomiting (PONV) affects about 20-70% of postoperative patients and are highly distressing to patients. It is mainly mediated by triggering of opioid-receptors in chemoreceptor trigger zone of the medulla. Opioid induced nausea and vomiting may prolong the recovery room time and a potential hospital stay and lower the degree of patient satisfaction. It has been shown in study that PONV has an impact on quality of recovery. In patients' perspective, PONV is one the most undesirable outcomes in the recovery period. In fact, in one survey, patients were willing to pay out of their own expense to rid of nausea and vomiting completely. Another common side effect of opioid is pruritus, affecting up to 50% patient receiving intravenous opioids and an even higher incidence with neuraxial opioids. The current treatment of pruritus is with antihistamines, 5-HT3-receptor antagonists, opiate-antagonists, propofol, and droperidol, with variable success and with each associated with its side effects. Physicians often respond by dose reduction or discontinuation, which leads to inadequate analgesia and patient discomfort. Another important side effect is opioid induced respiratory depression which is an important source of adverse events in hospitalized patients [33]. Respiratory depression is common in the postoperative period and largely unrecognized, causing significant hypoxemia and potential harm[34].

Worth noting is that opioids might theoretically increases the risk of infections, which might have implications in surgical site infections and infections of hardware in certain surgeries. Opioids have long been recognized as are immune modulators compromising compromise both cellular and humoral immune functions.[35-37] The exact mechanism of this immune modulation is unclear but opioids are hypothesized to act centrally on the hypothalamus-pituitary-adrenal axis and peripherally on the immune cells directly.[38] Opioids bind to 3 major types of receptors: mu-, delta-, and kappa-opioid receptors, which are all identified among immune cells, such as PMNs, macrophages, T-lymphocytes, splenocytes, and macrophages.[39] Opioids also alter the macrophage protein expression profile and impair macrophage function including chemo taxis and phagocytosis.[40-42] And finally, opioids reduce B-cell proliferation and antibody production.[43]

Opioid-induced immunodysfunction can potentially lead to surgical site infection. This, a theory is supported by multiple animal studies demonstrating the effect of opioids on mortality.[44] Breslow et al. compared the effect opioids on infection. Mu-receptor knockout and wild-type mice were both pretreated with morphine and were inoculated with Salmonella and the knockout mice were resistant to infection, while the wild-type had 100 percent mortality.[45] Furthermore, there is evidence that increased doses of opioids are associated with wound infections in patients who suffer from major burn injuries.[46] High-dose opioids have been associated with surgical site infection (SSI) after colorectal surgery possibly secondary to immunosuppression.[47] It is plausible to assume that high dose opioids might contribute to SSI.

Duration of hospitalization, or length of stay, is an important indicator of quality of care and inefficiencies of healthcare and has been used by multiple government agencies to measure quality of care from hospitals. The importance of this parameter was demonstrated by the effort to develop new surgical and anesthetic techniques that facilitate recovery in multiple areas of surgery to reduce stay in intensive care unit and length of stay in hospital. It was suggested that one major reason for prolonged duration of hospitalization is from postoperative complications and management of those complications. Prolonged hospitalization also translates to increased healthcare resources. In a study by Collins et al. examining risk factors that contribute to prolonged hospitalization of 23,919 adults undergoing major elective surgery, postoperative adverse events was associated with a high risk of prolonged hospitalization.[48] Opioids-related side effects affect postoperative recovery and contribute to prolonged hospital stay. For example, prolonged ileus has

multiple consequences, including decreased patients' comfort, delay of mobilization, and pulmonary complications. For example, patient with opioid-induced ileus significantly stay longer in the hospital after abdominal surgery than those who do not (20 vs. 11 days, $p<0.001$). Another study of patients who underwent spine surgery and reported urinary retention was associated with longer hospital stay (3.94 d vs. 2.34 d; $P=0.005$). PONV, a considerable cause of discomfort, should not be taken lightly. PONV has been shown to prolong hospital stay. In severe PONV, it has been documented to cause suture dehiscence and aspiration, which will likely lead to additional treatment and extended hospitalization. In summary, opioid-related side effects hinder recovery and prolongs hospital stay.

In summary, opioids provoke numerous severe complications that cause substantial patient morbidity. They also delay discharge, increase the cost of care, and reduce patient satisfaction. We have a strong need for a peripheral opioid antagonist that could be a part of a multimodal approach to manage and possibly prevent opioid induced side effects that has good oral bioavailability, effective, no effect on centrally mediated analgesia and favorable side effect profile.

C. Naloxegol

Peripheral opioid antagonists may prevent some opioid-induced side effects. Naloxegol (marketed as Movantik, by AstraZeneca) is a pegylated (PEG) derivative of naloxone that inhibits μ-opioid receptors. The PEG moiety offers several functions including reduced permeability and increased efflux (substrate for P-glycoprotein transporter) across the blood brain barrier making it a mainly peripherally acting μ -opioid receptor antagonist. At recommended doses, its ability to only act peripherally allows it to reverse peripheral opioid-related side effects without interfering with opioid-related analgesia or causing withdrawal, as seen with naloxone. The PEG moiety also increases oral bioavailability and allowing oral administration. Naloxegol was approved in 2014 by the U.S. Food and Drug Administration after it passed phase III trials for opioid-induced constipation in adults with chronic non-cancer pain.

Naloxegol binds to all three opioid receptors with greater affinity for μ- and K-receptors, the former (μ) being the main receptor implicated in its side effects related to the gut and bladder. The recommended dosage for adults is 12.5 mg to 25 mg daily. After intake orally, it is rapidly absorbed, reaching maximum concentration (C-max) in 2 hours with a second peak appearing 0.4-

3 hours after the first peak. Its absorption is increased by a fatty meal. Its volume of distribution at the terminal phase is 968-2,140 L and it has low plasma binding (~4.2%) in humans. Clearance is mainly by hepatic metabolism (P450-CYP3A) with metabolites whose actions are yet to be defined. A small portion of naloxegol is elimination by renal excretion. The half-life of naloxegol is 6-11 hours.

Naloxegol does not significantly inhibit the CYP1A2, CYP2C9, CYP2D6, CYP3A4 or CYP2C19 or induce CYP1A2, CYP2B6 or CYP3A4 and is thus not expected to affect concentrations of drugs metabolized by these enzymes. Drugs that inhibit CYP3A4 (e.g. ketoconazole, verapamil, cimetidine) might increase Naloxegol concentration, and might need dose adjustment. Naloxegol does not appear to affect the efficacy of other opioids when administered together. In a clinical study of healthy volunteers receiving morphine (5 mg/70 kg), naloxegol has no effect on the pharmacokinetics and metabolic profile of morphine.[49]

Naloxegol is a well-tolerated drug for long-term use (up to 52 weeks) based on clinical trials.[50] The incidence of adverse events ranges from 8-19% and is dose-related.[51] Most adverse events were mild to moderate in intensity and mostly gastrointestinal related including abdominal pain, diarrhea, with a minority experiencing headache and hyperhidrosis.[51] The cardiovascular safety for naloxegol was extensively studied during phase III trials. AstraZeneca organized an independent committee, called Cardiovascular Event Adjudication Committee (CV-EAC) to authenticate major adverse events including MACE (CV death, MI, stroke). Naloxegol was not associated with increased CV risk. The incidence of MACE was 0.6% for placebo versus 0.4% for naloxegol and the incidence of MI was 0.3% for placebo versus 0.2% for naloxegol.[52]

Multiple clinical trials have demonstrated the efficacy of naloxegol including relief of opioid-related side effects while without affecting increasing pain score and daily opioid dose. Two identical phase III, randomized, multi-centered, double blinded studies (KODIAC-04 and KODIAC-05) investigated the efficacy of 12.5 mg/day and 25 mg/day naloxegol versus placebo in adults patients with opioid-induced constipation over a 12 week treatment period.[51] Naloxegol was associated with a significant improvement in bowel function with 25 mg/day and was more effective than 12.5 mg/day. Furthermore, naloxegol did not alter pain scores, daily opioid requirements, or the incidence of opioid-withdrawal across all control and treatment groups.[51]

These findings prove naloxegol's utility as a peripheral opioid antagonist in decreasing opioid's side effects while maintaining analgesia.

D. Rationale of the study

Previous clinical evidence has already demonstrated naloxegol's efficacy and safety in the treatment of opioid-induced constipation in the outpatient setting. To our knowledge, there have been no clinical studies that investigated its potential in the perioperative setting. Opioid analgesia has potential downsides including urinary retention, prolonged ileus, which translates to potential prolonged hospital stay and costs. The aim of this study is to test if the novel peripheral opioid receptor antagonist naloxegol is effective in mitigating these opioid-related side effects and reducing duration of hospitalization and overall costs.

1. STUDY OBJECTIVES

This will be a prospective, randomized, double-blinded study and will be performed at the Cleveland Clinic Foundation. The study group will receive Naloxegol 25 mg to be given once in the morning every day and the control group will receive placebo.

Specifically, the proposed research will have the following aims:

A. Primary Aim

To assess whether patients who received Naloxegol have a lower volume of residual urine in bladder.

Hypothesis: Our primary hypothesis is that patients who received Naloxegol 25 mg given once in the morning every day will have lower volume of residual urine in bladder when compared to placebo.

Post-void residual volume will be measured after asking patient to urinate independent of their previous urination. Post-void residual is a measurement of the urine that remains in the bladder less than 30 minutes following voiding that identifies urinary retention.

Ultrasound has been used as an imaging modality to evaluate bladder function, and its use in the perioperative period as a diagnostic tool for POUR has gained popularity in the past decade. Several studies have shown good correlation between the volumes measured by bladder catheterization and by ultrasound.

B. Secondary Aims

Secondary Aim 1:

To evaluate the effect of Naloxegol on other opioid related side effects.

Hypothesis. Patients in Naloxegol group have fewer opioid-related side effects than control group. We will use a validated composite outcome, Opioid–Related Symptom Distress Scale (ORSDS), to evaluate opioid-related side effect. ORSDS is 4-point scale that evaluates 3 symptom distress dimensions (frequency, severity, bothersomeness) for 12 opioid related side

effects [53]. ORSDS questionnaire will be administered by a trained research fellow on first, second, and third postoperative mornings while patients remain hospitalized.

Secondary Aim 2:

To assess whether Naloxegol is associated with lower need for indwelling urinary catheterization.

Hypothesis: Our hypothesis is that patients who received Naloxegol 25 mg given once in the morning every day will have less need of indwelling catheterization determined by the residual volume to be above 400 ml when compared to placebo.

Secondary Aim 3:

To assess whether Naloxegol is associated with improved quality of recovery, as measured by the 15-item Quality of Recovery scale.

Hypothesis: Our hypothesis is that patients who received Naloxegol 25 mg given once in the morning every day will have improved quality of recovery. Quality of recovery in the postoperative period is an important measure of the early postoperative health status of patients, and the 15-item Quality of Recovery scale is a validated and efficient measure[32]. Patients will be questioned on the morning of postoperative day (POD) 2 or day of discharge (whichever comes earlier).

C. Exploratory Aims

Exploratory Aim 1:

To assess patient satisfaction with the quality of recovery.

Hypothesis: Our hypothesis is that patients who received Naloxegol 25 mg given once in the morning every day will have improved satisfaction with the quality of recovery, as measured on a subjective 100-point scale (where 0 means not satisfied at all and 100 means completely satisfied).

Exploratory Aim 2:

To assess the effect of Naloxegol on opioid-related prolongation of hospital stay after surgery.

Hypothesis. Patients in control group will have prolonged length of hospital stay compared to Naloxegol patients due to opioid-related adverse events.

2. STUDY DESIGN and METHODS

A. Study Overview

We propose to assess the effect of Naloxegol on reversing opioid-related side effects in patients recovering from elective primary hip surgery under spinal anesthesia who will be randomly assigned to oral Naloxegol or placebo for two postoperative days or until the date of discharge, whichever occurs earlier (**Table 1**). The design will be a randomized, double-blind, placebo-controlled trial of oral Naloxegol in adults having elective primary hip or knee surgery under spinal anesthesia. The study will be performed at the Cleveland Clinic hospitals.

Table 1: study flowchart.(Detailed information will be in the CRF`s)

	Preoperative visit	Morning of surgery	During surgery	PACU*	POD** 1	POD 2	Day of discharge	
Screening for eligibility	X	X						
Consenting	X							
Baseline medical, demographics, Apfel score, Patient functionality and drug history	X	X						
Pertinent blood studies (laboratory)	X				X	X		
AE/SAE collection		X			X	X		
Study drug (in morning, 1 hr before or 2 hr after meal)		X			X	X		
Bladder scan at least 2 hours after study drug (morning)					X	X		
Bladder scan (evening)				X	X	X		
Intraoperative record data collection			X					
Opioid–Related Symptom Distress Scale (ORSDS)					X	X	X	
Opioid complications survey***				X	X	X	X	
Numerical pain score				X	X	X	X	X
Quality of recovery survey							X	

* PACU = post-anesthesia care unit

** POD = post-operative day

*** Opioid complications survey includes nausea, vomiting, itching, ileus, anti-emetic use, anti-pruritic use, anti-opioid use

B. Setting and Population

i. Inclusion criteria

For inclusion in the study subjects should fulfill the following criteria:

1. Provision of informed consent prior to any study specific procedures
2. Female or male aged at least 18 years
3. American Society of Anesthesiologists physical status 1-4;
4. Scheduled for elective primary or revision hip or knee surgery under spinal or general anesthesia;
5. Expected to have significant postoperative pain requiring administration of opioids
6. Negative pregnancy test

ii. Exclusion criteria

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

1. Severe hepatic impairment, with/or twice the upper normal levels of liver enzymes
2. Severe renal impairment, or creatinine level > 2.0
3. History of bladder cancer
4. Patients receiving perioperative regional anesthesia blocks
5. Presence of a sacral nerve stimulator
6. Medications (anticholinergic), conditions or comorbidity causing urinary retention
7. Patient with planned requirement of indwelling urinary catheter insertion before or immediately post-surgery due to immobility
8. Urinary Tract Infections and other urogenital comorbidity (incontinence, cysto-ureteric reflux, known bladder retention) or conditions which can cause urinary retention
9. Severe peptic ulcer disease, diverticular disease, infiltrative gastrointestinal tract malignancies, or peritoneal metastases

10. Patients with known or suspected disruption of blood brain barrier, which may include but not limited to: Alzheimer's disease, stroke, poliomyelitis, cerebral palsy, multiple sclerosis, spinal lesions, and Parkinson's disease
11. Gastrointestinal obstruction/Gastrointestinal perforation
12. Strong CYP3A4 inhibitors (some antibiotics, antifungals, protease inhibitors, and antidepressants), Strong CYP3A4 inducers, Other opioid antagonists
13. Hypersensitivity to MOVANTIK (naloxegol) or any of its excipients

C. Withdrawal Criteria

Patients will be free to withdraw from study at any time. Withdrawn patients will no longer receive study drug but will be contacted for follow up and safety checks if patient allows.

D. Administration of Naloxegol

The investigational drug for this study is Naloxegol 25 mg per dose to be given once in the morning every day (morning of surgery & on postoperative days- 1 hour before or 2 hours after the morning meal). The placebo control is equal in size, shape, and color to the active tablets and administered according to the same protocol. The Pharmacy team will have the appropriate randomization in case of a safety or emergency situation, and the study drug label will mention that it is "Naloxegol or Placebo".

E. Protocol

Patients must meet all inclusion and exclusion criteria to be eligible for the study. After eligibility is confirmed, patients will receive complete information about the study both verbally and in writing. Informed consent must be obtained from the patients prior to randomization and study-specific procedures.

Anesthetic management will follow pre-established clinical and institutional guidelines. Patients can be pre-medicated and will receive spinal or general anesthesia per institutional routine according to attending anesthesiologist discretion. Spinal anesthesia will include the standard monitoring for the given operation, and will occur after the electrocardiogram and monitoring equipment are placed on the patient. Prophylactic antibiotics will be given per surgical routine. During the induction of general anesthesia, indwelling urinary catheters will be inserted only in

the patients with operation time exceeding 3 h or who required meticulous monitoring of the intraoperative fluid status. Intraoperative and postoperative fluid management will be left to discretion of the clinicians, who will be administrating them using institution standards.

Randomization (1:1) will be web-based and initiated prior to conclusion of surgery; allocation will thus be concealed from investigators. Randomization will be stratified based on chronic opioid use (if present) to ensure balance between treatment groups within chronic opioid users and nonusers. Chronic opioid use will be defined as opioid use for more than 30 consecutive days, at a daily dose of 15 mg or more of morphine or equivalent, within the 3 months before surgery. The treatment groups will be oral Naloxegol and placebo.

Naloxegol or placebo will be administered starting the first morning of surgery and continued for two postoperative days or until hospital discharge (whichever occurs first) with 25 mg (or equivalent size and shape of Placebo). The post-operative study drug doses will be given in the morning 1 hour before or 2 hours after the morning meal. Intraoperative and postoperative pain medications will be left to discretion of the anesthesiologist.

In the PACU and postoperative periods, patients will be managed at the discretion of the primary care team and the staff anesthesiologist. The need for straight catheterization in PACU and/or on the floor when it is medically indicated (volumes exceeding 400 ml) will be recorded by the study team and subsequent bladder scan will therefore not be done. Postoperatively, all patients will be given intravenous or oral opioids for pain control. Clinicians will adjust analgesic management as necessary in an effort to adjust verbal response pain scores to less than 4.

Clinical evaluators for the outcomes will be blinded to group allocation and Pharmacy personnel not involved in evaluations will prepare the study drugs. Clinicians including nurses will be blinded to monitoring and will be required to perform their standard of care management after surgery.

Enrollment procedures

The following events will occur in order:

1. Screening for eligible patients
2. Informed consent
3. Randomization

4. Administration of study drug starting the morning of surgery and for 2 additional mornings
5. Collection of data
6. Completion of CRF information

The treatment periods extends from the morning of surgery until the earlier of POD 2 or hospital discharge. Study personnel will follow the study subject until the earlier of POD 2 or hospital discharge. In the case of an adverse event, the study subject will be followed until the resolution of the event.

Handling incorrect randomization

Any event where a subject receives the incorrect treatment or is assigned to the incorrect group will be recorded and judged as an unanticipated problem or protocol deviation at the discretion of the principal investigator.

F. Measurements

Data will be recorded on a case report form (CRF) which will be available electronically and on paper format.

Demographic data to be obtained includes height (cm), weight (kg), age (yr), gender, physical status (ASA), and self-declared ethnicity. Patients will be questioned for social history (tobacco) and medical history (pulmonary disease, kidney disease, diabetes mellitus, neurological disease, chronic pain conditions, illegal drug usage, alcohol abuse, myocardial infarction, previous surgery or stent placement and medications usage). Available preoperative laboratory tests and medication list will be recorded. Individual risk for nausea and vomiting will be determined using the Apfel score.

Data obtained from electronic medical records will include: operation time, surgery type, intraoperative opioid consumption, postoperative opioid consumption in PACU and in ward,

breakthrough pain medication requirements, pain scores in PACU and ward, requirement of oxygen in PACU and ward, nausea and vomiting, requirement of antiemetics, pruritus, requirement of antihistaminic medications, ambulation time, flatus, ileus, bowel movements, constipation, length of stay and any side effects or complications. Preoperative and postoperative laboratory data including but not limited to liver function and coagulations test results will also be collected from electronic medical records. Patient functionality will also be recorded including bathing, toileting, walking and moving.

The Residual volume will be measured within 30 minutes after urination using the battery-powered, portable Bladder scan™ BVI 3000® (Verathon, Bothell, WA, USA). The scanner will be placed on the suprapubic area and held stationary during measurement scanning. The diameter of the bladder and volume of urine will be calculated from the scan data. Scans will be repeated several times to ensure accuracy in measurements. The average of the measurements at each measurement time will be analyzed. All clinical procedures will be performed by trained MD research fellows in the ward twice daily. Surgical team will be blinded to volume determined by scanning and we will also record if they had ordered indwelling catheterization.

We will use Myles QoR scale to formally evaluate quality of recovery on 2 or day of discharge (whichever comes earlier). Myles QoR scale is a validated scoring system allows quantification of patient's early postoperative health status, which is also a description of quality of recovery[32]

ORSDS is 4-point scale that evaluates 3 symptom distress dimensions (frequency, severity, bothersomeness for 12 opioid related side effects[53]. ORSDS questionnaire will be administered by a trained research fellow on first and second postoperative days/day of discharge (whichever comes earlier)

Patient satisfaction with their recovery will be questioned before discharge using a 0-100 scale (where 0 indicates no satisfaction and 100 indicates complete satisfaction).

Adverse events and serious adverse events occurring at any time during the study period will be recorded on a specific form in the CRF.

G. Data Analysis

Naloxegol group and placebo group will be compared for balance of baseline characteristics using standard descriptive statistics (i.e., mean ± standard deviation, median [Q1, Q3], or N (%) as appropriate) and standardized difference. The standardized difference is the difference in means or proportions divided by the pooled standard deviation. Any covariable with a standardized difference greater than 0.2 in absolute value will be regarded as a potential confounder, and will be adjusted for when comparing Naloxegol and placebo groups on all the outcomes.

Primary analysis.

We will test the primary hypothesis that subjects who received Naloxegol 25 mg given once in the morning every day will have lower volume of residual urine in bladder when compared to placebo. We will compare the randomized groups on the volume of residual urine in bladder, which will be measured twice per day for up to 3 days (i.e., a maximum of 6 measurement times in total), using a linear mixed model adjusting for the within-subject correlation (using an autoregressive correlation structure). At each measurement time, the average of the measurements will be analyzed. Any imbalanced baseline characteristics and volume of residual urine in bladder prior to the procedure will be included as covariates in the model. If the group-by-time interaction is non-significant ($P > 0.20$), we will assess the group difference on the volume of residual urine across over all the measurements. In the presence of a group-by-time interaction, the group difference will be assessed separately at each measurement time and a Bonferroni correction will be made for multiple comparisons to maintain the hypothesis-wise 2-sided type I error at 0.05 (the significance criterion will be 0.05 / 6).

Second, we will assess the treatment effect within chronic opioid users and nonusers using the same statistical methods as above. The significance level will be 0.025 for each of the two subgroup analyses (Bonferroni correction).

Secondary and exploratory analysis.

We will test the following three secondary hypotheses: subjects who received Naloxegol 25 mg given once in the morning every day will have (1) fewer opioid-related side effects, (2) less need of indwelling catheterization determined by the residual volume to be above 400 ml, and (3) improved quality of recovery as compared to placebo.

The two groups will be compared on the incidence of any opioid-related side effects using a logistic regression. The frequency, severity, and bothersomeness for each of the 12 opioid-related side effects on POD 1 and 2 will be summarized. We will compare the two groups on incidence (any versus none) of need for indwelling urinary catheterization (defined as residual urine volume > 400 ml) using logistic regression. The two groups will also be compared on the Quality of Recovery scale measured on POD 2 (or day of discharge if it occurs earlier) using a linear mixed model with an autoregressive correlation structure. All the analyses will be adjusted for imbalanced baseline characteristics, if any. The hypothesis-wise 2-sided type I error for each of the secondary outcome will be controlled at 0.017 (i.e., 0.05/3, Bonferroni correction).

In addition, we will summarize the following exploratory outcomes, including satisfactory of the quality of recovery (a subjective 100-point scale) and length of hospital stay after surgery.

H. Sample Size Considerations

The sample size consideration was based on the test for the primary hypothesis that patients who received Naloxegol 25 mg given once in the morning every day will have lower volume of residual urine in bladder when compared to placebo. We would need 62 patients per group [56] to have 90% power at a 2-sided alpha level of 0.05 to detect an effect size of 0.4 or more. The effect size estimation of 0.4 was very conservative as compared to the mean difference of 120 ml (SD: approximate 60 ml) in the volume of residual urine observed by Jose Carlos, I. T., et al [57]. The effect size is the difference in means of the two randomized groups divided by the pooled standard deviation. A maximum of six measurements are planned, twice per day for 3 days. However, we assumed 4 measurements per patients with a correlation of 0.3 to be conservative for the sample size calculation. Considering a loss of follow-up rate of 10%, we will need 12 more patients to reach the planned power with an end sample size of 136. A blinded data quality check will be conducted at 50% (68 patients) of the planned enrollment of 136 patients. In addition to the 136 patients, we will enroll 2 pilot patients to test feasibility of recruitment, protocol adherence, randomization process, and data collection.

SAS software version 9.4 for Windows (SAS Institute, Cary, NC) will be used for all statistical analyses and graphics.

I. Blinding and unblinding

Study drug will be prepared by the hospital pharmacy and labeled as "Naloxegol 25 mg or Placebo". Placebo will have an identical shape and color. Blinding will be maintained unless unblinding is requested for an adverse event or any other reason as deemed necessary.

If clinically indicated, an investigator can request unblinding for a specific dose from the Pharmacy personnel. Such an event will be reported and documented. Unblinding can also be requested by the data safety and monitoring board at any time for safety concerns.

J. Treatment compliance

Subjects will be given clear instructions on medication doses and research-related follow-up prior to enrollment. A member of the study team will follow each patient for the duration of the intervention in order to ensure compliance with the protocol. Any deviations will be reported on the case report form and communicated as necessary.

If the need arises to discontinue the investigational product, the investigator will inform Pharmacy personnel to halt any further drug dispensing. The team will also communicate with the primary care nursing staff to return any unused investigational drug to the pharmacy for proper disposal.

4. Safety monitoring and reporting

Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal

results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

Adverse events of particular interest are:

Opioid withdrawal: hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, irritability

Severe abdominal pain (>8/10) and/or diarrhea

Gastrointestinal perforation

Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase that fulfills one or more of the following criteria:

Results in death

Is immediately life-threatening

Requires in-patient hospitalization or prolongation of existing hospitalization

Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions

Is a congenital abnormality or birth defect

Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to AstraZeneca.

Causality assessment

The Investigator will assess causal relationship between Investigational Product and each Adverse Event, and answer ‘yes’ or ‘no’ to the question ‘Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?’

For SAEs a causal relationship will also be assessed for other concomitant medications, study procedures, and comparator study drugs. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

Time period for collection of adverse events

Patients enrolled in the study will be followed until discharge from hospital. Adverse events occurring during this period will be recorded and communicated to the principal investigator and study team. Any events deemed serious by the principal investigator will be communicated to the IRB and Astra Zeneca as required and within 10 days of discovering the event.

Follow-up of unresolved adverse events

The principal investigator and the study team will follow any unresolved adverse events and communicate with the IRB and Astra Zeneca accordingly.

The following variables will be collected for each AE:

AE (verbatim)

The date when the AE started and stopped

Whether the AE is serious or not

Investigator causality rating against the Investigational Product (yes or no)

Action taken with regard to investigational product

AE caused subject's withdrawal from study (yes or no)

Outcome of AE(s)

In addition to the AE variables referenced above, the following variables will be collected for SAEs:

Date AE met seriousness criteria

Date Investigator became aware of serious AE

AE is serious due to which criterion

If hospitalization or prolongation of hospitalization:

Date of hospitalization

Date of discharge

If death:

Probable cause of death

Date of death

Autopsy performed (Yes/no) and conclusion of cause of death from autopsy

Causality assessment in relation to Study procedure(s)

Causality assessment in relation to Other medication

Description of AE(s)

An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

Adverse Events based on signs and symptoms

When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse Events based on examinations and tests

Deterioration as compared to baseline in protocol-mandated laboratory values and/or vital signs should only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

Disease progression

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

Overdose

Overdose in itself is not considered to be an AE or SAE.

Investigator/site staff are responsible for recording and reporting overdose in accordance with the clinical study protocol instructions. All overdoses with AstraZeneca product are collected and reported to AstraZeneca. Overdoses associated with SAEs will be reported according to SAE reporting. All other overdoses can be sent to AstraZeneca on a monthly basis.

The following information should be provided in the event of an Overdose (Overdose Report Form can be provided upon request):

Details of the Patient who was dispensed study medication (Randomization code)

Details of the Patient who took the overdose (demographic information, was patient a study participant?)

Details of the drug overdose (total daily dose, route, formulation, Overdose start and stop dates)

Was the overdose accidental or intentional?

Was the overdose associated with an adverse event (serious or non-serious)

Provide an Adverse Event description (use same wording as in CRF). Provide start and stop dates of the event, or indicate if the event is ongoing.

Provide Investigator's signature and date.

Pregnancy

Pregnancy in itself is not considered to be an AE or SAE. However, if the subjects become pregnant during the study, Investigator/site staff are responsible for recording and reporting pregnancies and their pregnancy outcomes until pregnancy resolution in accordance with the clinical study protocol instructions.

If a patient becomes pregnant during the course of the study the study medication should be discontinued immediately. The investigator must inform AstraZeneca of any pregnancies occurring in a female patient or a female partner of a male patient within 24 hours of when he or she becomes aware of it.

Maternal exposure

All reports of pregnancy with an AstraZeneca product (that is, those with or without associated SAE, AE or no symptoms) are collected and reported to AstraZeneca. If the pregnancy is accompanied by an SAEs (e.g. events of congenital abnormality/birth defect, spontaneous miscarriage or ectopic pregnancy, or any complications in the subject which meet the criteria for a serious adverse event), it should be reported according to the SAE reporting requirement. All other maternal exposure reports can be sent to AstraZeneca on a monthly basis.

Normal births and elective abortions without complications are not considered to be SAEs.

Paternal exposure

If paternal exposure pregnancy occurs in the course of the study, then the Sponsor/Investigators should inform AstraZeneca within the same timeframe as the maternal exposure. The female partner of the patient will be asked to consent to allow collection of information and follow-up on the pregnancy. The outcome of the pregnancy is also followed and reported in accordance with the processes written in maternal exposure section.

Reporting of serious adverse events

Investigators and other site personnel must inform the FDA, via a MedWatch/AdEERs form, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32, and will concurrently forward all such reports to AZ. A copy of the MedWatch/AdEERs report must be faxed or email to AstraZeneca at the time the event is reported to the FDA. It is the responsibility of the investigator to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting

requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

When reporting to AstraZeneca, a cover page should accompany the MedWatch/AdEERs form indicating the following:

Investigator Sponsored Study (ISS)

The investigator IND number assigned by the FDA

The investigator's name and address

The trial name/title and AstraZeneca ISS reference number

Investigative site must also indicate, either in the SAE report or the cover page, the causality of events in relation to all study medications and if the SAE is related to disease progression, as determined by the principal investigator.

Send SAE report and accompanying cover page to AstraZeneca by email to AE Mailbox Clinical Trial (TCS) <AEMailboxClinicalTrialTCS@astrazeneca.com> or by fax to 1-302-886-4114 (US Fax number). Email is the preferred method.

Serious adverse events that do not require expedited reporting to the FDA need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events on a monthly basis.

In the case of blinded trials, AstraZeneca will request that the Sponsor either provide a copy of the randomization code/ code break information or unblind those SAEs which require expedited reporting.

All SAEs have to be reported to AstraZeneca, whether or not considered causally related to the investigational product. All SAEs will be documented in the study database. The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

5. Ethical and regulatory requirements

A regulatory binder will be kept at the Department of Outcomes Research including the following:

- Delegation log: names and responsibilities of all study team members
- Copy of the most recent study protocol
- Copy of the most recent consent form

- Copy of the most recent case report form
- Copies of any relevant communications with the IRB, sponsor, DSMB, pharmacy, or other entities
- Audit reports

The study site pharmacy will be responsible for the storage and control of study drug and placebo doses. Adequate records of receipt and dispensing of study drug will be kept and will be available for inspection if required. Any expired or unused drug will be disposed of as per an agreement with the sponsor.

An independent data safety and monitoring board (DSMB) will be formed and will consist of at least 2 anesthesiologists and 1 statistician not included in the study team. The DSMB will review study data at the time of the blinded data quality check (Section H) and as required throughout the study. The DSMB can request unblinding of study data and has the authority to terminate the study if significant harm to study patients is suspected.

The study will be conducted preserving the privacy and rights of all patients to the best of the study team's ability. Protected health information will not be shared outside of the entities described in the consent form. All study-related information will be kept at the Department of Outcomes Research in compliance of existing rules.

6. Study Drug handling

Identity of investigational product(s)

Naloxegol 25mg tablets and matching placebo will be used in the study. This material will be supplied by AstraZeneca in unlabeled HDPE bottles containing 18 tablets per bottle. Labels will be prepared at the study site according to Good Manufacturing Practice (GMP) and local regulatory guidelines. Labels will fulfill GMP Annex 13 requirements for labels.

Storage

Naloxegol will be stored in a secure location under appropriate storage conditions. All study drug will be stored in original containers until dispensed to study subjects. Naloxegol and matching

placebo must be stored at controlled room temperature between 20-25°C (68-77°F). Storage temperature must be monitored and temperature excursions reported to AstraZeneca.

Accountability

The PI and the study staff are responsible for maintaining accountability records for all study drugs according to local regulatory requirements. Unused and expired study drugs will be disposed of in accordance with sponsor regulations. Copies of the study medication accountability records will be retained at completion of the study and will be made available for review in the event of an inspection or audit.

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Appendix

Opioid-Related Symptom Distress Scale (ORSDS) [53]

ORSDS Questionnaire[3]

In the last 24 h, have you experience any of the following?	Did not experience	If yes, how frequently did it occur?				If yes, how severe?				And how bothersome was the experience?				
		Rarely	Occasionally	Frequently	Almost constantly	Slightly	Moderately	Severe	Very	Not at all	A little bit	Some what	Quite a bit	Very much
Nausea		1	2	3	4	1	2	3	4	0.8	1.6	2.4	3.2	4.0
Vomiting		1	2	3	4	1	2	3	4	0.8	1.6	2.4	3.2	4.0
Constipation		1	2	3	4	1	2	3	4	0.8	1.6	2.4	3.2	4.0
Difficulty passing urine		1	2	3	4	1	2	3	4	0.8	1.6	2.4	3.2	4.0
Difficulty concentrating		1	2	3	4	1	2	3	4	0.8	1.6	2.4	3.2	4.0
Drowsiness/ difficulty staying awake		1	2	3	4	1	2	3	4	0.8	1.6	2.4	3.2	4.0
Feeling lightheaded or dizzy		1	2	3	4	1	2	3	4	0.8	1.6	2.4	3.2	4.0
Feeling confused		1	2	3	4	1	2	3	4	0.8	1.6	2.4	3.2	4.0
Feelings of general fatigue or weakness		1	2	3	4	1	2	3	4	0.8	1.6	2.4	3.2	4.0
Itchiness		1	2	3	4	1	2	3	4	0.8	1.6	2.4	3.2	4.0
Dry mouth		1	2	3	4	1	2	3	4	0.8	1.6	2.4	3.2	4.0
Headache		1	2	3	4	1	2	3	4	0.8	1.6	2.4	3.2	4.0

ORSDS = Opioid-Related Symptom Distress Scale.

Quality of Recovery Scale

QoR-15 (Development and Psychometric Evaluation of a Postoperative Quality of Recovery Score[32]

QoR-15 Patient Survey

Date: _ _ / _ _ / _ _ Study #: _____

Preoperative ☐ Postoperative ☐

PART A

How have you been feeling in the last 24 hours?

(0 to 10, where: 0 = none of the time [poor] and 10 = all of the time [excellent])

1. Able to breathe easily	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
2. Been able to enjoy food	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
3. Feeling rested	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
4. Have had a good sleep	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
5. Able to look after personal toilet and hygiene unaided	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
6. Able to communicate with family or friends	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
7. Getting support from hospital doctors and nurses	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
8. Able to return to work or usual home activities	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
9. Feeling comfortable and in control	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
10. Having a feeling of general well-being	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time

PART B

Have you had any of the following in the last 24 hours?

(10 to 0, where: 10 = none of the time [excellent] and 0 = all of the time [poor])

11. Moderate pain	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
12. Severe pain	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
13. Nausea or vomiting	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
14. Feeling worried or anxious	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
15. Feeling sad or depressed	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time