Protocol

Risk Factors and Mechanisms for Persistent Postsurgical Pain After Total Knee Replacement (Investigator-Initiated)

ORA # 10081110

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Research Strategy

Significance

The ability to perform physical activity unhindered by pain is a key component of a person's quality of life. It is estimated that 10 million Americans suffer from knee osteoarthritis (OA),[1,2] and for those aged 64 and older, as many as 1 in 10 have knee OA.[3] With attendant near-crippling pain and activity restriction, OA is an important disease requiring intervention. Total knee replacement (TKR) is regarded as a safe, cost-effective treatment for OA,[4] providing substantial improvements in functional status and quality of life, with about 85% of patients reporting satisfaction.[3] However, for the 15% of patients dissatisfied after TKR (75,000/yr), persistent postsurgical pain (PPP) of the operated knee is their most frequent complaint.[4-7] Whereas most patients experience pain relief within 6-12 weeks (wks) after TKR,[4] about 13-20%[5-10] report knee pain lasting more than 3 months (mo), despite radiological indicators of surgical success. In addition, approximately 10% of TKR patients do not show improvement in functional status and consequently suffer from depression and reduced quality of life.[3] Limitations on physical activity by PPP interferes with performance and enjoyment of social, work, and family pursuits, thereby reducing quality of life. With more than 500,000 TKR surgeries performed in 2007,[11] and projections estimated to be 3.48 million annually by 2030,[12] a half million patients/yr in the USA could develop PPP of the knee. The resulting decreased quality of life and the consequent increased utilization of medical services to manage PPP thus poses a significant public health problem for our aging population.

Chronic pain after surgery is in general a largely under-recognized clinical problem, with an incidence of 10-50%,[13,14] depending on the surgical procedure.[5-7,13-15] So alarming is this problem that the FDA embarked on an ACTION (Analgesic Clinical Trial Innovations, Opportunities and Network) initiative workshop, for the prevention of PPP in September of 2009.[16] In our own basic study of surgical trauma in a thoracotomy model, we[17] and others[18] have demonstrated that 50% of rats developed mechanical allodynia after 6 wk, which corresponds with the chronic post-thoracotomy pain syndrome in patients, interfering with normal daily life.[19] Unfortunately, the efficacy of existing treatments is limited and many patients remain refractory to currently available therapies. For these reasons the development of new interventions that prevent PPP will have a major impact on public health.[20] To formulate a successful preventive strategy, initial clinical studies need to assess the risk factors and pathogenic mechanisms underlying the development of PPP. Recent research has implicated a number of risk factors ranging from preoperative pain sensitivity and psychosocial factors, to surgical variables and greater acute postoperative pain intensity.[21] While offering promising avenues of inquiry, no definitive risk factors have been identified.

What is known, judging from other attempts to develop models of the transition from acute to chronic pain is that the development of PPP *cannot be universally attributed to a single factor*, and that neurophysiologic and psychosocial factors all play important but varying roles. To date, however, most studies of PPP in general, or knee pain following TKR in particular, have examined the role of risk factors in isolation and/or within a single domain; a shortcoming that we believe has contributed to the paucity of consistent predictors and mechanisms and thereby undermined efforts to understand how PPP develops.

We submit that any strategy used to investigate risk factors for PPP must not only consider multiple risk factors across various domains, ***but must also examine how these risk factors inter-relate, interact and combine over time to predict and/or influence the incidence of PPP following surgery****.* Doing so would greatly facilitate the development of predictive models for PPP after surgery, improve the capacity to identify patients during the preoperative period who are at highest risk, and thus promote work on interventions to prevent this chronic condition. Our proposed study will undertake such a multi-factorial prospective approach.

Risk Factors for PPP: Preoperative pain intensity has been implicated as a possible factor for PPP after TKR in some studies.[5, 22-24] These studies utilized validated patient measures of pain such as the numerical rating scale of pain intensity,[25] Short Form 36 health survey,[23,24] Western Ontario and McMaster Universities Osteoarthritis Index,[23] and Knee Society Score.[26-28] Recent studies have used experimental pain stimuli (e.g. heat) to quantify pain sensitivity[29,30] and to predict acute postoperative pain.[30] *The value of preoperative pain sensitivity in predicting outcomes will be enhanced in our proposed study by including both self-report of knee pain and sensitivity to experimental pain*. To our knowledge, no published studies have used a multi-domain approach to quantify pain intensity and sensitivity prior to TKR. The significance of our project will be increased by our ability to examine the degree to which pain sensitivity to experimental pain stimuli – distinct from patient self-report of perceived knee pain – predicts the incidence of PPP 6-mo post-TKR.

Preoperative levels of depressed mood and anxiety have been linked to PPP at 1 yr after TKR.[5] Pain anxiety and pain catastrophizing are also implicated in the development of PPP after surgery.[10,13,31-35] Pain anxiety is defined as the tendency to have fear-like symptoms when pain is anticipated or experienced. A crucial component of the pain anxiety construct for the proposed study is "behavioral avoidance." This component describes the tendency to avoid movement because of fear of pain due to movement. Patients scoring high on behavioral avoidance may tend to restrict movement of their operated knees, leading to poor range of motion and PPP. Pain catastrophizing is defined as the tendency to magnify and ruminate on the most negative aspects of pain. High pain catastrophizers tend to report higher pain intensity because they focus considerably more attention on how awful the pain may be. The mechanism by which catastrophizing is thought to impact the experience of pain is by promoting sensitization or interfering with pain inhibition in the central nervous system.[32,36-38] In OA patients, catastrophizing has been associated with high pain intensity[39] and hyperalgesia (to electrical stimulation).[40] Studies have shown that preoperative pain catastrophizing was predictive of PPP after TKR.[33,38]

Surgical trauma induces neuroplastic changes in pain sensitivity, so that mechanical hyperalgesia can be demonstrated in both the area of inflammation (primary hyperalgesia) and in the non-inflamed surrounding tissue (secondary hyperalgesia). Primary hyperalgesia depends mainly on sensitization of peripheral nociceptors while secondary mechanical hyperalgesia occurs as a result of central sensitization in the spinal cord.[41] Central sensitization is thought to be triggered by C-fibre nociceptive input,[42] with activation of NMDA receptors in the spinal dorsal horn.[43, 44] Once central sensitization is established, dorsal horn nociceptive neurons become sensitized to previous sub-threshold stimuli and input from low threshold mechanically sensitive fibers (A-β). This process is accompanied by a spread of sensitivity well beyond the peripheral site of injury, termed secondary hyperalgesia.[13,45,46] Recent studies have employed a technique[47-49] to measure the *area of punctate mechanical hyperalgesia* surrounding thoraco-abdominal surgical wounds. We propose to use punctate mechanical testing in the area around the knee to assess the development of secondary hyperalgesia after TKR. In neuropathic pain conditions, it is hypothesized that central sensitization and secondary hyperalgesia persist over time so that a chronic pain state is established, and the same sequence of events most probably contributes to PPP after TKR.[13,46] Moreover, it is important to note that the significance of studying the area of punctate mechanical hyperalgesia surrounding the surgical wound goes beyond basic understanding of a mechanism contributing to PPP. Unlike other potential neurobiological mechanisms (e.g. cytokines), the procedure for assessing secondary hyperalgesia can be swiftly implemented by personnel in clinical settings at a low cost (although some training is required). Thus, our proposal gains significance with regard to actual clinical practice and treatment decision-making insofar as this potential neurophysiological risk factor – secondary hyperalgesia – can be readily and frequently measured by the practitioners administering care to the TKR patient.

Multi-Factorial Approach: Prior literature indicates that the above described risk factors may be predictive of PPP development, but most studies considered factors one at a time.[13] Although possible mechanisms by which psychosocial risk factors influence chronic pain severity have been offered,[32, 36-38] no TKR studies have advanced models to explain, by what mechanisms, these factors exert effects on the development of PPP over time. *Much of the significance of our proposed project in extending our understanding of PPP rests on testing prospective models that link neurophysiologic and psychosocial factors.* To this end, we propose a series of mediation models that cross these domains, and which are centered on secondary hyperalgesia as the chief neurophysiologic mechanism. Mediation models will allow us to partition the change within and across these factors so as to reveal a true (often masked) effect of the underlying mechanism.

Using pain catastrophizing as an example, we expect that this factor (assessed pre-surgery) not only exerts a significant "direct effect" on incidence of PPP at 6 mo, but also has an "indirect effect" on PPP development through its effect on secondary hyperalgesia. The "direct effect" is the kind of effect typically reported that takes into account only the observed independent association of pain catastrophizing with PPP development, but doesn't reveal what actually translates a patient's tendency to view pain as awful and terrible into later chronic pain. We hypothesize that high pain catastrophizers experience heightened central nervous system sensitization post-surgery, manifested as greater secondary hyperalgesia, which then lead to development of PPP over the ensuing weeks. *The significance of this project is magnified by explicit testing of these multi-factorial conceptual models that allow us to uncover the full array of multiple inter-related causal pathways in what have heretofore remained partial single risk-factor relationships. Such discoveries will reveal a host of*

important points of intervention. For instance, high pain catastrophizers identified at pre-surgery may not only be appropriate for specific psychological interventions,[33-36] but may also be appropriate for pharmacological treatments targeting secondary hyperalgesia.

Results on whether age is a significant predictor of PPP after TKR have been conflicting.[27,28] The effect of age on PPP may be more complex, because age can influence both the psychosocial and neurophysiological mechanisms for development of PPP.[50] Therefore, in our study, age will be evaluated in mediation models in addition to being used as a moderator. One caveat about age in all of our models is that there can be age-related changes in the nociceptive system and so the neurophysiological assessment tools may be age biased.[50] Nevertheless, the prediction models remain valid but interpretation of the mechanisms may need further refinement.

The significance of this project is further amplified by consideration of functional and quality of life outcomes following TKR. Pain level and level of physical activity are not synonymous, and represent two important determinants of quality of life. We expect that preoperative pain sensitivity and psychosocial factors, and post-operative hyperalgesia will also be associated with decreased mobility and poorer quality of life at 6-mo post-TKR. These direct and independent effects may be further mediated by PPP at 6-mo. The ability to predict knee-related physical activity restrictions from preoperative or immediate postoperative factors will allow early implementation of effective targeted interventions prior to development of a PPP syndrome. In our recent randomized, controlled, clinical trial of 240 TKR patients with perioperative pregabalin administration, we demonstrated decreased neuropathic pain and improved knee function (rising from bed, bending to floor, etc.) at 6 mo compared to the placebo group.[51]

Implications for Clinical Practice: Patients who develop PPP after TKR suffer substantial loss of function and productivity in society.[21] In addition to increasing costs of healthcare, these patients consult multiple physicians and require additional diagnostic and treatment modalities. If the incidence of PPP post-TKR (13-20% of patients) can be drastically reduced, the economic, quality of life and mobility benefits promised by TKR for the OA sufferer will be fully realized. At present, given the limited research on factors underlying transitions from acute to chronic pain, standardized and effective algorithms to guide clinical decisions are precluded. The multi-factorial and prospective approach to uncovering risk factors we propose in this application seems an appropriate and necessary step in understanding the complex phenomenon of PPP. Doing so will ultimately provide foundations upon which to develop clinical decision rules and interventions. Variables such as pain intensity and patients' cognitive/affective state are modifiable through cognitive-behavioral therapies.[52,53] Also, the area of postoperative secondary hyperalgesia has been shown to be reduced by NMDA antagonists.[54] *Explicitly addressing multi-variable, cross-domain models of modifiable risk factors will allow identification of a number of possible intervention targets.* A structured prospective clinical evaluation to determine the relative risk of each of these modifiable factors will enable physicians and patients to determine the relative risk of developing PPP after TKR and the risk/benefit of this *elective* surgical procedure and the long-term outcome.

Approach

Overall Strategy: The primary aim of this application is to investigate relationships of risk factors to the development of PPP at 6 mo following TKR, through independently predictive and mediated models. These risk factors are preoperative thermal pain sensitivity, pain anxiety and catastrophizing; postoperative area of secondary mechanical hyperalgesia or hypoalgesia (numbness) and pain intensity. **PPP** for this study will be defined as "**pain in the operated knee at six months after TKR, with other causes of pain excluded and reported intensity on 0-10 NRS scale of ≥4**". The study will also evaluate the relationship of PPP incidence with the severity of functional impairment. This is a single-site prospective clinical investigation of 300 consented OA patients undergoing primary, unilateral TKR. Although we realize the importance of genetic susceptibility on the development of PPP, the complexity of determining the multiple genes that may contribute to this condition is beyond the scope of this proposal.[13] However, prior to surgery we will obtain a blood sample (8.5 mL) from all patients, process it for DNA analysis [82], and store at -80º C for future studies by Dr. Dionne, NINR (letter of support) to screen for genetic predictors of PPP[83], such as COMT[84] and GCH1.[85] We will also obtain three blood samples (5ml each) for RNA analysis. In a previous IRB approved study[95], we also obtained blood samples for RNA analysis prior to hip replacement surgery and 24 hours afterward and found that IL18R1 was up-regulated while IL-8RB was down-regulated and may be related to the normal acute post

operative inflammation. However, we now need to examine the changes in cytokine gene expression in the TKR patients. All of the blood samples will be sent for analysis to Dr. Dionne's laboratory. The patients' genetic information will stay confidential, and will be identified by a study number, and not a name. This information will not be disclosed to any other third party. Personal data will be stored at Rush University Medical Center. The samples sent to Dr. Dionne's laboratory will be appropriately coded so that the patient's name does not appear on the samples. Data will be kept for 1 year from the time the last patient is enrolled in the study.

Study Calendar	Preop	Post-Incision				Post-operative			
		24h	36h	48h	72h	3 wk	6 wk	3 mo	6 mo
General Physical Examination	X					X	X	X	X
Analgesic Consumption	X	X	X	X	X	X	X	X	X
Knee X-Ray Medical Chart Results	X						X		X
Pain Intensity	X	X	X	X	X	X	X	X	X
Neurophysiologic Assessments	X		X						X
Functional Tests	X		X	X	X	X	X	X	X
Psychosocial tests	X								X

***ROM will be the only functional test assessed at 36, 48, and 72 hours**

Screening and recruitment feasibility: A research coordinator/nurse (RN) will screen patients scheduled for Drs. Della Valle (Co-Investigator), Rosenberg, Sporer, Berger and Levine (participating orthopedic surgeons) to undergo TKR using the criteria detailed below. We will recruit 100 patients/yr. Patient recruitment will be completed within 36 mo; however the 6- mo follow-up extends the study period to a total of 3.5 yrs. If a patient meets study criteria, the RN will contact the patient to obtain verbal consent and assess study eligibility. Selection for inclusion will not be based on race or socioeconomic status.

Inclusion & exclusion criteria: *Inclusion Criteria* are: (1) undergoing standard tricompartmental primary TKR; (2) 18- 85 yrs of age; (3) knee to be replaced is the primary source of patient's pain; (4) patient agrees to preoperative and follow-up visits and to comply with the assessment tests; (5) patient consents to standard anesthetic and analgesic protocol, with medical care as deemed necessary by the anesthesiologist, and has no contraindications. (6) Patient has been diagnosed with osteoarthritis. *Exclusion criteria* will include: (1) chronic opioid use ≥ 10 mg/day of morphine equivalents within one wk prior to the surgery, and duration of use > 4 wks; (2) history of opioid abuse; (3) inability to understand and communicate with the investigators to complete the study related questionnaires ; (4) patient is planning to undergo another elective joint replacement procedure during the 6-mo period of participation; (5) any co-morbidity which results in severe systemic disease limiting function {as defined by the American Society of Anesthesiology (ASA) physical status classification > 3}[56] (6) taking medication for severe depression .

Enrollment & Pre-surgery Assessments: Prior to pre-operative assessments, up to 8 weeks prior to surgery, written informed consent will be obtained. Demographic data such as age, BMI[55], ASA status and a physical examination will be performed by PI and RN. All of the assessments below will be coordinated by the RN, in conjunction with the routine preoperative laboratory tests for undergoing TKR. We will obtain an 8.5mL DNA blood sample as well as a 5mL RNA blood sample. A knee radiograph (AP and lateral weight bearing views) will also be reviewed by the study's orthopedic surgeon to determine OA severity (scale) and documented. Patients will be instructed to discontinue non-steroidal anti-inflammatory drugs (NSAIDs) a wk prior to surgery as routine clinical practice. A prescription for tramadol hydrochloride 50 mg tablets with a maximum of 3 tablets /day will be provided to the patients to be taken if the pain in the knee is of moderate-to-severe intensity prior to the surgical date.

All measures selected for this study are established, reliable and validated and listed in order of importance. These measures will be classified into Pain, Neurophysiologic Assessment, Psychosocial and Functional test categories and may be used as predictors, mediators, moderators, or outcome measures, depending on specific hypotheses, and will be assessed at various time points as shown in the study calendar.

(1) Pain Intensity*: Numerical Rating Scale (NRS) of pain intensity***:**[25,57] The NRS score has been selected as the primary instrument to quantify pain intensity. Subjects will be presented by the RN with 11-point NRS, (0 = "no pain" and 10 = "worst pain imaginable"), accompanied by the instructions "Please rate your pain by

indicating the number that best describes your pain on average in the past 2h of the affected knee joint." The NRS will be evaluated at rest, and also with movement (patient-initiated flexion). The NRS is used extensively in clinical trials reported in the orthopedics, pain and surgical literature.[58] Within the pain literature, a NRS <4 is considered mild pain, while a NRS ≥4 is moderate-to-severe pain.[25,59,60]

(2) Neurophysiologic Assessment: The following neurophysiologic assessments will be performed at the Department of Anesthesiology Clinical Research Section (Room 1487 Jelke), where the PI or Co-PI (Dr. Kroin) will supervise the RN in the performance of these tests. These assessments have been performed by the PI and Dr. Kroin (Co-investigator) for other clinical and basic research respectively.

(a) Thermal pain stimulation:[29,61] Prior to surgery, a heat probe (3x3 cm; TSAII instrument; Medoc®) will be applied 16 cm above the center of the patella as a measure for **thermal pain sensitivity**. Probe temperature will be ramped up from 32**º** C at a rate of 4**º**C/sec until 47 **º**C is reached, and then maintained for 5 sec. After the 5 sec period, subjects will rate pain intensity (0-10 NRS scale). If subject requests removal of probe before 5 sec period due to intolerable discomfort, it will be removed and a maximal value of 10 will be given. The test will be repeated 4 times and the average of the responses will be calculated. This procedure will be repeated on the contralateral leg. *(b) Examination of the knee for peripheral neuropathic pain (StEP)*[62] using the following 9 parameters and calculating a score to determine the presence of neuropathic pain (total score ≥ 4). The StEP will detail the symptoms and signs of the pain in the knee. This test will be performed 5 cm medial and 5 cm rostral to the center of the patella on the un-operated knee as a control and then the operated knee.

- Sympathetic: Recording of skin characteristics (yes/no evaluation of color, sweating, trophic changes)
- Tactile allodynia (touch): Numbness, allodynia or hyperalgesia to von Frey filament stimulation, with corresponding NRS pain intensity
- Tactile hyperalgesia (blunt pressure): Decreased or increased response, with corresponding NRS pain intensity
- Dynamic tactile allodynia (brush movement): Decreased or increased response, with corresponding NRS pain intensity
- Vibration sense (tuning fork): yes/no to decreased response to stimulation at the tibia bone ventral midline, 15 cm below lower point of proposed incision
- Evoked pain (pinprick): decreased or increased response, with corresponding NRS pain intensity
- Non-painful warm stimulus (TSAII instrument, Medoc®): decreased or increased response, with corresponding NRS pain intensity
- Non-painful cold stimulus (TSAII instrument, Medoc®): decreased or increased response, with corresponding NRS pain intensity
- Mechanical temporal summation: yes/no to increased pain with repetitive von Frey stimulation.

(3) Psychosocial measures: These measures will be supervised by the PI and administered by the RN.

(a) Pain Catastrophizing Scale (PCS):[63] The PCS will be used to measure catastrophizing. The 13-item measure asks respondents to rate, using a 5-point Likert scale ranging from 0 (*not at all*) to 4 (*all the time*), the degree to which they have certain thoughts and feelings when experiencing pain. Higher scores indicate greater use of catastrophic thinking. The PCS has exhibited strong internal consistency (α=0.93), concurrent and discriminant validity,[64] and high test-retest reliability over a 6 wk period (r = 0.78).[63,65] Research suggests that the PCS is responsive to treatment (measure is in public domain-no permission required for study).[66]

(b) Beck Depression Inventory (BDI-II):[25,57,67,68] The BDI-II assesses emotional function by measuring the level of depressed mood based on attitudes and symptoms that are common among depressed subjects and uncommon among those not depressed. BDI-II, which has been widely used in pain studies, consists of a 21-item self-report measure of depressive symptoms experienced during the past wk. BDI-II is an update with modifications made to conform scoring to diagnosis as defined by the DSM-IV (permission obtained for study).

(c) State-Trait Anxiety Inventory (STAI): STAI has two variations, STAI-state and STAI-trait, and each is a 20-item self-report assessment device, one for state anxiety and one for trait anxiety.[69] The state anxiety score reflects a transient evaluation of anxiety and in particular the current self-report state. Trait anxiety measures a subject's dominant response style although modification can be seen with psychological interventions (permission obtained for study).

(4) Functional measures: Measures of the study will be supervised by the PI and administered by RN.

(a) *Knee range of motion (ROM)*:[70,71] The degree of active (patient moving the knee) and passive (movement of the knee with the aid of RN) knee flexion, will be measured using a goniometer. The PI has previously performed ROM measures with the aid of physical therapists.[70]

(b) *Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)*:[23,57,72] A widely used measure of symptoms and physical disability specifically designed for patients with OA of the lower extremity. This instrument evaluates 3 dimensions: pain, stiffness and physical functional disability (permission obtained).

(c) SF-36 (SF-36):[25,57,73] A self-report survey containing 36 items and is the most commonly used measure of physical functioning. The SF-36 is a general measure of health status as opposed to one that targets specific population. Accordingly, the SF-36 can provide a benchmark with which to compare specific populations. It has well described properties and sensitivity (permission obtained for current study use).

(5) Skin Temperature: Skin temperature, the abnormalities of which have been associated with neuropathic pain conditions[97], will be measured medial and lateral to the center of the patella on the operated knee, and on the contralateral knee, as is standard at the Rush Pain Center.

Day of surgery: Patients will not receive oral adjuvant analgesics preoperatively on the day of surgery. The method of anesthesia for the case will be that which is deemed appropriate by the attending anesthesiologist. For patients receiving general anesthesia, standard anesthesiology practice will be followed. In the case of patients receiving epidural anesthesia, on the morning of surgery, patients will be sedated with midazolam (0.05 mg/kg titrated to effect) and an epidural catheter at the L3-L4 or L4-L5 vertebral level. This procedure will be carried out in the designated regional room with the patient in sitting position. The skin will be infiltrated with lidocaine and using an 18G Touhy needle®, the epidural space will be identified via the loss of resistance technique with air and glass syringe. A 20G catheter will then be threaded 3-5 cm in the epidural space and a test dose with 1.5% lidocaine and epinephrine will be performed. The PI will place all the epidural catheters for consented study patients, to minimize variability.

The standard ASA monitors will be placed. Written standard instructions will be given to the anesthesiologist assigned to provide intraoperative care of these patients, who will be one of the members of the orthopedic anesthesia section, of which the PI is the director. Epidural anesthesia will be induced with titration of 2.0% lidocaine (10-20 mL) with epinephrine (1:200,000). Prior to commencing surgery, a dermatomal sensory and motor level will be obtained. Patients will be sedated with propofol titrated to effect at a rate of 20-50 μg/kg/min. They will be maintained normothermic with fluid warmer and active heating devices. In addition, hemodynamic parameters will be titrated to maintain mean blood pressure within 20-30% of baseline hemodynamic status (and not below 60 mmHg mean blood pressure). All intraoperative variables such as heart rate, blood pressure, O_2 saturation and temperature, intraoperative local anesthetics, sedative drugs used, amount of fluid given, blood loss, duration of surgery and tourniquet time will be documented. Once the surgery is completed, patients will be transported to the recovery room.

*Standard TKR***:** Skin incision will be considered time zero; and the length of incision will be recorded. TKR will be performed under tourniquet control, using an abbreviated medial parapatellar approach with the arthrotomy extending into the quadriceps tendon for 2-4 cm above the superior pole of the patella, and without patellar eversion. A primary, cruciate retaining tricompartmental TKR will be performed in all cases (NexGen CR, Zimmer, Warsaw, IN®); all components will be cemented and the patella will be resurfaced. No local anesthetic will be infiltrated at closure of the surgical wound. The knee will be closed in 90 deg of flexion over a drain. Any intraoperative complications, especially nerve trauma, will be recorded.

Post-Incision to Hospital Stay: *Acute postoperative pain management***:** For patient's that received general anesthesia, standard post-operative analgesic practice will be followed. For patients with epidural catheters in place, an epidural infusion of bupivacaine (0.1%) and fentanyl (5 μg/ml) will be started upon entry to the recovery room, using a continuous basal infusion at 6 mL/h with superimposed patient-controlled epidural analgesia (PCEA) bolus dose of 1 mL every 15 min, with a 4 h lockout of 40 mL to be delivered by the infusion pump. Patients will be instructed prior to surgery, on PCEA operation (routine clinical practice) by the acute-pain service nurses, who report to the PI. If the patient complains of severe pain, the acute pain nurse will be

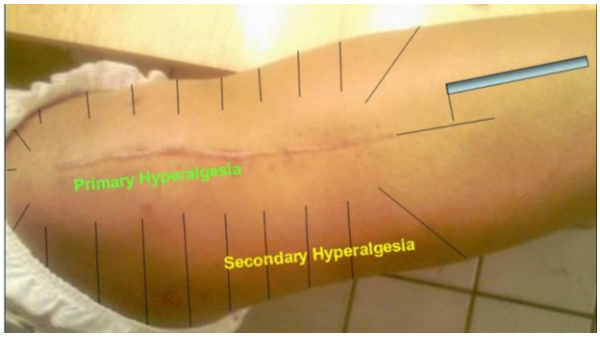
contacted and the epidural infusion titrated (per previous published protocol).[70] However, if these measures fail and the patient has severe pain, intravenous opioids (morphine 2 mg bolus) will be administered. Records will be kept of the total amount of epidural solution consumed, including morphine boluses, in increments of 4h for the 24h postoperative period. After 24 hours, the epidural catheter will be removed. We customarily administer warfarin (oral 5 mg) for deep venous thrombosis prophylaxis on the night of TKR. An International Normalized Ratio will be obtained prior to removing the catheter.[78] Once the epidural catheter is removed, all patients will receive hydrocodone 10 mg/acetaminophen 325 mg, 1-2 tablets every 4-6h depending on the NRS pain score for a maximum of 6 tablets/ day (to keep within current geriatric guidelines <3.25 mg/day acetaminophen),[79] until discharged from the hospital. Patients having NRS ≥ 4 for more than 1h will receive intravenous morphine 2-4 mg as needed every 15 min for a maximum of 15 mg over a period of 2h. Patients allergic to intravenous morphine or oral hydrocodone will receive an equivalent dose of intravenous hydomorphone or oral oxycodone respectively. All analgesics administered over 0-72h will be recorded in the data collection book for inclusion as covariates in analyses. Although a more complex algorithm for pain management, including multimodal non-opioid analgesia, could be used and continued for at least 2 wks later,[51] those analgesics might become factors themselves that influence the development of PPP, and therefore will not be used in this proposed study. We will also obtain a 5mL blood sample for RNA analysis during the hospital stay (when wound inflammation is maximum).

Postoperative Management: Routine vital signs will be recorded on the floor and transferred to the data collection book. The patients will undergo routine physical therapy sessions twice/daily until they meet the hospital discharge criteria as determined by the therapist.

Acute Postoperative Assessments (total time approximately 30 min)**:**

(1) **Pain Intensity:** The 11-point NRS pain intensity will be recorded every 4h for 0-72h postoperatively of the operated knee, then twice daily thereafter until discharge. The area-under-curve (AUC) for NRS over 0-72h will be calculated and interpreted as the burden of acute postoperative pain.
(2) **Neurophysiologic Assessment** *of mechanical (punctate) hyperalgesia and hypoalgesia* will be performed at least 6 hours after removal of epidural, post-incision by the RN under the supervision of PI. The elasticized (ACE) wrap around the knee will have already been removed at 24h post-incision. With the subject in a relaxed supine position with eyes closed, stimulation with a hand-held von Frey filament (4 g) will begin on the lateral aspect of the knee where the patient reports no pain sensation (Figure below), and move in 2 cm steps toward the incision until the subject reports a distinct change in sensation. [47-49, 80] The first point where the subject reports the sensation as 'painful', 'sore', or 'sharper', will be marked with an alcohol pen. To map the area of this mechanical sensitivity around the knee, testing will be done every 2.5 cm around the mid-line along radial lines. If no change in sensation is found, stimulation will be stopped at 5 cm from the surgical incision to restrict our testing to the area of **secondary mechanical hyperalgesia**.[47,81] Any areas of numbness will also be noted. To quantify the area, a transparent plastic sheet with pre-marked grid marks will be placed over the knee to facilitate the transfer of the skin markings to our template. The area will then be measured with a digital planimetry software.

(a): In preliminary studies we found the mean area to be 37 cm^2. Areas of numbness will also be noted.



(3) **Functional Measures** (ROM only): The active and passive ROM of the knee will be recorded every day in the hospital by the physical therapist. In addition, the RN will measure active and passive ROM at least 6 hours

after removal of epidural, (performed at the same time as assessment *of* mechanical (punctate) hyperalgesia and hypoalgesia.
*Discharge from hospital***:** Patients will be discharged from the hospital with the same oral opioid medications used in the post-operative period. Prior to discharge, patients will be given a questionnaire (one for each wk, to be mailed to PI in pre-paid envelope weekly) to record analgesics consumed during the first 3 wks postoperative period. For the first 3 wks after surgery, patients will be contacted by e-mail, telephone or facsimile on a weekly basis and queried about NRS pain intensity and medications used by the RN. Serious adverse events will be reported to the PI and the orthopedic surgeon.

Postoperative Follow-up and Outpatient Management: At 3 and 6 wks after surgery, patients will return to the orthopedic surgeon (Orthopedic Building) for follow-up. At their visit, the functional assessments noted below and analgesic consumption questionnaires (if not previously mailed in) will be collected by the RN, after which patients will be given new analgesic consumption and functional assessment questionnaires. Their oral opioids will be gradually weaned and converted to NSAID or cyclo-oxygenase (COX)-2 inhibitor (celecoxib 200 mg) daily and tramadol hydrochloride 50 mg tablets as required, with a maximum of 6/day. The outpatient physical therapy data from the time the patient was discharged to the 3 wk visit will be collected. The results of the knee radiographs at follow-up visits will be collected. Over the 3 wk to 3 mo postoperative period, study patients will be contacted by email, telephone, or facsimile by the RN, at 10-14 day intervals, and queried about NRS pain intensity, medications used, and any adverse events.

Coinciding with the orthopedic surgeon visit at 3 mo, the functional assessmentsand analgesic consumption questionnaires will be collected by the RN. They will then be given new analgesic consumption and functional assessment questionnaires, and new prescriptions for analgesic drugs if needed (NSAIDs or COX-2 inhibitor). Over the 3 to 6-mo postoperative period, they will be contacted by email, telephone, or facsimile, every 20-30 days and queried about NRS pain intensity, medications used. A full analgesic treatment protocol as mentioned above will be followed for all patients in the study. At 6 mo, patients will return to the Orthopedic Building for their final visit at which time the functional assessments, BDI, and analgesic consumption questionnaires will be collected by the RN, and they will undergo a knee radiograph. . An additional questionnaire, the SF-MPQ-2, will be administered at 6 mo to better characterize the subject's sensory qualities of pain.[96] In addition, they will return to the Department of Anesthesiology Clinical Research Section (Room 1487 Jelke) for e*xamination of the knee for peripheral neuropathic pain (StEP)* and ROM measurement (total time approximately 1 hour), as was performed pre-surgery. At this time we will collect the third and final 5mL RNA blood sample.

Long-term Assessments (same methods used pre-surgery):
(1) **Pain Intensity**: NRS of the operated knee will be obtained by RN from the patients at the 3 wk, 6 wk, 3 mo and 6 mo scheduled visits.
(2) **Neurophysiologic Assessment** will be performed at the 6 mo scheduled visit.
(a) Examination of the knee for peripheral neuropathic pain (StEP)
(3) **Psychosocial Measures:** Beck Depression Inventory will be administered at 6 mo by RN.
(4)**Functional Measures:** ROM, WOMAC and SF-36 questionnaires will be administered at 3 wk, 6 wk, 3 mo and 6 mo.
(5) **Skin Temperature:** Skin temperature will be performed at 6 months

*Patients who have NRS≥4 at three wks and beyond***:** For patients having NRS≥4 at 3 wk and beyond, the oral opioid regime will be continued. If the hydrocodone/acetaminophen regime does not maintain a NRS<4, then oral long-acting opioids such as time-release oxycodone 10 mg twice/day will be prescribed. The purpose of closely following the analgesics and NRS for the study patients is to ensure that at the 6-mo time point the analgesic consumption is within a standard protocol for all patients, whether they do or do not have PPP. Patients who have persistent pain at the 3 and 6-mo visits will be evaluated by the orthopedic surgeon for prosthetic-related failure. An examination will be performed to evaluate instability of the tibial femoral joint or patellar maltracking. Plain radiographs will be reviewed by the orthopedic surgeons (Co-investigators) for evidence of prosthetic loosening, malposition and patellar maltracking, as well as overall axial alignment to ensure coronal alignment is within the range of neutral to 10 deg of valgus. If this evaluation is negative, an erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) measurement will be obtained as a screening tool for infection.[82] If these indices are abnormal (ESR>30 mm/h; CRP>10μg/mL), an aspiration of the knee will be performed, including a synovial fluid white blood cell count with differential and culture to rule

out infection. These parameters are based on previous work by Dr. Della Valle (Co-investigator) in this specific topic.

Statistical Analysis: *Power analysis and sample size calculation*: The sample size calculation was based on power estimates using our preliminary data on how acute postoperative pain contributes to PPP using the SAS "powerlog" macro.[83] An updated analysis of our multi-center (three) chronic pain after total knee and hip arthroplasty survey study,[84] evaluated one yr postoperatively, provided data for sample size calculation. The one yr follow-up data from this survey provides a conservatively estimate for the incidence of PPP at 6 mo, our primary outcome. To evaluate the effect of acute postoperative pain on incidence of PPP, our multi-center data was stratified based on chronic pain using our PPP criteria. Across the three centers, 259 TKR patients fell within criteria, of which 46 (**17.8%**) were identified with PPP at one year after surgery. Using a logistic regression, the acute postoperative NRS pain intensity was significant (P=0.0005) with an odds ratio of 1.24 for each 1 point increase in acute postoperative NRS pain (95% Wald Confidence limits: 1.098-1.390). The average acute postoperative NRS pain for the entire sample was 5.5 (SD=2.9). Using the data to estimate predicted probability of PPP at the mean acute postoperative pain level, we have an incidence of 15.5% at the mean and 30.3% at the mean plus one standard deviation (NRS=8.4). A power analysis with 90% power and alpha of 0.05, using a logistic regression with no other covariates gives us a required sample size of 130. However, because we plan on utilizing multiple covariates, we estimate the multiple squared correlations at 0.5, raising our sample size estimated to 259. With a 15% dropout rate this values climbs to 298 (round to **300**).

Blinding of data: To reduce bias, each co-investigator will only be involved in measurements specifically related to their specialization (Pain, Neurophysiologic, Psychosocial or Functional outcomes) and no others.

Data collection and management: Data will be collected on a series of password-protected Microsoft Excel worksheets, with data access limited to research personnel. Data will be imported from the Excel sheets and stored as a database using the SAS statistical analysis system on the statistician's workstation where all analysis will take place. The workstation is password protected, with key information encrypted and managed by the biostatistician on his own network, protected by router and software based firewalls. Data will be encrypted (AES 256-Bit) and backed up bi-monthly onto DVD's and will be stored in a locked cabinet in the biostatistician's office. Data will be indexed by a subject identification number. Each subjects' identifying information (name, telephone number) will be recorded in a separate password protected database, indexed by subject ID number, and will not be used in any analyses.

General statistical analysis: Descriptive statistics will be reported as mean and standard deviation (SD) for continuous normally-distributed variables, and reported as counts and percentages for dichotomous variables. Assumptions will be evaluated and, if violated, either corrective measures will be taken (data-transformation) or other less restrictive methods will be implemented. Error inflation for multiple pre-planned comparisons will be corrected by using the Bonferroni step-down method. Models will be examined with no risk factors, with individual risk factors, and with multiple risk factors. The distribution of the primary outcome, NRS pain scores at 6 mo, will be evaluated, transformed to normal and then modeled as a continuous variable. If this is not possible, *then the dichotomous version*, as defined for PPP, will be used. We expect that the primary outcome of PPP (dichotomous) will be modeled using a logistic regression because the distribution of NRS pain scores from our preliminary survey data was strongly bi-modal (modes:0, 3). Thus it appears that this kind of distribution represents two distinct populations (a normally distributed pain population and a unimodal 'no-pain' population). Pain intensity (continuous) will be separately modeled for those patients who report a non-zero pain level. Risk factors will be evaluated, for **independent** association with the outcome variable, first for linearity and then for model fit using backward stepwise logistic regression (criterion P<0.05). Model fit will be assessed by the Hosmer-Lemeshow test and validity of the fit models and predictive accuracy will be assessed using bootstrapping methods as well as the AUC 'c-index'. Analysis will also be performed on the raw NRS score (at 6 mo) using general linear models and mixed model regression as this may elucidate additional details about relationships among the factors and how they relate to pain at 6 mo. **Mediation** models will be evaluated based on techniques pioneered by Baron and Kenny,[85] but with the modification of bootstrapping techniques[86] to produce multiple mediator results with confidence intervals. Sobel method[87,88] and R^2 effect-size measures[89] will be used to test and evaluate the mediation effects as well. Distributional assumptions and

model fit will be evaluated for all models. **Moderating** effects will be tested using model building with predefined interactions for linear or logistic models.

Due to the extensive monitoring designed into our protocol we do not expect a large amount of missing data; however, the missing data that does arise will be handled using multivariate multiple imputation. Data not assumed to be missing at random, will be evaluated for systematic effects using sub-groups stratification. Statistical analyses will be performed using SAS version 9.1 (SAS Institute Inc, Cary, NC) or SPSS (SPSS for Windows, Rel. 16.0.1. 2007. Chicago: SPSS Inc.), with statistical significance determined with a Type I error threshold of $\alpha = 0.05$. For continuous outcome mediation analysis we will use a SAS macro (INDIRECT macro)[86] and for dichotomous outcomes the SPSS macro version (INDIRECT macro)[86] will be used, as the SAS macro version does not allow for dichotomous outcome variables.

Primary endpoint: The *primary endpoint* for the **Primary Aim** will be the incidence of PPP after TKR (similar to our power analysis), evaluated at 6 mo. For the **Secondary Aims**, the *primary endpoint* will be functional outcomes (ROM, WOMAC, SF-36,).

Secondary endpoints: The *secondary endpoint* for the Primary and Secondary Aims will examine additional parameterizations of PPP at 6 mo (NRS pain non-dichotomous, StEP neuropathic pain examination). Use of raw NRS pain scores may highlight functional (e.g. linear) relationships between pain and the predictive factors. Analysis will be performed as described for the primary outcome variable (incidence of PPP) but with the re-parameterized outcome variable and different model assumptions, depending on distributional properties. Each re-parameterization will be evaluated with respect to and compared with the primary outcome.

Covariates: Preoperative covariates included are as follows: age, weight/BMI, OA severity and ASA status. Perioperative covariates include: postoperative analgesic consumption and duration of surgery. Complications after TKR will be recorded and included as a summed incidence. Patient questionnaires of drug use in the first three wks postoperatively will be converted to daily morphine equivalents and included as a covariate in the predictive models. Although the protocol stipulates uniformity in medication use during the acute postoperative period, once the patient leaves the hospital, their analgesic use over the next 6 mo cannot be rigidly controlled. To reduce variation we will prescribe analgesics as needed (per protocol above mentioned) and will remain in contact with the patients to record additional medication.

Detailed Analyses:

Primary Aims: are to investigate the relationships of *risk factors* and the development of PPP at 6 mo post-TKR, through independently predictive (for clinical prediction models, Hypothesis 1) and mediated models (to reveal underlying mechanisms, Hypothesis 2). These risk factors are preop thermal pain sensitivity; anxiety and catastrophizing; postop area of secondary mechanical hyperalgesia and pain intensity.

A. **Independent Risk Factors**: Risk factors will be individually predictive of the PPP (primary endpoint):
   Hypothesis 1 is that greater (↑) preop pain sensitivity, higher levels of preop pain anxiety and catastrophizing, larger areas of secondary hyperalgesia post-TKR and higher postop pain intensity will independently predict increased incidence of PPP at 6 months post-TKR.
   1) **Pain Intensity**: Expected Result: (Hypothesis 1): Higher postop pain intensity (↑), will independently predict increased incidence of PPP at 6 mo post-TKR (ex. ↑ postop NRS → ↑ PPP incidence).
   2) **Neurophysiologic**: Expected Result: (Hypothesis 1): Greater preop pain sensitivity (↑) and larger areas of secondary hyperalgesia (cm^2) post-TKR will independently predict increased incidence of PPP at 6 mo post-TKR (ex. ↑ preop thermal pain sensitivity → ↑ PPP incidence).
   3) **Psychosocial**: Expected result: (Hypothesis 1): is that greater (↑) catastrophizing (PCS score) will independently predict increased incidence of PPP at 6 months post-TKR (ex. ↑ PCS score → ↑ PPP).
   4) **Demographics**: Expected result: Patients 65-85 yrs will have a lower incidence of PPP than patients 18-64 yrs.

B. **Mediation Models**: Effects of preoperative factors on development of PPP occur through interrelated neurophysiologic mechanisms*:*
   Hypothesis 2 is that the effects of preoperative factors on development of PPP occur through interrelated neurophysiologic mechanisms. Thus, it is expected that the area of secondary hyperalgesia post-TKR will mediate links between preoperative pain sensitivity and PPP incidence, as well as mediate links between pain anxiety/catastrophizing and PPP incidence at 6 mo after TKR.

1) **Neurophysiologic**: Expected Result: (Hypothesis 2): Area of secondary hyperalgesia post-TKR will mediate links between preoperative pain sensitivity and PPP incidence: (preop thermal sensitivity score affects area of mechanical secondary hyperalgesia which in turn leads to increased PPP incidence) will *fit the data significantly better* than the independently predictive model (preop thermal sensitivity score will directly affect PPP incidence).
2) **Psychosocial**: Expected result: (Hypothesis 2): Area of secondary hyperalgesia will mediate links between pain anxiety/catastrophizing and PPP (ex. pain anxiety PASS score → area of secondary hyperalgesia → PPP incidence).

Secondary Aims: Test for risk moderators.

C. **Moderation Models**: Test for risk moderators*:*

Hypotheses 4 postulates that patient age will moderate the relationship between risk factors and PPP development. We expect the predictive relationship between preop pain sensitivity and PPP incidence to be stronger (enhanced) among younger as opposed to older patients

1) **Demographics:** Expected Result: The effect of preop pain sensitivity on PPP will be moderated by age (ex. direct effect is: ↑ preop thermal NRS score → ↑PPP incidence; but moderating effect is: ↑ preop thermal NRS score x ↓age→ ↑↑PPP incidence)

Omnibus Model: To create a more complete description of the factors, mechanisms and interrelationships involved in development of PPP, several omnibus models will be created and evaluated. Knowledge gained from each of the individual aims will be utilized to create this model, using principal component and factor analysis for variable reduction and predictive modeling with particular focus on mediation between the domains and the aims.[90-92]

The prediction equation: To highlight the risk factors for PPP, including importance (weighting) and interactions, in not only the preoperative phase but in the postsurgical phase, a prediction equation will be described. The use of the prediction equation can then be validated and fine tuned in later studies. A simple example formula for the prediction equation:

$$\Pr_i = \frac{1}{1+\exp(a+\beta_1 Age_i+\beta_2 preOpPainSens_i+\beta_3 SecHyperal_i+\beta_4 postOpNRS_i+\beta_5 TraitAnxiety_i+\beta_6 Catastrophizing_i)}$$

Potential Difficulties and Limitations

1. We have no way of directly assessing minor nerve damage following TKR.
2. Patient may decide to undergo another elective joint replacement procedure during the 6-mo postop period
3. Although power analysis is based on 17.8% PPP incidence, TKR procedures may vary over the 3-yr duration of study. However our power estimates are conservative and our multivariate analyses are robust and powerful.
4. 6 mo assessment of PPP can be complicated by opioid use in some patients. However, this factor is considered as a covariate in the analysis.

Future Directions

- Modeling of disease trajectory: Change over time (presurgery to 6 mo) for risk factors (e.g. secondary hyperalgesia) and dynamic interactions will be modeled using analytic techniques such as growth curve models to model the dynamic etiology of PPP. Trajectory information is critical to describe and identify critical time points for intervention.
- The blood sample analysis of DNA and RNA expression for “pain genes” (from blood collected on the day of surgery) can be completed and lead to future incorporation of genetic risk factors for prediction of PPP incidence.
- Results from this study will enable researchers to construct enriched enrollment clinical trials with patients at *high risk* for developing PPP.[93] This will enable therapeutic interventions that can lead prevention of PPP.[94]

References

1. **Jordan JM.** Helmick CG. Renner JB. Luta G. Dragomir AD. Woodard J. Fang F. Schwartz TA. Abbate LM. Callahan LF. Kalsbeek WD. Hochberg MC. Prevalence of knee symptoms and radiographic and symptomatic knee osteoarthritis in African Americans and Caucasians: the Johnston County Osteoarthritis Project. J Rheumatology 2007;34:172-80.
2. **Murphy L,** Schwartz TA, Helmick CG, Renner JB, Tudor G, Koch G, Dragomir A, Kalsbeek WD, Luta G, Jordan JM. Lifetime risk of symptomatic knee osteoarthritis. Arthritis Rheum 2008;59:1207-13.
3. **NIH** Consensus Statement on total knee replacement. NIH Consens State Sci Statements 2003;20:1-34.
4. **Jones CA**, Beaupre LA, Johnston DW, Suarez-Almazor ME. Total joint arthroplasties: current concepts of patient outcomes after surgery. Rheum Dis Clin North Am 2007;33:71-86.
5. **Brander VA,** Stulberg SD, Adams AD, Harden RN, Bruehl S, Stanos SP, Houle T. Predicting total knee replacement pain: a prospective, observational study. Clin Orthop Relat Res 2003;416:27-36.
6. **Brander V,** Gondek S, Martin E, Stulberg SD. Pain and depression influence outcome 5 years after knee replacement surgery. Clin Orthop Relat Res 2007;464:21-6.
7. **Baker PN,** van der Muelen, Lewsey J., Gregg PJ. The role of pain function in determining patient satisfaction after total knee replacement. JBJS 2007; 89: 893-900.
8. **O'Brien S**, Bennett D, Doran E, Beverland DE. Comparison of hip and knee arthroplasty outcomes at early and intermediate follow-up. Orthopedics 2009;32:168.
9. **Wylde V**, Dieppe P, Hewlett S, Learmonth ID. Total knee replacement: is it really an effective procedure for all? Knee 2007;14: 417-23.
10. **Harden RN**, Bruehl S, Stanos S, Brander V, Chung OY, Saltz S, Adams A, Stulberg SD. Prospective examination of pain-related and psychological predictors of CRPS-like phenomena following total knee arthroplasty: a preliminary study. Pain 2003;106:393–400.
11. **HCUPnet.** National statistics on all stays:2007 outcomes by patient and hospital characteristics for ICD-9-CM principal procedure code 81.54 total knee replacement. http://hcupnet.ahrq.gov/HCUPnet.jsp. Accessed August 18, 2009.
12. **Kurtz S,** Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. J Bone Joint Surg Am 2007;89:780-5.
13. **Kehlet H,** Jensen TS, Woolf CJ**.** Persistent postsurgical pain: risk factors and prevention. Lancet 2006;367:1618-25.
14. **Katz J**, Seltzer Z. Transition from acute to chronic postsurgical pain: risk factors and protective factors. Expert Rev Neurother 2009;9:723-44.
15. **Fortin PR**, Clarke AE, Joseph L, Liang MH, Tanzer M, Ferland D, Phillips C, Partridge AJ, Belisle P, Fossel AH, Mahomed N, Sledge CB, Katz JN. Outcomes of total hip and knee replacement: preoperative functional status predicts outcomes at six months after surgery. Arthritis Rheum 1999;42:1722-8.
16. **Rappaport BA,** Cerny I, Sanhai WR. ACTION on the prevention of chronic pain after surgery. Anesthesiology 2010;112:509-10.
17. **Buvanendran A**, Kroin JS, Kerns JM, Nagalla SNK, Tuman KJ. Characterization of a new animal model for evaluation of persistent post-thoracotomy pain. Anesth Analg 2004; 99: 1453-60.
18. **Shin JW,** Pancaro C, Wang CF, Gerner P. Low dose systemic bupivicaine prevents the development of allodynia after thoracotomy in rats. Anesth Analg 2008; 107: 1587-91.
19. **Perttunen K,** Tasmuth T, Kalso E. Chronic pain after thoracic surgery: a follow-up study. Acta Anaesthesiol Scand 1999; 43:563-7.
20. **Dworkin RH**, McDermott MP, Raja SN. Preventing chronic postsurgical pain: how much of a difference makes a difference? Anesthesiology 2010; 112:516-8.
21. **Kehlet H**, Rathmell JP. Persistent postsurgical pain. Anesthesiology 2010; 112:514-5.
22. **Lingard EA**, Katz JN, Wright EA, Sledge CB; Kinemax Outcomes Group. Predicting the outcome of total knee arthroplasty. J Bone Joint Surg Am 2004;86-A:2179-86.
23. **Jones CA**, Voaklander DC, Johnston DW, Suarez-Almazor ME. The effect of age on pain, function, and quality of life after total hip and knee arthroplasty. Arch Intern Med. 2001;161:454-60.
24. **Fitzgerald JD,** Orav EJ, Lee TH, Marcantonio ER, Poss R, Goldman L, Mangione CM. Patient quality of life during the 12 months following joint replacement surgery. Arthritis Rheum 2004;51:100-9.
25. **Breivik H,** Borchgrevink PC, Allen SM, Rosseland LA, Romundstad L, Hals EK, Kvarstein G, Stubhaug A. Assessment of pain. Br J Anaesth 2008;101:17-24.

26. **Elson DW**, Brenkel IJ. Predicting pain after total knee arthroplasty. J Arthroplasty 2006;21:1047-53.
27. **Singh JA,** Gabriel S, Lewallen D. The impact of gender, age, and preoperative pain severity on pain after TKA. Clin Orthop Relat Res 2008;466:2717-23.
28. **Ritter MA**, Wing JT, Berend ME, Davis KE, Meding JB. The clinical effect of gender on outcome of total knee arthroplasty. J Arthroplasty 2008;23:331-6.
29. **Naert AL**, Kehlet H, Kupers R. Characterization of a novel model of tonic heat pain stimulation in healthy volunteers. Pain 2008;138:163-71.
30. **Granot M.** Can we predict persistent postoperative pain by testing preoperative experimental pain? Curr Opin Anaesthesiol 2009;22:425-30.
31. **Lingard EA**, Riddle DL. Impact of psychological distress on pain and function following knee arthroplasty. J Bone Joint Surg Am 2007;89:1161-9.
32. **Edwards RR,** Fillingim RB, Maixner W, Sigurdsson A, Haythornthwaite J. Catastrophizing predicts changes in thermal pain responses after resolution of acute dental pain. J Pain 2004;5:164–70.
33. **Forsythe ME,** Dunbar MJ, Hennigar AW, Sullivan MJ, Gross M. Prospective relation between catastrophizing and residual pain following knee arthroplasty: two-year follow-up. Pain Res Manag 2008;13:335-41.
34. **Feeney SL.** The relationship between pain and negative affect in older adults: anxiety as a predictor of pain. Anxiety Disorders 2004; 18: 733-44.
35. **Jones CA**, Voaklander DC, Johnston DW, Suarez-Almazor ME. Health related quality of life outcomes after total hip and knee arthroplasties in a community based population. J Rheumatol 2000;27:1745-52.
36. **Sullivan MJL**, Thorn B, Haythornthwaite JA, Keefe F, Martin M, Bradley LA, Lefebvre JC. Theoretical perspectives on the relation between catastrophizing and pain. Clin J Pain 2001;17:52–64
37. **Gracely RH,** Geisser ME, Giesecke T, Grant MA, Petzke F, Williams DA, Clauw DJ. Pain catastrophizing and neural responses to pain among persons with fibromyalgia. Brain 2004;127:835–43.
38. **Riddle** DL, Wade JB, Jiranek WA, Kong X. Preoperative pain catastrophizing predicts pain outcome after knee arthroplasty. Clin Orthop Relat Res 2010;468:798–806.
39. **Keefe FJ,** Affleck G, France CR, Emery CF, Waters S, Caldwell DS, et al. Gender differences in pain, coping, and mood in individuals having osteoarthritic knee pain: a within-day analysis. Pain 2004;110:571-7.
40. **France CR,** Keefe FJ, Emery CF, Affleck G, France JL, Waters S, Caldwell DS, Stainbrooka D, Hackshaw KV, Edwards C. Laboratory pain perception and clinical pain in post-menopausal women and age-matched men with osteoarthritis: relationship to pain coping and hormonal status. Pain 2004;112:274–81.
41. **Coderre TJ**, Katz J, Vaccarino AL, Melzack R. Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence. Pain 1993; 52:259-85.
42. **Woolf CJ**, Wall PD. Relative effectiveness of C primary afferent fibers of different origins in evoking a prolonged facilitation of the Flexor Reflex in the Rat. J Neuroscience 1986; 6:1433-42.
43. **Davies SN**, Lodge D. Evidence for involvement of N-methylaspartate receptors in 'wind-up' of class 2 neurones in the dorsal horn of the rat. Brain Research 1987; 424:402-6.
44. **Dickenson AH**, Sullivan AF. Evidence for a role of the NMDA receptor in the frequency dependent potentiation of deep rat dorsal horn nociceptive neurones following C fibre stimulation. Neuropharmacology 1987; 26:1235-8.
45. **Edwards RR**, Ness TJ, Weigent DA, Fillingim RB. Individual differences in diffuse noxious inhibitory controls (DNIC): association with clinical variables. Pain 2003; 106:427-37.
46. **Cervero F**: Pain. friend or foe? A neurobiologic perspective. Reg Anesth Pain Med 2009;34: 569-74.
47. **Stubhaug** A, Breivik H, Eide PK, Kreunen M, Foss A. Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery. Acta Anaesthesiol Scand 1997; 41:1124-32.
48. **Lavand'homme P**, De Kock M, Waterloos H. Intraoperative epidural analgesia combined with ketamine provides effective preventive analgesia in patients undergoing major digestive surgery. Anesthesiology 2005; 103:813-20.
49. **Landau R**, Kraft JC, Flint LY, Carvalho B, Richebé P, Cardoso M, Lavand'homme P, Granot M, Yarnitsky D, Cahana A. An experimental paradigm for the prediction of post-operative pain (PPOP). J Vis Exp. 2010 27. pii: 1671. doi: 10.3791/1671.I
50. **Gibson SJ**, Farrell M. A review of age differences in the neurophysiology of nociception and the perceptual experience of pain. Clin J Pain 2004; 20:227-39.

51. **Buvanendran A**, Kroin JS, Della Valle CJ, Kari M, Moric M, Tuman KJ. Pregabalin reduces chronic pain and improves range of motion after total knee arthroplasty: a prospective, randomized trial. Anesth Analg 2010; 110:199-207.
52. **Tulipani C**, Morelli F, Spedicato MR, Evaristo Maiello E, Todarello O, Porcelli P. Alexithymia and cancer pain: The effect of psychological intervention. Psychother Psychosom 2010;79:156–163.
53. **Thieme K**, Gracely RH. Are psychological treatments effective for fibromyalgia pain? Curr Rheumatol Rep 2009;11:443-50.
54. **De Kock, M** Lavand'homme P, Waterloos H. 'Balanced analgesia' in the perioperative period: is there a place for ketamine? Pain 2001; 92:373-80.
55. **Frankel HM**. Determination of body mass index. JAMA 1986;255:1292.
56. **Froehner M**, Koch R, Litz R, Heller A, Oehlschlaeger S, Wirth MP. Comparison of the American Society of Anesthesiologists Physical Status classification with the Charlson score as predictors of survival after radical prostatectomy. Urology 2003;62:698-701.
57. **Dworkin RH**, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, Kerns RD, Stucki G, Allen RR, Bellamy N, Carr DB, Chandler J, Cowan P, Dionne R, Galer BS, Hertz S, Jadad AR, Kramer LD, Manning DC, Martin S, McCormick CG, McDermott MP, McGrath P, Quessy S, Rappaport BA, Robbins W, Robinson JP, Rothman M, Royal MA, Simon L, Stauffer JW, Stein W, Tollett J, Wernicke J, Witter J; IMMPACT. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005;113:9-19.
58. **Bergh I**, Sjöström B, Odén A, Steen B. An application of pain rating scales in geriatric patients. Aging (Milano) 2000;12:380-7
59. **Hoffman DL**, Sadosky A, Alvir J. Cross-national burden of painful diabetic peripheral neuropathy in Asia, Latin America, and the Middle East. Pain Pract 2009;9:35-42.
60. **Hans G**, Sabatowski R, Binder A, Boesl I, Rogers P, Baron R. Efficacy and tolerability of a 5% lidocaine medicated plaster for the topical treatment of post-herpetic neuralgia: results of a long-term study. Curr Med Res Opin 2009;25:1295-305.
61. **Weissman-Fogel** I, Granovsky Y, Crispel Y, Ben-Nun A, Best LA, Yarnitsky D, Granot M. Enhanced presurgical pain temporal summation response predicts post-thoracotomy pain intensity during the acute postoperative phase. J Pain 2009;10:628-36.
62. **Scholz J**, Mannion RJ, Hord DE, Griffin RS, Rawal B, Zheng H, Scoffings D, Phillips A, Guo J, Laing RJ, Abdi S, Decosterd I, Woolf CJ. A novel tool for the assessment of pain: validation in low back pain. PLoS Med 2009;6(4):e1000047.
63. **Sullivan MJL**, Bishop SR, Pivek J. The Pain Catastrophizing Scale: Development and Validation. Psychological Assessment 1995; 7:524-32.
64. **Osman A**, Barrios FX, Kopper BA, Hauptmann W, Jones J, O'Neill E. Factor structure, reliability, and validity of the Pain Catastrophizing Scale. J Behav Med 1997;20:589-605.
65. **Van Damme S**, Crombez G, Bijttebier P, Goubert L, Van Houdenhove B. A confirmatory factor analysis of the Pain Catastrophizing Scale: invariant factor structure across clinical and non-clinical populations. Pain 2002;96:319-24.
66. **de Jong JR**, Vlaeyen JW, Onghena P, Cuypers C, den Hollander M, Ruijgrok J. Reduction of pain-related fear in complex regional pain syndrome type I: the application of graded exposure in vivo. Pain 2005;116:264-75.
67. **Beck AT**, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561-71.
68. **Beck AT**, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. J Pers Assess 1996;67:588-97.
69. **Spielberger CD**, Gorsuch RL, Lushene PR, Vagg PR, Jacobs AG. Manual for the State-Trait Anxiety Inventory (Form Y). Consulting Psychologists Press, Inc.; Palo Alto, 1983.
70. **Buvanendran A**, Kroin JS, Tuman KJ, Lubenow TR, Elmofty D, Moric M, Rosenberg AG: Effects of perioperative administration of a selective cyclooxygenase 2 inhibitor on pain management and recovery of function after knee replacement. JAMA 2003;290:2411-8.
71. **Norkin CC**, White DJ. Measurement of joint motion: a guide to goniometry. 2nd ed., Philadelphia, PA: FA Davis Co; 1995, p 142.

72. **Bellamy N**, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15:1833-40.
73. **Ware JE Jr**, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83.
74. **Kim H**, Dionne RA. Lack of influence of GTP cyclohydrolase gene (GCH1) variations on pain sensitivity in humans. Mol Pain 2007,3:6.
75. **Kim H,** Lee H, Rowan J, Brahim J, Dionne RA. Genetic polymorphisms in monoamine neurotransmitter systems show only weak association with acute post-surgical pain in humans. Mol Pain 2006,2:24.
76. **Zubieta JK**, Heitzeg MM, Smith YR, Bueller JA, Xu K, Xu Y, Koeppe RA, Stohler CS, Goldman D. COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor. Science 2003 21;299:1240-3.
77. **Tegeder I,** Costigan M, Griffin RS, Abele A, Belfer I, Schmidt H, Ehnert C, Nejim J, Marian C, Scholz J, Wu T, Allchorne A, Diatchenko L, Binshtok AM, Goldman D, Adolph J, Sama S, Atlas SJ, Carlezon WA, Parsegian A, Lötsch J, Fillingim RB, Maixner W, Geisslinger G, Max MB, Woolf CJ. GTP cyclohydrolase and tetrahydrobiopterin regulate pain sensitivity and persistence. Nat Med 2006;12:1269-77.
78. **Horlocker TT**, Wedel DJ, Benzon H, Brown DL, Enneking FK, Heit JA, Mulroy MF, Rosenquist RW, Rowlingson J, Tryba M, Yuan CS.Regional anesthesia in the anticoagulated patient: defining the risks (the second ASRA Consensus Conference on Neuraxial Anesthesia and Anticoagulation). Reg Anesth Pain Med 2003; 28:172-97.
79. **Kuehn BM**. FDA focuses on drugs and liver damage: labeling and other changes for acetaminophen. JAMA 2009;302:369-71.
80. **Yarnitsky D**, Crispel Y, Eisenberg E, Granovsky Y, Ben-Nun A, Sprecher E, Best LA, Granot M: Prediction of chronic post-operative pain: pre-operative DNIC testing identifies patients at risk. Pain 2008; 138:22-8.
81. **Martinez V,** Fletcher D, Bouhassira D, Sessler DI, Chauvin M: The evolution of primary hyperalgesia in orthopedic surgery: quantitative sensory testing and clinical evaluation before and after total knee arthroplasty. Anesth Analg 2007;105:815-21.
82. **Della Valle CJ**, Sporer SM, Jacobs JJ, Berger RA, Rosenberg AG, Paprosky WG. Perioperative testing for sepis prior to revision total knee arthroplasty. J Arthroplasty 2007;22:suppl 2,90-93.
83. **Friendly M**. Visualizing Categorical Data. SAS Publishing; 2000.
84. **Shin N.** Chronic pain after total knee and hip arthroplasty: a survey of outcomes. ASA 2009 Annual Meeting: A587.
85. **Baron RM**, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J Pers Soc Psychol 1986;51:1173-82.
86. **Preacher KJ**, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. Behav Res Methods 2008;40:879-91.
87. **Sobel ME**. Asymptotic Confidence Intervals for Indirect Effects in Structural Equation Models in Sociological Methodology, Vol. 13, Hoboken, NJ , John Wiley & Sons, 1982, p 290-312.
88. **Stone CA**, Sobel ME. The robustness of estimates of total indirect effects in covariance structure models estimated by maximum likelihood. Psychometrika 1990;55:337-52.
89. **Fairchild AJ**, Mackinnon DP, Taborga MP, Taylor AB. R2 effect-size measures for mediation analysis. Behav Res Methods 2009;41:486-98.
90. **Pearson K.** On lines and planes of closest fit to systems of points in space. Philosophical Magazine 1901;2: 559.
91. **McDonald RP.** Factor analysis and related methods. Lawrence Erlbaum Associates; 1985
92. **Fukuda K**, Nisenbaum R, Stewart G, et al. Chronic multisymptom illness affecting Air Force veterans of the Gulf War. JAMA 1998;280:981-988.
93. **Quessy SN.** Two-stage enriched enrolment pain trials: A brief review of designs and opportunities for broader application. Pain 2010; 148:8-13.
94. **Scholz J,** Yaksh TL. Preclinical research on persistent postsurgical pain. Anesthesiology 2010; 112:511-2
95. Buvanendran A, Mitchell K, Kroin JS, Iadarola MJ. Cytokine gene expression after total hip arthroplasty: Surgical site versus circulating neutrophil response. Anesthesia & Analgesia 2009; 103; 959-964.

96. Wylde V, Hewlett S, Learmonth ID, Dieppe P. Persistent pain after joint replacement: Prevalence, sensory qualities, and postoperative determinants. Pain 2011; 152: 566-572.
97. Maihofner C, Seifert F, Markovic K. Complex regional pain syndromes: new pathophysiological concepts and therapies. European Journal of Neurology 2010; 17: 649-660.