Pain relief after musculoskeletal trauma

Helmerhorst, G.T.T.

Publication date
2018
Document Version
Final published version
License
Other

Gijs T.T. Helmerhorst

Pain Relief after Musculoskeletal Trauma

PAIN RELIEF AFTER MUSCULOSKELETAL TRAUMA

Gijs T.T. Helmerhorst

ISBN: 978-94-6182-887-3

Layout and printing production: Off Page, Amsterdam
Cover design: Gijs Helmerhorst

The research described and publication of this thesis was supported by a grant from Stichting de Merel.
Printing of this thesis was financially supported by:
Academisch Medisch Centrum, Department of Orthopaedic Surgery
Anna Fonds
Bauerfeind
CayMedic
Chipsoft
iMove Medical
Implantcast
LEUK Orthopedie
Mathys Orthopaedics BV
MC Slotervaart
Nederlandse Orthopaedische Vereniging
Nederlandse Vereniging voor Orthopaedische Traumatologie
Qmediq
Traumaplatform

PAIN RELIEF AFTER MUSCULOSKELETAL TRAUMA

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. ir. K.I.J. Maex
ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel
op donderdag 17 mei 2018, te 12:00 uur

door

Gijsbert Thomas Theodoor Helmerhorst
geboren te Amsterdam

PROMOTIECOMMISSIE

Promotor(es):	prof. dr. G.M.M.J. Kerkhoffs	AMC-Universiteit van Amsterdam
	prof. dr. D.C. Ring	The University of Texas at Austin
Copromotor:	dr. P. Kloen	AMC-Universiteit van Amsterdam
Overige leden:	prof. dr. D. Eygendaal	AMC-Universiteit van Amsterdam
	prof. dr. dr. M.W. Hollmann	AMC-Universiteit van Amsterdam
	prof. dr. A. van Kampen	Radboud Universiteit Nijmegen
	prof. dr. M.J.M.H. Lombarts	AMC-Universiteit van Amsterdam
	prof. dr. M.H.J. Verhofstad	Erasmus Universiteit Rotterdam

Faculteit der Geneeskunde

TABLE OF CONTENTS

1

GENERAL INTRODUCTION

PAIN VERSUS NOCICEPTION

The most common reason for seeking medical care is pain and more than half of American adults (125 million) had a musculoskeletal pain disorder in 2012.[1] According to the European Commission around 50% of the population reported musculoskeletal pain for at least one week in the last month.[2] There were more than 116 million Americans (roughly 40%) with persistent pain in 2011, and although assessment of the financial costs for pain is difficult, estimates range somewhere between $560 billion to $635 billion per year in the United States (US) alone.[3,4] It is fair to say that pain is a major health and socio-economic burden.

Every person knows the concept of pain, yet it is very difficult to explain exactly what pain is. Most will consider it a negative sensation, but even this simplified explanation is at least questionable.[5] Hippocrates believed pain was caused by an imbalance of vital fluids, and in 1644 it was Descartes who first described pain using a 'mind-body' model.[6] There is a wide variation in (the experience of) pain and in satisfaction with pain relief among individuals, gender, age, and races.[7-13] In his Thesis in 2006, Ring described pain as maybe the most difficult symptom for physicians and surgeons to diagnose specifically and treat effectively.[14] Pain is strongly psychosocially mediated rather than biomedical (i.e. greater pathophysiology, inadequate pain medication), and psychosocial factors such as self-efficacy, elevated mood, and optimal circumstances help limit pain and disability.[15-17]

Nociception is the neurophysiologic mechanism by which actual or potential tissue damage is communicated from the periphery to the central nervous system. Somatic nociception can be superficial or deep, according to the location of injury. Superficial nociception (arising from the superficial skin) is usually sharp and short. It transmits fast along myelinated A-delta fibers at 4-36 m/s. Deep nociception (arising from e.g. ligaments, tendons, muscles, bones) is usually dull and aching. It always indicates tissue damage and transmits slowly along unmyelinated C-fibers at 0.4-1 m/s. Both superficial and deep pain fibers synapse in the dorsal horn of the spinal cord transferring the message to postsynaptic neurons via neurotransmitters (e.g. glutamate and substance p) and then finally delivery to the brain. The nociceptive threshold is roughly the same for everyone. For instance, we perceive heat as painful at 44-46° Celsius (not coincidentally the threshold for potential tissue damage). However, the reaction (or tolerance) to this nociception varies among individuals.[18]

Pain can then be defined as the unpleasant cognitive, emotional, and behavioral response to nociception. The relationship of pain to nociception is variable and it is possible to have pain in the absence of nociception as well as nociception with little pain.[19] Some people have substantial nociception and little pain (e.g. a sportsman getting up after a major collision resulting in a fracture and continuing the game). Other people have substantial pain without detectable nociception (e.g. fibromyalgia). Orthopaedic surgeons are familiar with this discrepancy between pain and nociception. Every surgeon has experience treating patients that had extensive surgery but took few if any pain medications. In contrast, they also have experience treating patients with intense pain after only a minor procedure. Part of the explanation for these observations can be found in the evidence that pain intensity for a given nociception is greater when there is greater stress or distress, and it is greater with less effective coping strategies.[20-23]

OPIOIDS

The most prevalent pain relief strategy is prescription of painkillers (analgesics). There are many types and forms of painkillers, each with another mechanism of action and subsequent side effects. An often-used class of painkillers for musculoskeletal trauma are opioids. Opioids are narcotic drugs that act by binding to opioid-receptors in the central nervous system, inhibiting nerves that transmit nociception. They include opiates (e.g. morphine), derived from the opium poppy (*Papaver Somniferum*), and (semi-)synthetic prescription drugs (e.g. oxycodone, fentanyl, hydrocodone). Heroin—another infamous opioid—was developed around 1900 by pharmaceutical companies and was once marketed for the treatment of morphine addiction, but is now illegal.[24] Opioids carry the unwanted risk of addiction (i.e., impaired control over drug use, compulsive use, continued use despite harm, and craving— particularly observed in biologically and psychosocially vulnerable individuals), misuse, physical dependence and tolerance.[25,26] They also bind to opioid receptors in the gastrointestinal tract and other organs, hence explaining other adverse effects as sedation, constipation, nausea, pruritus and respiratory depression.[25,27] The use of opioids is not contemporary. In the *Odyssey*, Homer told of Telemachus (son of Odysseus) who was so worried for his father's fate, that he was given opium to help him forget about his anxieties.[28] Hippocrates thought they should be used sparingly and under controlled conditions.[28]

Nowadays, misuse of prescription opioids is rapidly increasing and has a major impact on health, society, economy, and safety.[29-31] The most prescribed drug in the US is an opioid and in 2011 more than 370.000 emergency department visits involved nonmedical use of prescription opioids.[32,33] The overall annual number of opioid prescriptions dispensed by retail pharmacies increased from 76 million prescriptions in 1991 to 219 million prescriptions in 2011.[34] In 2009 drug poisoning surpassed motor vehicle collisions as the leading cause of accidental death in the US, and the vast majority were overdoses of prescriptions opioids.[35] Both prescription opioid sales and overdose deaths have quadrupled since 1999. More than half of all US opioid overdose deaths involve a prescription opioid, and at least 165,000 people have died in the US from overdoses related to prescription opioids since the millennium (18,893 deaths in 2014). Currently, 46 people die each day from an overdose of prescription opioids in the US.[36,37]

VARIATION IN PAIN MANAGEMENT

There is substantial variation among physicians, hospitals, communities and cultures in prescribing medications for analgesia in patients with skeletal trauma. Post-operative pain management can be based on the three-step WHO pain ladder for treatment of pain (originally developed for palliative cancer care: (1) non-opioids (e.g., paracetamol (acetaminophen) and NSAIDs), (2) mild opioids (e.g., tramadol and codeine), and (3) strong opioids (e.g., oxycodone, fentanyl, hydromorphone, and morphine).[38] The rationale for this ladder is that NSAIDs and especially paracetamol are relatively safe, inexpensive and effective analgesics. Opioids are more expensive and dangerous.[25-27]

A similar approach is often used for general post-operative pain management in the Netherlands, but there is currently no official protocol for pain-management after skeletal trauma.[39] American physicians and patients tend to prefer stronger painkillers (opioids) and seem to bypass the first

steps of the WHO pain ladder. Explanations for this can be sought in a variety of factors including pathophysiological, cultural (patient and physician) or psychological. Pathophysiological factors seem unlikely as operative techniques and spectra of injury are fairly uniform worldwide. Cultural and psychological are more likely. For example, in the US and Canada opioids were marketed and promoted by advocates and pharmaceutical companies.[40-42]

There seem to be large differences between the two countries and this emphasizes how much there is to learn in this area of investigation. Given the divide between pain and nociception, and the seemingly differences in pain management used between different countries, it would be interesting to know what the most effective and safe pain-management is for patients after operative treatment of skeletal trauma.

This thesis will investigate the effects of various pain management strategies on pain relief, satisfaction with pain relief, and disability after extremity fractures. It will focus on the pharmacological aspect of pain management and will explore other aspects. The main objectives are to 1) evaluate the differences in pain management after skeletal trauma in the Netherlands and the US, 2) test if current analgesic prescription in fracture patients is suitable, 3) find factors associated with continued use of opioids after surgery for skeletal trauma in the United States. This will hopefully benefit patients, physicians and cultures by providing a basis for uniform and safe pain management after skeletal trauma.

OUTLINE OF THE CHAPTERS

CHAPTER 2

Differences in prescription of narcotic pain medication after operative treatment of hip and ankle fractures in the United States and the Netherlands

Helmerhorst GT, Lindenhovius AL, Schnellen AC, Vrahas M, Ring D, Kloen P

J Trauma. 2009 Jul;67(1):160-4

As mentioned, the experience of pain varies greatly among individuals, gender, age, and races.[7-13] Factors that influence the perception of pain include symptoms of depression, effective coping strategies, symptoms of anxiety, and secondary gain issues.[21,43-45] We observed differences in prescription habits for opioid pain medication between orthopaedic surgeons from the United States and the Netherlands that seemed noteworthy. This was consistent with other studies that demonstrated that countries where fewer or weaker opioids were prescribed had comparable satisfaction with pain relief.[46,47]

In chapter 2, we therefore studied the differences in opioid prescription habits of orthopaedic surgeons in two major representative trauma centers in the United States and the Netherlands after operative treatment of skeletal trauma in a large series of patients. Percentages of patients receiving inpatient and outpatient prescriptions for opioids were compared between the two countries.

This study tested the hypothesis that opioid pain medication is prescribed more frequently in the United States as compared with the Netherlands after operative treatment of hip and ankle fractures.

CHAPTER 3

Satisfaction with pain relief after operative treatment of an ankle fracture

Helmerhorst GT, Lindenhovius AL, Vrahas M, Ring D, Kloen P

Injury. 2012 Nov;43(11):1958-61.

American patients are prescribed more opioid pain medication than Dutch patients after operative treatment of hip and ankle fractures.[48] There are two possible explanations for this. First, since it was not measured, it is possible that pain is undertreated in Dutch patients. On the other hand, given that these patients would be expected to have comparable nociception (as a result of similar fracture pathophysiology and operative treatment), and appeared to be satisfied in clinical practice, this seems unlikely. Second, the use of less opioid pain medication by Dutch patients might be explained by cultural or psychosocial differences (e.g. differences in health provider training, health practice, and psychological differences such as effective coping strategies, greater self-efficacy, and better mood).

It would be helpful to evaluate the variation in pain-management after skeletal trauma in the USA and the Netherlands, to see if there are obvious differences, if Dutch patients are not undertreated, and if these differences contribute to overall pain perception.

In chapter 3, we prospectively studied the difference in (satisfaction with) pain relief between 60 patients (30 American and 30 Dutch) that took an opioid compared to patients that took a non-opioid pain regimen after operative treatment of an ankle fracture, in order to evaluate pain relief and satisfaction with pain relief. Patients rated pain and satisfaction with pain relief on post-operative day 1 and at time of suture removal. Pain and satisfaction scores were compared and multivariable analysis identified their predictors.

This study tested the null hypothesis that there is no difference in pain and satisfaction with pain relief between American and Dutch patients on the first postoperative day and at the time of suture removal after surgical treatment of ankle fractures, in spite of the fact that Dutch patients typically use nothing stronger than tramadol or paracetamol (acetaminophen) for pain relief.

CHAPTER 4

Pain relief after operative treatment of an extremity fracture: a noninferiority randomized controlled trial

Helmerhorst GTT, Zwiers R, Ring D, Kloen P

J Bone Joint Surg Am. 2017 Nov 15;99(22):1908-1915

In chapter 2 we found that about 80% of American patients with hip fractures were prescribed opioids after discharge, compared to none of the Dutch patients.[48] Chapter 3 showed that in patients having surgery for an ankle fracture (with comparable injury and surgery related factors) all American patients used strong opioids one day after surgery, compared to only 17% of the Dutch patients. At time of suture removal, 63% of the American patients still used strong opioids, compared to none of the Dutch patients. Dutch patients reported less pain and equal satisfaction with pain relief.[49]

This expanded use of opioids in the US created an epidemic of opioid misuse and overdose deaths.[29,31,50,51] Although countries in Europe are gradually increasing the prescription of opioids and

seeing greater opioid-related mortality, there is substantial variation between different countries in pain management for patients recovering from operative fracture treatment. In particular tramadol and oxycodone prescriptions are increasing, and even tramadol related deaths doubled in three years' time from 2009 to 2012.[34,52-55]

Satisfaction with pain relief is increasingly used to measure quality of care, and many organizations use algorithms to treat pain using pain scores. Considering comparable surgical technique and that most fractures are stable after surgery, we can advocate that a non-opioid-based analgesic regimen (step 1) can be as effective for patient satisfaction as a weak opioid-based analgesic regimen (step 2), after operative treatment of extremity fractures.

In chapter 4, we randomly assigned 52 patients to receive either step 1 (paracetamol) or step 2 (paracetamol + tramadol) pain medication, to assess satisfaction with pain relief among patients recovering from extremity fracture surgery. Patients rated satisfaction with pain relief and pain intensity scores on post-operative day 1 and two weeks post-operatively. In addition, disability and psychological questionnaires were measured. Pain satisfaction and pain intensity scores were compared between the two groups, and multivariable analysis identified their predictors.

This study tested the hypothesis that patient satisfaction after prescription of step 1 pain medications is non-inferior to step 2 pain medications after operative treatment of an extremity fracture. The secondary hypothesis addressed differences in pain intensity between the groups and factors associated with greater satisfaction with pain relief and greater pain intensity.

CHAPTER 5

Risk factors for continued opioid use one to two months after surgery for musculoskeletal trauma

Helmerhorst GT, Vranceanu AM, Vrahas M, Smith M, Ring D

J Bone Joint Surg Am. 2014 Mar 19;96(6):495-9.

Chapter 2 to 4 demonstrate wide variation in pain (and satisfaction with pain relief) for a given nociception. They also reveal great variance in the actual intake of oral opioid pain medications between individuals. To aid clinical decision making and to assess further management it would be helpful to find predictors for pain intensity, disability, and continued opioid intake when levels of nociception are expected to have considerably decreased.

The mediation of nociception and pain is largely psychosocial (i.e. coping strategies, mood, circumstances) rather than biomedical (i.e. greater pathophysiology, inadequate pain medication).[56-59] Therefore, although still somewhat unconventional in orthopaedic surgery, it is important to take psychosocial factors into account as well.

In chapter 5, we used our assembled database of 145 prospectively assigned patients, who were operatively treated for musculoskeletal trauma and evaluated one to two months after surgery. Patients indicated if they were taking opioid pain medication and completed several psychological questionnaires: the Center for Epidemiologic Studies Depression Scale, the Pain Catastrophizing Scale, the Pain Anxiety Symptoms Scale, and the Posttraumatic Stress Disorder Checklist, civilian version. The Numeric Rating Scale was used to measure pain intensity. Disability was measured with use of the Short Musculoskeletal Function Assessment Questionnaire and injury severity

was measured with use of the Abbreviated Injury Scale. All factors of patient characteristics were analyzed in bivariate and multivariable analysis to try to find these predictors.

This study tested the hypothesis that psychosocial factors contribute to the perception of pain to a higher extent than trauma related factors. The aim was to determine factors associated with self-reported ongoing use of opioid medications one to two months after operative treatment of musculoskeletal trauma.

CHAPTER 6

An epidemic of the use, misuse and overdose of opioids and deaths due to overdose, in the United States and Canada: is Europe next?

Helmerhorst GT, Teunis T, Janssen SJ, Ring D

Bone Joint J. 2017 Jul;99-B (7) 856-864

The differences in prescription of opioid medications between different cultures described in chapter 2-4 are apparent. To appreciate the educational value of these differences, we need to understand how and why these differences originated.

Pain is the most common reason for seeking medical care in the US. More than half of American adults (125 million) had a musculoskeletal pain disorder in 2012.[1] For some time, pain relief in the US and Canada has focused on opioids. In the last two decades, the sales of prescription opioids quadrupled along with the rates of misuse, overdose, and death.[36,60] This put the United States and Canada in the midst of an iatrogenic epidemic of prescription opioid misuse and overdose deaths. The epidemic is the result of overstatement of the benefits and understatement of the risks of opioids by advocates and pharmaceutical companies.[40-42] Large amounts of prescription opioids entered the community and were often diverted and misused. It seems that much of the world is not aware of what is going on in the US and Canada and the misconceptions about opioids are now finding their way around the world.[52,54,61] The world should be mindful of the mistakes made in the US and Canada and do everything possible to avoid repeating them.

In chapter 6 we studied the trends of opioid prescription medication in recent years in North America and compared these to the trends found in Europe. In addition, we did an extensive review of the literature to find evidence of what caused the opioid epidemic. Furthermore, we gather best evidence to find other sources and strategies to counterattack, or prevent further escalation of the opioid crisis. Finally, we present practical steps to help surgeons and other health care providers manage the opioid crisis.

This study tested if European countries are following the trend of the crisis of opioid misuse, overdoses, and overdose deaths in the United States and Canada and how do we prevent it?

SUMMARY OF INTRODUCTION

The general aim of this doctoral thesis is to investigate the effects of various pain management strategies after skeletal trauma. The main objectives are to 1) evaluate the differences in pain management after skeletal trauma in the Netherlands and the US, 2) test if current analgesic prescription in fracture patients is suitable, 3) find factors associated with continued use of opioids after surgery for skeletal trauma in the United States.

REFERENCES

1. Clarke TC, Nahin RL, Barnes PM, Stussman BJ. Use of Complementary Health Approaches for Musculoskeletal Pain Disorders Among Adults: United States, 2012. *Natl Health Stat Report*. 2016(98):1-12.
2. European Commission - Public Health. Musculoskeletal conditions. 2017; https://ec.europa.eu/health/major_chronic_diseases/diseases/musculoskeletal_en. Accessed 9-2017.
3. Pizzo PA, Clark NM. Alleviating suffering 101--pain relief in the United States. *N Engl J Med*. 2012;366(3):197-199.
4. Institute of Medicine (US) Committee on Advancing Pain Research C, and Education. In: *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*. Washington (DC)2011.
5. Leknes S, Berna C, Lee MC, Snyder GD, Biele G, Tracey I. The importance of context: when relative relief renders pain pleasant. *Pain*. 2013;154(3):402-410.
6. Linton S. *Understanding Pain for Better Clinical Practice: A Psychological Perspective*. Elsevier; 2005.
7. Fillingim RB. Individual differences in pain responses. *Curr Rheumatol Rep*. 2005;7(5):342-347.
8. Edwards RR. Genetic predictors of acute and chronic pain. *Curr Rheumatol Rep*. 2006;8(6):411-417.
9. Fillingim RB, Gear RW. Sex differences in opioid analgesia: clinical and experimental findings. *Eur J Pain*. 2004;8(5):413-425.
10. Paller CJ, Campbell CM, Edwards RR, Dobs AS. Sex-based differences in pain perception and treatment. *Pain Med*. 2009;10(2):289-299.
11. Wiesenfeld-Hallin Z. Sex differences in pain perception. *Gend Med*. 2005;2(3):137-145.
12. 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(4):227-239.
13. Kim HJ, Yang GS, Greenspan JD, et al. Racial and ethnic differences in experimental pain sensitivity: Systematic review and meta-analysis. *Pain*. 2016.
14. Ring D. *Psychosocial aspects of arm pain*. Amsterdam, Universiteit van Amsterdam; 2006.
15. Vranceanu AM, Barsky A, Ring D. Psychosocial aspects of disabling musculoskeletal pain. *J Bone Joint Surg Am*. 2009;91(8):2014-2018.
16. Granot M, Ferber SG. The roles of pain catastrophizing and anxiety in the prediction of postoperative pain intensity: a prospective study. *Clin J Pain*. 2005;21(5):439-445.
17. Rosenberger PH, Jokl P, Ickovics J. Psychosocial factors and surgical outcomes: an evidence-based literature review. *J Am Acad Orthop Surg*. 2006;14(7):397-405.
18. Marieb EN, Hoehn K. Human anatomy & Physiology. In: 7th ed. San Francisco: Pearson Education, Inc.; 2007:496.
19. Goroll AH, Mulley AG. Psychiatric problems: approach to the patient with chronic nonmalignant pain. In: Goroll AH, Mulley AG, eds. *Primary Care Medicine: Office Evaluation and Management of the Adult Patient*. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2006:1214 –1422.
20. Vranceanu AM, Bachoura A, Weening A, Vrahas M, Smith RM, Ring D. Psychological factors predict disability and pain intensity after skeletal trauma. *J Bone Joint Surg Am*. 2014;96(3):e20.
21. Severeijns R, Vlaeyen JW, van den Hout MA, Weber WE. Pain catastrophizing predicts pain intensity, disability, and psychological distress independent of the level of physical impairment. *Clin J Pain*. 2001;17(2):165-172.
22. Menendez ME, Ring D. Factors Associated with Greater Pain Intensity. *Hand Clin*. 2016;32(1):27-31.
23. Veehof MM, Trompetter HR, Bohlmeijer ET, Schreurs KM. Acceptance- and mindfulness-based interventions for the treatment of chronic pain: a meta-analytic review. *Cogn Behav Ther*. 2016;45(1):5-31.
24. Sneader W. The discovery of heroin. *Lancet*. 1998;352(9141):1697-1699.

25. Hanks G, Cherny NI, Fallon M. Opioid analgesic therapy. In: Doyle D, Hanks G, Cherny N, Calman K, eds. *Oxford Textbook of Palliative Medicine*. 3rd ed. New York: Oxford United Press; 2004.
26. Savage SR, Joranson DE, Covington EC, Schnoll SH, Heit HA, Gilson AM. Definitions related to the medical use of opioids: evolution towards universal agreement. *J Pain Symptom Manage*. 2003;26(1):655-667.
27. Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. *Pain Physician*. 2008;11(2 Suppl):S105-120.
28. Booth M. *Opium: A History*. St. Martin's Press; 2013.
29. Bohnert AS, Valenstein M, Bair MJ, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA*. 2011;305(13):1315-1321.
30. International Narcotics Control Board (INCB). Opioid Consumption Maps. 2009-2016; https://ppsg.medicine.wisc.edu/. Accessed November 2016, 2016.
31. Florence CS, Zhou C, Luo F, Xu L. The Economic Burden of Prescription Opioid Overdose, Abuse, and Dependence in the United States, 2013. *Med Care*. 2016;54(10):901-906.
32. IMS Health. National Prescription Audit; Top 25 Medicines by Dispensed Prescriptions (U.S.). 2012; https://www.imshealth.com/files/web/Corporate/News/Top-Line Market Data/US_Top_25_Medicines_Dispensed_Prescriptions.pdf. Accessed November, 2016.
33. Crane EH. Emergency Department Visits Involving Narcotic Pain Relievers. In: *The CBHSQ Report*. Rockville (MD)2013.
34. van Amsterdam J, van den Brink W. The Misuse of Prescription Opioids: A Threat for Europe? *Curr Drug Abuse Rev*. 2015;8(1):3-14.
35. Paulozzi LJ. Prescription drug overdoses: a review. *J Safety Res*. 2012;43(4):283-289.
36. Centers for Disease Control and Prevention (CDC). Wide-ranging online data for epidemiologic research (WONDER). 2016; https://wonder.cdc.gov/. Accessed November, 2016.
37. Centers for Disease Control and Prevention (CDC), National Vital Statistics System, Mortality File. Number and age-adjusted rates of drug-poisoning deaths involving opioid analgesics and heroin: United States, 2000–2014. 2014; http://www.cdc.gov/nchs/data/health_policy/AADR_drug_poisoning_involving_OA_Heroin_US_2000-2014.pdf. Accessed November, 2016.
38. World Health Organization. Pain Ladder. 2016; http://www.who.int/cancer/palliative/painladder/en/. Accessed 11-06, 2016.
39. Nederlandse Vereniging voor Anesthesiologie. Postoperatieve pijnbehandeling. In. Alphen aan den Rijn: Van Zuiden Communications B.V.; 2003.
40. Van Zee A. The promotion and marketing of oxycontin: commercial triumph, public health tragedy. *Am J Public Health*. 2009;99(2):221-227.
41. Kolodny A, Courtwright DT, Hwang CS, et al. The prescription opioid and heroin crisis: a public health approach to an epidemic of addiction. *Annual review of public health*. 2015;36:559-574.
42. US General Accounting Office. PRESCRIPTION DRUGS: OxyContin Abuse and Diversion and Efforts to Address the Problem. In. Vol GAO-04-110. Washington, D.C.2003.
43. Meredith P, Strong J, Feeney JA. Adult attachment, anxiety, and pain self-efficacy as predictors of pain intensity and disability. *Pain*. 2006;123(1-2):146-154.
44. Meredith PJ, Strong J, Feeney JA. The relationship of adult attachment to emotion, catastrophizing, control, threshold and tolerance, in experimentally-induced pain. *Pain*. 2006;120(1-2):44-52.
45. MacDermid JC, Donner A, Richards RS, Roth JH. Patient versus injury factors as predictors of pain and disability six months after a distal radius fracture. *J Clin Epidemiol*. 2002;55(9):849-854.

46. Carragee EJ, Vittum D, Truong TP, Burton D. Pain control and cultural norms and expectations after closed femoral shaft fractures. *Am J Orthop (Belle Mead NJ)*. 1999;28(2):97-102.

47. Senden IP, van du Wetering MD, Eskes TK, Bierkens PB, Laube DW, Pitkin RM. Labor pain: a comparison of parturients in a Dutch and an American teaching hospital. *Obstet Gynecol*. 1988;71(4):541-544.

48. Lindenhovius AL, Helmerhorst GT, Schnellen AC, Vrahas M, Ring D, Kloen P. Differences in prescription of narcotic pain medication after operative treatment of hip and ankle fractures in the United States and The Netherlands. *J Trauma*. 2009;67(1):160-164.

49. Helmerhorst GT, Lindenhovius AL, Vrahas M, Ring D, Kloen P. Satisfaction with pain relief after operative treatment of an ankle fracture. *Injury*. 2012;43(11):1958-1961.

50. Ballantyne JC, LaForge KS. Opioid dependence and addiction during opioid treatment of chronic pain. *Pain*. 2007;129(3):235-255.

51. Drug Control and Access to Medicines Consortium. Opioid Consumption Maps. 2009-2016; ppsg-production.heroku.com, 2016.

52. Schubert I, Ihle P, Sabatowski R. Increase in opiate prescription in Germany between 2000 and 2010: a study based on insurance data. *Dtsch Arztebl Int*. 2013;110(4):45-51.

53. The Pain & Policy Studies Group (PPSG). Opioid Consumption Data. 2016; http://www.painpolicy.wisc.edu/opioid-consumption-data. Accessed November, 2016.

54. Giraudon I, Lowitz K, Dargan PI, Wood DM, Dart RC. Prescription opioid abuse in the UK. *Br J Clin Pharmacol*. 2013;76(5):823-824.

55. Ruscitto A, Smith BH, Guthrie B. Changes in opioid and other analgesic use 1995-2010: repeated cross-sectional analysis of dispensed prescribing for a large geographical population in Scotland. *Eur J Pain*. 2015;19(1):59-66.

56. Chapman CR. Pain perception and assessment. *Minerva Anestesiol*. 2005;71(7-8):413-417.

57. Sullivan MD. Finding pain between minds and bodies. *Clin J Pain*. 2001;17(2):146-156.

58. Jackson T, Pope L, Nagasaka T, Fritch A, Iezzi T, Chen H. The impact of threatening information about pain on coping and pain tolerance. *Br J Health Psychol*. 2005;10(Pt 3):441-451.

59. DeGood DE, Tait RC. Assessment of pain beliefs and pain coping. In: Turk DC, Melzack R, eds. *Handbook of pain assessment*. 2nd ed. New York: Guilford Press; 2001:320-345.

60. Rudd RA, Seth P, David F, Scholl L. Increases in Drug and Opioid-Involved Overdose Deaths - United States, 2010-2015. *MMWR Morb Mortal Wkly Rep*. 2016;65(5051):1445-1452.

61. International Narcotics Control Board (INCB). *Estimated world requirements of narcotic drugs in grams for 2016; October update*. New York: United Nations;2016.

DIFFERENCES IN PRESCRIPTION OF NARCOTIC PAIN MEDICATION AFTER OPERATIVE TREATMENT OF HIP AND ANKLE FRACTURES IN THE UNITED STATES AND THE NETHERLANDS

2

Helmerhorst GT, Lindenhovius AL, Schnellen AC,
Vrahas M, Ring D, Kloen P

J Trauma. 2009 Jul;67(1):160-4

ABSTRACT

Background

Interactions between American and Dutch surgeons suggested differences in prescription habits for pain medication after fracture treatment.

Methods

The percentages of 190 American [100 after hip open reduction and internal fixation (ORIF) and 90 after ankle ORIF] and 116 Dutch patients (69 after hip ORIF and 47 after ankle ORIF) receiving inpatient and outpatient prescriptions for narcotics were retrospectively compared between countries, to test the hypothesis that narcotics are prescribed more frequently in the United States as compared with the Netherlands after operative fracture treatment.

Results

Among patients with hip fractures, 85% of American and 58% of Dutch patients were prescribed narcotics during hospitalization ($p < 0.001$). After discharge, 77% of American and none of the Dutch patients were prescribed narcotics ($p < 0.001$). The multivariate model including country accounted for 11% of the variation in inpatient narcotic prescription ($p < 0.001$), and the model including country and surgeon accounted for 55% of the variation in outpatient narcotic prescription ($p < 0.001$). Among patients with ankle fracture, 98% of American and 64% of Dutch patients were prescribed narcotics during hospitalization ($p < 0.001$). After discharge, 82% of American patients and 6% of Dutch patients were prescribed narcotics ($p < 0.001$). Predictors included country and surgeon and they accounted for 20% of the variation in inpatient narcotics prescription ($p < 0.001$) and 49% of the variation in outpatient narcotic prescription ($p < 0.001$).

Conclusions

American patients are prescribed significantly more inpatient and outpatient narcotic pain medication than Dutch patients after operative treatment of hip and ankle fractures.

INTRODUCTION

Pain has been defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". The conscious understanding of pain may be altered by a variety of factors.[1] In contrast, nociception is the neurophysiologic mechanism by which tissue damage is communicated to the central nervous system as pain. Pain is strongly psychosocially mediated. The relationship of pain to nociception is variable and it is possible to have pain in the absence of nociception.[2]

The experience of pain differs among individuals,[3,4] gender,[5-7] age,[8] cultures, and races.[9,10] Factors that influence the perception of pain include depression, coping strategies and anxiety disorders,[11-13] and secondary gain issues such as active litigation and insurance claims.[14,15] A mail survey asking questions about management of hypothetical patients among British and Dutch general practitioners found that medication prescribing habits differ between countries.[16] Interactions between American and Dutch orthopaedic surgeons in our research unit suggested apparent differences in the prescription habits for narcotic pain medication.

This study tested the hypothesis that narcotic pain medication is prescribed more frequently in the United States as compared with the Netherlands after operative treatment of hip and ankle fractures.

PATIENTS AND METHODS

Three hundred six consecutive patients who were 18 years or older had operative treatment of a hip (169) or ankle (137) fracture at one of the two level I trauma centers, one in the United States and one in the Netherlands. One hundred ninety American patients were treated in 2006, and of the 116 Dutch patients, the 69 patients with hip fractures were treated in 2006 and 2007, and the 47 patients with ankle fractures were treated from 2005 to 2007. The Human Research Committee approved a retrospective review of medical records of these patients to retrieve the following information: age, gender, fracture type, duration of admission, surgeon, inpatient pain medication (narcotic vs. non-narcotic), and prescriptions for outpatient medication (narcotic vs. non-narcotic). Narcotic pain medication was defined as opioid or mild opioid analgesic drugs, i.e., opium or opium derivatives, and their synthetic substitutes (e.g., tramadol). Non-narcotic pain medication was defined as non-opioid analgesics, i.e., acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs).

American Patients

Thirty-one male and 69 female American patients with an average age of 78 years (range, 26 – 96 years) had operative treatment of a hip fracture. Fifty-one patients had a type A fracture, 47 had a type B, and 2 had a type C fracture according to the Comprehensive Classification of Fractures.[17] Patients were treated by nine different orthopaedic trauma surgeons. The average duration of the postoperative hospital stay was 8 days (range, 2 – 77 days) (Table 1).

Fifty-three male patients and 37 female patients with an average age of 45 years (range, 19 – 85 years) had operative treatment of an ankle fracture. Three patients had a type A fracture, 57 had a type B fracture, and 30 had a type C fracture.[17] Patients were treated by seven orthopaedic trauma

surgeons and the average duration of postoperative hospital stay was 4 days (range, 1 – 22 days) (Table 2).

Dutch Patients

Twenty-two male and 47 female Dutch patients with an average age of 77 years (range, 20 – 98 years) had operative treatment of a hip fracture. Twenty had a type A fracture and 49 patients had a type B fracture according to the Comprehensive Classification of Fractures.[17] Patients were treated by five different orthopaedic surgeons. The average duration of postoperative hospital stay was 14 days (range, 2 – 74 days) (Table 1).

Nineteen male patients and 28 female patients with an average age of 46 years (range, 19 – 88 years) had operative treatment of an ankle fracture: type C in 28 and type B in 19 patients.[17] Patients were treated by five different orthopaedic surgeons. The average duration of postoperative hospital stay was 6 days (range, 1 – 92 days) (Table 2).

Comparison of American and Dutch Patients

There was no significant difference in age ($p = 0.63$) or gender ($p = 0.58$) between the Dutch and American cohorts among patients with hip fractures. Dutch patients were hospitalized for an average of 6 days longer than American patients ($p < 0.001$).

Among patients with ankle fractures, there was no difference in age ($p = 0.71$) and duration of postoperative hospital stay ($p = 0.13$) between Dutch and American patients. The proportion of female to male patients was significantly greater in the Dutch cohort ($p < 0.05$).

Statistical Analysis

Two separate but identical statistical analyses were performed: one for hip fractures and one for ankle fractures. Dutch and American cohorts were compared using Student's t test for continuous variables and using the χ^2 test for dichotomous or nominal variables. p values of less than 0.05 were considered statistically significant.

Univariate analysis was performed to assess association between independent (or explanatory) variables and dependent (or response) variables. Response variables investigated included inpatient

Table 1. American vs. Dutch Patients with Hip Fractures

	American	Dutch
Male	31	22
Female	69	47
Age	78	77
Fracture type A	51	20
Fracture type B	47	49
Fracture type C	2	None
Number of surgeons	9	5
Hospitalization (days)	8	14

Table 2. American vs. Dutch Patients with Ankle Fractures

	American	Dutch
Male	53	19
Female	37	28
Age	45	46
Fracture type A	3	None
Fracture type B	57	19
Fracture type C	30	28
Number of surgeons	7	5
Hospitalization (days)	4	6

and outpatient prescription of narcotic versus non-narcotic medication. The association between response variables with continuous explanatory variables (age and duration of postoperative hospital stay) was assessed with Student's t test, and the association with dichotomous or nominal explanatory variables was assessed (gender, country, and surgeon) with the use of the χ^2 test.

Backward conditional binary logistic regression was used to analyze the ability of the explanatory variables to influence the response variables, accounting for confounding between the explanatory variables. A logistic regression model produces a statistic called the adjusted Cox Snell R-squared, which reflects the proportion of the variation in the response variable that can be explained or accounted for by the explanatory variables included in the logistic regression model. The number of explanatory variables that can be included in a logistic regression model is limited by the overall sample size of the study. Therefore, instead of entering all of our potential explanatory variables into the binary logistic regression analysis, we chose to enter only those variables that were either significant ($p < 0.05$) or nearly significant ($p < 0.10$) in the univariate analysis, a common cutoff value for inclusion of variables in regression modeling. We ran two models: (1) a backward conditional binary logistic regression model that includes all the entered variables initially and then iteratively removes variables from the model until the best-fit model is achieved according to set criteria, and (2) a logistic regression model with country alone. Comparison of the variation accounted for by each of the models (the Cox Snell R-squared) provides a measure of the relative influence of each explanatory variable on the overall variation in the response variable.

The model χ^2 (the χ^2 for covariates) was performed to assess adequacy of the model. A significant result suggests that at least one variable is significantly associated with the response variable. SPSS software was used for statistical analysis (version 15.0, SPSS, Chicago, IL).

RESULTS

Hip Fractures

Comparison of Cohorts

Two of the American patients (2%) died during their postoperative stay in the hospital. For one patient (1%) inpatient pain medication could not be retrieved. Eighty-five American patients (85%) used narcotic pain medication during the postoperative hospital stay compared with 40 patients

in the Dutch cohort (58%; $p < 0.001$). After patients were discharged, 77 patients in the American cohort (77%) were prescribed narcotic pain medication compared with none of the patients in the Dutch cohort ($p < 0.001$) (Table 3).

Predictors of Inpatient Narcotic Prescription

In univariate analysis, there was only a significant association between inpatient narcotic use with country ($p < 0.001$). The logistic regression model including country accounted for 11% of the variation in narcotic use ($p < 0.001$).

Predictors of Outpatient Narcotic Prescription

There was significant association between outpatient narcotic prescription with duration of postoperative hospital stay ($p < 0.01$), country, and surgeon (both $p < 0.001$) in univariate analysis. The best logistic regression model included country and surgeon and accounted for 55% of the variation in narcotic prescription ($p < 0.001$). The model with country alone also accounted for 55% of the variation in narcotic prescription ($p < 0.001$).

Ankle Fractures

Comparison of Cohorts

For three patients in the American cohort (3%), inpatient pain medication could not be retrieved retrospectively. Eighty-five American patients (98%) used narcotic pain medication during the postoperative hospital stay compared with 30 Dutch patients (64%; $p < 0.001$). Seventy-one American patients (82%) were prescribed narcotic pain medication after discharge from the hospital compared with three of the Dutch patients (6%; $p < 0.001$) (Table 3).

Predictors of Inpatient Narcotic Prescription

In univariate analysis, there was significant association between inpatient narcotic use with country and surgeon (both $p < 0.001$). The best logistic regression model included country and surgeon and accounted for 20% of the variation in narcotic use ($p < 0.001$). A model with country alone accounted for 19% of the variation in narcotic use ($p < 0.001$).

Table 3. Comparison of Narcotics Prescription Between Countries

	American %	Dutch %	p Value
Hip fractures			
Inpatient	85	58	<0.001
Outpatient	77	0	<0.001
Ankle fractures			
Inpatient	98	64	<0.001
Outpatient	82	6	<0.001

Predictors of Outpatient Narcotic Prescription

There was significant association between country and surgeon (both $p < 0.001$) with outpatient narcotic prescriptions in univariate analysis. The best logistic regression model included country and surgeon and accounted for 49% of the variation in narcotic prescriptions ($p < 0.001$). The model with country alone accounted for 45% of the variation in narcotic prescription ($p < 0.001$).

DISCUSSION

Our hypothesis was confirmed: American patients were prescribed significantly more inpatient and outpatient narcotic pain medications after operative treatment of hip and ankle fractures than Dutch patients ($p < 0.001$). Non-opioid pain medication, such as acetaminophen (paracetamol) and NSAIDs, apparently offered sufficient pain relief for many Dutch patients in situations in which American patients would more likely receive narcotic pain medications, although this should be tested prospectively to be certain that Dutch patients are not undertreated and suffering needlessly.

Multivariable analysis affirmed that country is a strong predictor of narcotic prescription, even when accounting for confounding with age, surgeon, and duration of hospital stay. The culture — or accepted standards for pain control among physicians and patients — seems to have a substantial influence on prescribing practices. We think that factors affecting the differences in prescribing behavior between countries are both physician related (e.g., training, and the physician's attitude toward pain and use of narcotics) and patient related (e.g., attitude toward pain and narcotics, tolerance, perceived and expressed pain, acceptance, coping skills and other psychosocial factors, and secondary gain).

Although there is no official protocol for pain management after operative fracture treatment in the Netherlands, the limited prescription of narcotic pain medications by the Dutch orthopaedic surgeons participating in our study represents, to our knowledge, usual pain management strategy among orthopaedic surgeons in the Netherlands. In the Dutch patients described in this study, narcotic pain medications were — if prescribed — usually discontinued within approximately 1 or 2 days after surgery and nearly always before discharge from the hospital. The observed differences in outpatient pain medication were striking. As we understand it, general practitioners in the Netherlands do not prescribe narcotics after fracture treatment — but this needs to be studied prospectively. We think that the nursing approach toward pain has no or only a limited influence on prescription of pain medication. In both countries, nurses usually ask patients to rate their pain at several time points during the postoperative period, rendering it less likely that there would be a heightened awareness of pain among the treating medical personnel in one of the two countries. Apparently, non-opioid pain medication, such as acetaminophen (paracetamol) and NSAIDs, not only offered sufficient pain relief in Dutch patients in the outpatient setting but also during hospitalization. However, this assumption should be tested prospectively to be certain that Dutch patients are not undertreated and suffering needlessly. Prospective investigation should include standardized and consistently collected pain ratings, which were not available in this retrospective study.

Dutch patients with hip fractures were hospitalized significantly longer than American patients. We do not think that this difference is related to the use of narcotics, as we think that it is explained by the waiting lists for skilled nursing facilities in the Netherlands. This assumption is strengthened by the fact that there was no significant difference in the duration of hospitalization between Dutch and American patients with ankle fractures: a much younger and more independent group of patients.

Prospective research would also be useful for determining the characteristics of Dutch patients that allow them to recover from ankle and hip operations with less narcotic pain medication. Efforts to enhance those characteristics in American patients would be expected to both decrease suffering and limit problems associated with narcotic pain medications. Several studies have described cultural or ethnic differences in pain perception and expectations regarding pain.[9,10,18] Carragee et al.,[18] for instance, compared American and Vietnamese patients after intramedullary rod fixation of femoral shaft fractures and found that American patients were generally more dissatisfied with pain control than Vietnamese patients (80% vs. 8% of patients), despite the fact that they received much more narcotic analgesia (30 mg vs. 1 mg per kg bodyweight). In addition, 76% of the Vietnamese patients versus 4% of the American patients felt that they had an accurate impression of how much a femur fracture would hurt (and preconceptions were the same about postoperative pain). More than 50% of the American patients felt there had to be some explanation other than the fracture to explain the severity of the pain (such as a missed injury or inappropriate medical care). In another study,[10] expectations of labor pain and availability of pain medication as well as the actual perception of pain and use of analgesia and anesthesia were compared between American and Dutch women. American women expected labor to be more painful and received significantly greater amounts of pain medication. These studies reinforce our interest to further investigate intercultural differences in patients' characteristics regarding, for instance, the influence of psychological distress, effective coping mechanisms, heightened illness concern, pain anxiety, and expectations on the experience of pain.

The World Health Organization formulated a three-step pain ladder for treatment of pain in palliative cancer care that can also be used in patients with postoperative pain and other painful conditions: (1) non-opioids (e.g., acetaminophen and NSAIDs), (2) mild opioids (e.g., tramadol and codeine), and (3) strong opioids (e.g., dilaudid, fentanyl, oxycontin, and morphine).[19] A similar approach for the treatment of postoperative pain has been recommended by others.[20,21] Apart from addictive characteristics (i.e., impaired control over drug use, compulsive use, continued use despite harm, and craving — particularly observed in biologically and psychosocially vulnerable individuals[22]), other negative consequences of opioid or "narcotic" pain medication include physical dependence and tolerance.[22,23] In addition, adverse effects of narcotic pain medications include, for instance, sedation, constipation, nausea, vomiting, and respiratory depression.[23,24] Step 1 pain medications, such as NSAIDs and acetaminophen, are quite safe to use and, based upon our data, may provide better analgesia after operative treatment of hip and ankle fractures than many surgeons realize. In a previous prospective study investigating analgesic efficacy in patients recovering from major abdominal surgery,[25] it was even found that the use of NSAIDs alone provided effective analgesia compared with NSAID use in combination with intravenous patient-controlled

analgesia or intermittent epidural morphine. In addition, several research studies demonstrated that immediate postoperative parenteral administration of an NSAID reduces subsequent patient-controlled morphine use.[26-30]

The international differences in pain management observed in this study are interesting and encourage us — and hopefully others — to investigate differences between populations prospectively. We hypothesize that Dutch patients using less narcotic pain medications do not suffer more than American patients who use more narcotics for identical medical conditions. Prospective investigation should also try to explicate the nature of these intercultural differences. A better understanding of those characteristics might improve pain management beyond what is capable with using pharmaceutical-based strategies alone.

REFERENCES

1. Spraycar M. In. *Stedman's Medical Dictionary*. 26th ed. Baltimore: Williams & Wilkins; 1995.
2. Goroll AH, Mulley AG. Psychiatric problems: approach to the patient with chronic nonmalignant pain. In: Goroll AH, Mulley AG, eds. *Primary Care Medicine: Office Evaluation and Management of the Adult Patient*. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2006:1214 –1422.
3. Fillingim RB. Individual differences in pain responses. *Curr Rheumatol Rep*. 2005;7(5):342-347.
4. Edwards RR. Genetic predictors of acute and chronic pain. *Curr Rheumatol Rep*. 2006;8(6):411-417.
5. Fillingim RB, Gear RW. Sex differences in opioid analgesia: clinical and experimental findings. *Eur J Pain*. 2004;8(5):413-425.
6. Wiesenfeld-Hallin Z. Sex differences in pain perception. *Gend Med*. 2005;2(3):137-145.
7. Vallerand AH, Polomano RC. The relationship of gender to pain. *Pain Manag Nurs*. 2000;1(3 Suppl 1):8-15.
8. 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(4):227-239.
9. Green CR, Anderson KO, Baker TA, et al. The unequal burden of pain: confronting racial and ethnic disparities in pain. *Pain Med*. 2003;4(3):277-294.
10. Senden IP, van du Wetering MD, Eskes TK, Bierkens PB, Laube DW, Pitkin RM. Labor pain: a comparison of parturients in a Dutch and an American teaching hospital. *Obstet Gynecol*. 1988;71(4):541-544.
11. Meredith P, Strong J, Feeney JA. Adult attachment, anxiety, and pain self-efficacy as predictors of pain intensity and disability. *Pain*. 2006;123(1-2):146-154.
12. Meredith PJ, Strong J, Feeney JA. The relationship of adult attachment to emotion, catastrophizing, control, threshold and tolerance, in experimentally-induced pain. *Pain*. 2006;120(1-2):44-52.
13. Severeijns R, Vlaeyen JW, van den Hout MA, Weber WE. Pain catastrophizing predicts pain intensity, disability, and psychological distress independent of the level of physical impairment. *Clin J Pain*. 2001;17(2):165-172.
14. MacDermid JC, Donner A, Richards RS, Roth JH. Patient versus injury factors as predictors of pain and disability six months after a distal radius fracture. *J Clin Epidemiol*. 2002;55(9):849-854.
15. Waddell G, Main CJ, Morris EW, Di Paola M, Gray IC. Chronic low-back pain, psychologic distress, and illness behavior. *Spine (Phila Pa 1976)*. 1984;9(2):209-213.
16. Hull FM, Westerman RF, Jonkers R. Comparison of prescribing habits of general practitioners in The Netherlands versus England and Wales. *Pharmacoeconomics*. 1992;2(1):77-86.
17. Müller ME, Nazarian S, Koch P, Schatzker J. *The comprehensive classification of fractures of long bones*. Berlin: Springer-Verlag; 1990.
18. Carragee EJ, Vittum D, Truong TP, Burton D. Pain control and cultural norms and expectations after closed femoral shaft fractures. *Am J Orthop (Belle Mead NJ)*. 1999;28(2):97-102.
19. World Health Organization. Pain Ladder. 2016; http://www.who.int/cancer/palliative/painladder/en/. Accessed 11-06, 2016.
20. Myles PS, Power I. Clinical update: postoperative analgesia. *Lancet*. 2007;369(9564):810-812.
21. Fischer HB, Simanski CJ. A procedure-specific systematic review and consensus recommendations for analgesia after total hip replacement. *Anaesthesia*. 2005;60(12):1189-1202.
22. Savage SR, Joranson DE, Covington EC, Schnoll SH, Heit HA, Gilson AM. Definitions related to the medical use of opioids: evolution towards universal agreement. *J Pain Symptom Manage*. 2003;26(1):655-667.
23. Hanks G, Cherny NI, Fallon M. Opioid analgesic therapy. In: Doyle D, Hanks G, Cherny N, Calman K, eds. *Oxford Textbook of Palliative Medicine*. 3rd ed. New York: Oxford United Press; 2004.

24. American College of Physicians. Common side effects of opioids. http://www.acponline.org/journals/news/dec04/pain/side_effects.htm. Accessed January 24, 2007.

25. Shapiro A, Zohar E, Hoppenstein D, Ifrach N, Jedeikin R, Fredman B. A comparison of three techniques for acute postoperative pain control following major abdominal surgery. *J Clin Anesth*. 2003;15(5):345-350.

26. Hanna MH, Elliott KM, Stuart-Taylor ME, Roberts DR, Buggy D, Arthurs GJ. Comparative study of analgesic efficacy and morphine-sparing effect of intramuscular dexketoprofen trometamol with ketoprofen or placebo after major orthopaedic surgery. *Br J Clin Pharmacol*. 2003;55(2):126-133.

27. Burns JW, Aitken HA, Bullingham RE, McArdle CS, Kenny GN. Double-blind comparison of the morphine sparing effect of continuous and intermittent i.m. administration of ketorolac. *Br J Anaesth*. 1991;67(3):235-238.

28. Sevarino FB, Sinatra RS, Paige D, Silverman DG. Intravenous ketorolac as an adjunct to patient-controlled analgesia (PCA) for management of postgynecologic surgical pain. *J Clin Anesth*. 1994;6(1):23-27.

29. Laitinen J, Nuutinen L, Kiiskilä EL, Freudenthal Y, Ranta P, Karvonen J. Comparison of intravenous diclofenac, indomethacin and oxycodone as post-operative analgesics in patients undergoing knee surgery. *Eur J Anaesthesiol*. 1992;9(1):29-34.

30. Anderson SK, al Shaikh BA. Diclofenac in combination with opiate infusion after joint replacement surgery. *Anaesth Intensive Care*. 1991;19(4):535-538.

SATISFACTION WITH PAIN RELIEF AFTER OPERATIVE TREATMENT OF AN ANKLE FRACTURE

3

Helmerhorst GT, Lindenhovius AL, Vrahas M,
Ring D, Kloen P

Injury. 2012 Nov;43(11):1958-61

ABSTRACT

Background

American patients are prescribed more opioid pain medication than Dutch patients after operative treatment of an ankle fracture, but it is possible that pain is undertreated in Dutch patients. This study tests if there is a difference in pain and satisfaction with pain relief between Dutch and American patients after operative treatment of ankle fractures.

Methods

Thirty American and 30 Dutch patients were enrolled in a prospective comparative study prior to operative treatment of ankle fractures. Patients rated pain and satisfaction with pain relief on postoperative day 1 (POD1) and at time of suture removal (SR). Pain and satisfaction scores were compared and multivariable analysis identified their predictors.

Results

At POD1, a third of Dutch patients used no opioids and a sixth took strong opioids. At SR, only 4 of 30 (13%) were taking tramadol and half were taking no medication. All of the American patients used strong opioid pain medication on POD1 and 19 of 30 (63%) were still taking strong opioids at SR. Patients that did not use opioids and Dutch patients had less pain and equivalent satisfaction with pain relief compared to patients that used opioids and American patients respectively. Nationality was the best predictor of pain intensity at POD1. Opioid medication was the best predictor of pain at SR and decreased satisfaction with pain management.

Conclusions

Pain and satisfaction with pain relief are culturally mediated. Patients that use non-opioid pain medication report less pain and greater satisfaction with pain relief than patients managed with opioid pain medication.

Level of evidence

Level I, Prognostic Study with more than 80% follow-up.

INTRODUCTION

American patients undergoing operative treatment of ankle fractures are prescribed more opioid pain medication than Dutch patients.[1] Given that these patients would be expected to have similar nociception (neurophysiological aspects of pain created by actual or potential tissue damage) as a result of fracture pathophysiology and operative treatment, the use of less opioid pain medication by Dutch patients might be explained by cultural differences, differences in health provider training and practice, and psychological differences such as effective coping strategies, greater self-efficacy, and better mood. On the other hand, it is possible that Dutch patients and patients that are not taking opioids after ankle surgery are being undertreated and suffering needlessly.

In this prospective open-label cohort study we test the null hypothesis that there is no difference in pain and satisfaction with pain relief between Dutch and American patients on the first postoperative day and at the time of suture removal after surgical treatment of ankle fractures, in spite of the fact that Dutch patients typically use nothing stronger than tramadol or paracetamol for pain relief.

Patients and methods

The human research committees at two Level 1 trauma hospitals (one in the United States and one in the Netherlands) approved a prospective open label study of pain relief after operative treatment of ankle fractures. All patients aged 18 years or greater with an ankle fracture for which operative treatment was recommended were eligible. Exclusion criteria included: (1) another fracture at any other site, (2) a pathological fracture, or (3) inability to fill out questionnaires.

Over the period from October 2007 until January 2009, thirty-four American and thirty Dutch patients were enrolled. Four American patients did not return to our hospital for suture removal, so the analysis was based on the remaining 60 patients. Patient and treatment characteristics are described in Table 1.

On the first postoperative day (POD1) and at the time of suture removal between 10 and 14 days after surgery (SR), all patients were asked to rate their pain at that moment, the average pain since surgery, the worst pain since surgery, and the level of pain that would be acceptable to them on 5-point Likert scales (none, mild, moderate, severe or extreme). Furthermore, they rated their level of satisfaction with pain relief (very unsatisfied, unsatisfied, neutral, satisfied and very satisfied) and compared their pain at SR to their pain at POD1 (much worse, worse, same, better, much better). For statistical analysis, these scores were converted to a 1 – 5 scale, with higher scores representing more pain and greater satisfaction with pain relief.

Furthermore, all inpatient and outpatient medications that patients used over the period from surgery until suture removal were documented. For statistical analysis, opioid pain medication was defined as all opioid analgesic drugs including centrally acting synthetic opioid derivatives (e.g. tramadol, a weak m-opioid receptor agonist).[2-5] Non-opioid pain medications were acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs).

Table 1. Patient and treatment characteristics

	United States of America	The Netherlands
Men	14	12
Women	16	18
Mean age (range)	42 (22 – 75)	49 (18 – 88)
Fracture class		
Weber A	1	0
Weber B	21	21
Weber C	8	9
Anaesthesia		
General	28	22
Spinal	1	8
Popliteal block	1	0
Syndesmotic screw	10	3
Average number of days from injury to surgery (range)	3 (1 – 13)	5 (0 – 16)

Statistical analysis

The primary outcome variable of this investigation was satisfaction with pain relief rated on a 5-point Likert scale from very unsatisfied to very satisfied. A power analysis indicated that a sample size of 23 subjects in each of the cohorts would provide 90% statistical power ($\alpha = 0.05$, $\beta = 0.10$) using the Mann–Whitney U test to detect a 1-point difference in mean satisfaction with pain relief assuming a standard deviation of 1 point. We used a very large effect size based on prior studies and because we felt that only very large differences between the cohorts were clinically relevant. To account for a possible loss to follow-up of 25%, we enrolled a minimum of 30 subjects in each country.

In a bivariate analysis to address differences between the cohorts, continuous variables (age, days between injury and surgery; actual pain, average pain since surgery, worst pain since surgery, acceptable pain and satisfaction with pain relief at POD1 and SR were compared between patients using opioid vs. non-opioid pain medication with the Mann–Whitney U test. Categorical variables (nationality, gender, use of opioid pain medication, use of a syndesmotic screw, Weber classification, and type of anaesthesia) were compared between cohorts using the Fisher Exact test. p values of less than 0.05 were considered statistically significant.

In a bivariate analysis to determine the association between explanatory variables and response variables, which included the "pain intensity at that moment" at POD1 and SR and satisfaction with pain relief at POD1 and SR, the association between the response variables with continuous explanatory variables (age and days between injury and surgery) was analyzed using Spearman correlation, with binominal explanatory variables (nationality, gender, use of opioid pain medication, use of a syndesmotic screw) using the Mann–Whitney U test, and with multinominal explanatory variables (Weber classification and type of anaesthesia) using the Kruskal–Willis test. A multivariable backward linear regression model was created to account for confounding between the explanatory variables. We entered the variables that were either significant ($p < 0.05$) or nearly significant ($p < 0.10$) in the bivariate analysis, which is a common cut-off value for inclusion of variables in regression modelling when the total number of study subjects is small.

RESULTS

Postoperative day 1

Thirty American (100%) and 20 Dutch (67%) patients used opioid pain medication on POD1 ($p < 0.001$). The mean time to surgery was not significantly different between the American and Dutch patients (3 vs. 5 days; $p = 0.49$). There was a significant difference in between general and regional anaesthesia between American and Dutch patients ($p = 0.08$) (Table 1). The majority of Dutch patients (15 of 20 patients) used tramadol whereas all American patients used a strong opioid (e.g. oxycodone) (Table 2).[5] Patients that used opioids had worse average pain scores (3.0 vs. 2.5; $p < 0.05$) and time to surgery (4.1 vs. 2.0 days; $p < 0.05$) at POD1 than patients not using opioids. However, at POD1 there was no difference in satisfaction with pain relief ($p = 0.71$) between the two cohorts (Table 3). Furthermore, there were no significant differences between patients using non-opioid vs. opioid pain medication in terms of sex ($p = 0.74$), fracture type ($p = 0.58$), type of anaesthesia ($p = 0.45$), or the use of a syndesmotic screw ($p = 0.19$).

Suture removal

At the time of suture removal, 19 American patients compared to 4 Dutch patients used opioid pain medication (63 vs. 13%; $p < 0.001$). Of these patients, all Americans patients used a strong opioid (morphine or oxycodone), whereas the four Dutch patients used tramadol. Patients not using opioids rated less pain than patients using opioids (2.1 vs. 2.6; $p < 0.01$). Patients not using opioids were more satisfied with pain relief than patients using opioids (4.5 vs. 4.1; $p < 0.05$) (Table 4). There were no significant differences between patients using non-opioid or opioid pain medication in terms of gender ($p = 0.79$), time to surgery ($p = 0.27$), fracture type ($p = 0.24$), type of anaesthesia ($p = 0.16$), or the use of a syndesmotic screw ($p = 0.14$).

Table 2. Pain medication

	United States of America		The Netherlands	
	Postoperative day 1	**Suture removal**	**Postoperative day 1**	**Suture removal**
Non-opioid				
Acetaminophen/paracetamol	17	10	29	11
NSAID (ibuprophen, naproxen, diclofenac)	0	2	17	4
Total number of patients	17	12	30	12
Opioids				
Tramadol	0	0	15	4
Hydrocodone	3	4	0	0
Propoxyphen	1	1	0	0
Oxycodone	20	15	0	0
Morphine	6	1	5	0
Total number of patients	30	19	20	4

Table 3. Results at postoperative day 1

		Age	Days Inj–Surg	Pain at this moment[a]	Worst pain since surgery[a]	Average pain since surgery[a]	Satisfaction with pain relief[b]	Acceptable pain at this moment[a]
Non-opioid use	Mean	51	2.0	2.1	3.4	2.5	4.2	2.2
	Minimum	27	0.0	1.0	2.0	2.0	3.0	1.0
	Maximum	81	9.0	3.0	4.0	3.0	5.0	3.0
Opioid use	Mean	45	4.1	2.7	4.1	3.0	4.2	2.3
	Minimum	22	0.0	1.0	1.0	1.0	2.0	1.0
	Maximum	88	16.0	5.0	5.0	5.0	5.0	5.0
	p Value	ns[c]	<0.05	0.08	<0.05	<0.05	ns	ns
United States	Mean	42	2.9	3.0	4.3	3.2	4.2	2.2
	Minimum	22	1.0	1.0	2.0	2.0	2.0	1.0
	Maximum	75	13.0	5.0	5.0	5.0	5.0	4.0
The Netherlands	Mean	49	5.1	2.1	3.6	2.6	4.3	2.3
	Minimum	18	0.0	1.0	1.0	1.0	3.0	1.0
	Maximum	88	16.0	4.0	5.0	4.0	5.0	5.0
	p Value	ns	ns	<0.001	<0.01	<0.01	ns	ns

[a] No pain (1), mild pain (2), moderate pain (3), severe pain (4), extreme pain (5).
[b] Very unsatisfied (1), unsatisfied (2), neutral (3), satisfied (4), very satisfied (5).
[c] ns = not significant.

Table 4. Results at suture removal

		Age	Days Inj–Surg	Pain at this moment[a]	Worst pain since surgery[a]	Average pain since surgery[a]	Satisfaction with pain relief[b]	Acceptable pain at this moment[a]	Pain now compared to POD1[c]
Non-opioid use	Mean	50	3.9	1.6	3.5	2.1	4.5	1.8	4.5
	Minimum	18	0.0	1.0	2.0	1.0	3.0	1.0	3.0
	Maximum	88	16.0	3.0	5.0	4.0	5.0	3.0	5.0
Opioid use	Mean	41	3.9	2.5	4.1	2.6	4.1	2.2	4.5
	Minimum	22	1.0	2.0	2.0	2.0	2.0	1.0	3.0
	Maximum	68	13.0	4.0	5.0	3.0	5.0	4.0	5.0
	p Value	ns	ns	<0.001	<0.05	<0.01	<0.05	0.06	ns
United States	Mean	42	2.9	2.4	4.0	2.5	4.3	2.0	4.6
	Minimum	22	1.0	1.0	2.0	2.0	2.0	1.0	3.0
	Maximum	75	13.0	4.0	5.0	3.0	5.0	4.0	0.6
The Netherlands	Mean	49	5.1	1.7	3.6	2.2	4.4	1.9	4.4
	Minimum	18	0.0	1.0	2.0	1.0	3.0	1.0	3.0
	Maximum	88	16.0	3.0	5.0	4.0	5.0	3.0	0.7
	p Value	ns	ns	0.001	ns	0.06	ns	ns	ns

[a] No pain (1), mild pain (2), moderate pain (3), severe pain (4), extreme pain (5).
[b] Very unsatisfied (1), unsatisfied (2), neutral (3), satisfied (4), very satisfied (5).
[c] Much worse (1), worse (2), same (3), better (4), much better (5).

Predictors of pain intensity and satisfaction with pain relief

Postoperative day 1

In bivariate analysis, there was a significant association between pain intensity with nationality (American patients rated more pain; $p < 0.001$), pain medication (patients using opioids rated higher pain scores, $p < 0.001$), and near-significant association with age (younger patients rated more pain, $p = 0.07$), but not with time to surgery ($p = 0.16$) or type of anaesthesia ($p = 0.33$). The best multivariable regression model for pain intensity at POD1 included nationality and accounted for 17% of the variation in pain scores ($p < 0.001$).

There was no significant or near-significant association between satisfaction with pain relief and any of the explanatory variables, including time to surgery and type of anaesthesia.

Suture removal

In bivariate analysis, there was significant association between pain intensity and nationality (American patients rated more pain; $p < 0.001$) and pain medication (patients using opioids rated more pain, $p < 0.001$), but not time to surgery ($p = 0.54$) or type of anaesthesia ($p = 0.88$). The best multivariable model for pain intensity at suture removal included pain medication alone and explained 32% of the variation in pain scores ($p < 0.001$). A model with nationality alone accounted for 18% of the variation in pain scores ($p < 0.001$).

In bivariate analysis, there was significant association between satisfaction with pain relief and the type of pain medication (patients that used opioids were less satisfied with pain relief; $p < 0.05$), but not time to surgery ($p = 0.27$) or type of anaesthesia ($p = 0.53$). In the linear regression model, pain medication explained only 6% of the variation in satisfaction with pain relief ($p < 0.05$).

DISCUSSION

Dutch patients were satisfied with their pain relief using tramadol or paracetamol alone after ankle fracture surgery. In both America and the Netherlands, use of opioid pain medication was associated with greater pain and less satisfaction with pain relief. Explanations could include pathophysiological, cultural (patient and physician) or psychological factors. The observation that nationality (culture) is the only predictor of pain intensity the day after surgery is consistent with the extensive scientific evidence that pain is strongly psychosocially mediated.[6]

Dutch patients were not undertreated as measured by equal satisfaction with pain relief. The observation that use of opioid pain medication at the time of suture removal was the only predictor of dissatisfaction with pain relief merits additional study. We speculate that patients that continue on opioid pain medication until suture removal have less effective coping strategies, more depressive symptoms, or both. Said in another way, it may be that patients who take more opioids are more distressed by nociception and are more likely to place hope in medications as a means for resolving that distress. Patients that take less opioid medication may have more effective strategies for adapting to nociception resulting in less distress and less reliance on medication. These hypotheses merit additional study. It is notable, that a very small percentage of the variation in satisfaction with pain relief could be explained with the data available, which suggests that

satisfaction with pain relief is very complex and not explained solely by demographics or injury characteristics.

Previous studies have demonstrated that psychological distress (symptoms of anxiety and depression) and less effective coping strategies influence pain intensity and pain-related disability.[7-10] Injury compensation and other forms of secondary gain have also been found to be a powerful predictor of pain and disability.[11] One shortcoming of this study is that we did not investigate the influence of psychological factors on perception of and tolerance for postoperative pain, and the only sociological factor addressed was nationality.

Our data should be interpreted in light of some additional shortcomings. First, this is a small study and the findings may be specific to the two medical centers or the two countries involved. Larger multicenter studies would improve external validity. Second, we simplified the analysis to opioid and non-opioid pain medication rather than considering various types of opioid medication separately. We adopted this approach based on the analysis of retrospective data that we performed as pilot work for this study.[1] Specifically, we considered tramadol an opioid pain medication, while most patients and surgeons in the United States would not consider this in the same class as oxycodone. Finally, our study was small for practical reasons and because were interested in only very large and clinically important differences, but this could limit both the internal and external validity of the findings.

Our study is in line with several other studies in which non-opioid pain management proved to be very effective for postoperative analgesia, compared to opioid management. A recent prospective study showed lower mean pain scores during the first 24 h after primary total hip arthroplasty in patients using a non-opioid oral regimen, compared to opioid-based patient-controlled analgesia.[12] In a cardiac surgery study, NSAIDs (etodolac and diclofenac) provided better postoperative pain relief with less side-effects compared to a weak opioid (tramadol).[13] American physicians and patients may tend to move directly to Step 3 on the WHO pain ladder, relying on the most powerful analgesics for pain relief. Our data suggest that this may not be the most effective approach for achieving satisfaction with pain management, and that– given the marked cultural differences – cognitive and behavioral therapies merit consideration. Future studies should address all of these factors in attempt to help patients recovering from operative treatment of an ankle fracture to be as comfortable as possible.

REFERENCES

1. Lindenhovius AL, Helmerhorst GT, Schnellen AC, Vrahas M, Ring D, Kloen P. Differences in prescription of narcotic pain medication after operative treatment of hip and ankle fractures in the United States and The Netherlands. *J Trauma*. 2009;67(1):160-164.
2. Gutstein HB, Aki H. Opioid analgesics. In: Brunton LL, Lazo JS, Parker KL, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 11th ed. New York: McGraw-Hill; 2006:562.
3. U.S. Food and Drug Administration. Ultram Tramadol. http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/20281slr030,21123slr001_Ultram_lbl.pdf. Accessed January 8, 2010.
4. World Health Organization. Tramadol. http://www.who.int/entity/medicines/areas/quality_safety/5.2TramadolCritReview.pdf. Accessed January 8, 2010.
5. World Health Organization. Pain Ladder. 2016; http://www.who.int/cancer/palliative/painladder/en/. Accessed 11-06, 2016.
6. Vranceanu AM, Barsky A, Ring D. Psychosocial aspects of disabling musculoskeletal pain. *J Bone Joint Surg Am*. 2009;91(8):2014-2018.
7. Meredith P, Strong J, Feeney JA. Adult attachment, anxiety, and pain self-efficacy as predictors of pain intensity and disability. *Pain*. 2006;123(1-2):146-154.
8. Meredith PJ, Strong J, Feeney JA. The relationship of adult attachment to emotion, catastrophizing, control, threshold and tolerance, in experimentally-induced pain. *Pain*. 2006;120(1-2):44-52.
9. Severeijns R, Vlaeyen JW, van den Hout MA, Weber WE. Pain catastrophizing predicts pain intensity, disability, and psychological distress independent of the level of physical impairment. *Clin J Pain*. 2001;17(2):165-172.
10. Vranceanu AM, Jupiter JB, Mudgal CS, Ring D. Predictors of pain intensity and disability after minor hand surgery. *J Hand Surg Am*. 2010;35(6):956-960.
11. MacDermid JC, Donner A, Richards RS, Roth JH. Patient versus injury factors as predictors of pain and disability six months after a distal radius fracture. *J Clin Epidemiol*. 2002;55(9):849-854.
12. Post ZD, Restrepo C, Kahl LK, van de Leur T, Purtill JJ, Hozack WJ. A prospective evaluation of 2 different pain management protocols for total hip arthroplasty. *J Arthroplasty*. 2010;25(3):410-415.
13. Immer FF, Immer-Bansi AS, Trachsel N, et al. Pain treatment with a COX-2 inhibitor after coronary artery bypass operation: a randomized trial. *Ann Thorac Surg*. 2003;75(2):490-495.

PAIN RELIEF AFTER OPERATIVE TREATMENT OF AN EXTREMITY FRACTURE: A NONINFERIORITY RANDOMIZED CONTROLLED TRIAL

4

Helmerhorst GTT, Zwiers R,
Ring D, Kloen P

J Bone Joint Surg Am. 2017 Nov 15;99(22):1908-1915

ABSTRACT

Background

Opioid pain medication is frequently given to patients recovering from a surgical procedure for an extremity fracture in spite of evidence that acetaminophen may be adequate. The aim of this study was to determine whether prescription of step 1 pain medication (acetaminophen) is noninferior to step 2 pain medication (acetaminophen and tramadol) after operative treatment of an extremity fracture.

Methods

Fifty-two patients with a single extremity fracture were randomized from July 2012 to March 2015 in this 2-week follow-up, noninferiority trial in a level-I trauma center in the Netherlands. Patients were randomly assigned to receive step 1 (acetaminophen) or step 2 (acetaminophen and tramadol) medication in standard doses on an as-needed basis on discharge. Intention-to-treat and per-protocol analyses were conducted. The primary outcome was self-reported satisfaction with pain relief measured on an 11-point ordinal scale. The hypothesis being tested was formulated before the collection of data. The mean differences between the groups were reported for intention-to-treat and per-protocol analyses.

Results

A total of 52 patients, with equal baseline characteristics, were analyzed in this study; the step 1 group consisted of 27 subjects and the step 2 group consisted of 25 subjects. The mean satisfaction with pain management was 8.3 for step 1 and 8.5 for step 2 medications. This mean difference of 0.2 point (95% confidence interval [CI], -0.78 to 1.30 points) did not exceed the noninferiority margin of 2.0 points, indicating that step 1 was noninferior to step 2. A similar result was found in the per-protocol analysis (mean difference, 0.2 point [95% CI, -1.03 to 1.57 points]).

Conclusions

This study offers evidence to suggest that prescription of acetaminophen is not inferior compared with acetaminophen and tramadol in patients who underwent operative treatment for an extremity fracture. Given that tramadol has more side effects and is potentially habit-forming, acetaminophen should be considered the mainstay for pain relief in patients recovering from extremity fracture surgical procedures.

Level of Evidence

Therapeutic Level I.

INTRODUCTION

Nociception is the neurophysiologic mechanism by which actual or potential tissue damage is communicated from the periphery to the central nervous system. Pain can be defined as the unpleasant cognitive and emotional experience associated with nociception. The relationship of pain to nociception is variable, and it is possible to have pain in the absence of nociception as well as nociception with little pain.[1] Pain is strongly psychosocially mediated and factors such as self-efficacy, elevated mood, and optimal social support help to limit pain and disability.[2-4]

Satisfaction with pain relief is increasingly used to measure quality of care, and many organizations use algorithms using pain scores to treat pain. There is substantial variation among providers, hospitals, communities, and cultures in analgesia for patients recovering from fracture surgery, although surgical technique is comparable worldwide and nociception may be less once fractures are stabilized. Most patients in the United States are prescribed opioids after a fracture, although other parts of the world manage largely with non-opioid analgesics. The expanded use of opioids in the United States and Canada (based on advocacy and marketing that doctors were undertreating pain and were overly concerned about addiction) created an epidemic of opioid misuse and related overdose deaths.[5-8] Worldwide, patients take far fewer opioids compared with U.S. and Canadian patients, but report similar pain and satisfaction with pain relief.[9,10] Europe (especially the United Kingdom) is gradually increasing the prescription of opioids and seeing greater opioid-related mortality. In particular, tramadol and oxycodone prescriptions are increasing in the United Kingdom, and tramadol-related deaths doubled from 2009 to 2012.[11-14] In addition, a recent article in *The Wall Street Journal* reported on the alarming increase of tramadol addiction in the developing world.[15]

Postoperative pain management can be based on the 3-step World Health Organization (WHO) pain ladder for treatment of pain (originally developed for palliative cancer care): (1) non-opioids (e.g., acetaminophen and nonsteroidal anti-inflammatory drugs [NSAIDs]), (2) opioids for mild to moderate pain (e.g., tramadol, codeine, and hydrocodone) with adjuvant analgesics, and (3) opioids for moderate to severe pain (e.g., hydromorphone, fentanyl, oxycodone, and morphine) with adjuvant analgesics.[16] The rationale for this ladder is progression from relatively safe medication in step 1 to medications with greater risks and side effects (i.e., addiction, physical dependence, and tolerance) and costs in step 3.[17-19]

The aim of this study was to assess satisfaction with pain relief among patients recovering from an isolated extremity fracture surgical procedure who were randomly assigned to receive either step 1 pain medication (acetaminophen) or step 2 pain medication (acetaminophen and tramadol). The primary objective was to determine non-inferiority in patient satisfaction after prescription of step 1 WHO pain ladder medications compared with step 2 pain medications. The secondary hypotheses addressed differences in pain intensity between the groups and factors associated with greater satisfaction with pain relief and greater pain intensity.

MATERIALS AND METHODS

Study Design

This study was designed as a non-inferiority randomized controlled trial with a 2-week follow-up, conducted at the Orthopaedic Surgery Department of a level-I trauma center. The hypothesis being tested was formulated before the collection of data. Patients were recruited between July 2012 and March 2015. Because of referral patterns, most patients with fracture at our hospital have multiple injuries, making them ineligible for the trial. Subjects were randomly assigned to either an acetaminophen-based pain regimen (step 1 of the WHO analgesic ladder) or an acetaminophen and tramadol-based regimen (step 2 of the WHO analgesic ladder). Two weeks after the surgical procedure, the patients completed a questionnaire.

Participants

All adult patients (age ≥ 18 years) who underwent surgical treatment for a single extremity fracture were eligible for enrollment. Pregnant, breastfeeding, or possibly pregnant patients and patients with relevant drug allergies were excluded from study participation. In addition, patients with another fracture at any site, pelvic fractures, stress fractures, pathological fractures, other substantial injuries outside the skeletal system, liver or renal dysfunction, diagnosed constipation, or inability to complete the questionnaires were excluded. Patients already receiving any form of analgesic prior to injury or receiving monoamine oxidase (MAO) inhibitors were not included in this study. The study protocol was approved by the institutional review board and ethics committee. Written informed consent of all included patients was obtained. This study was registered at the European Clinical Trials Database (EudraCT) of the European Medicines Agency (EudraCT Identifier: 2012-000680-24).

Randomization and Masking

All subjects were randomly assigned by computer random number generation to either a step 1 regimen or a step 2 regimen, with a 1:1 allocation ratio. Blocking was used to balance the magnitude of the surgical procedure: relatively small (e.g., hand, wrist, foot, or clavicle) and relatively large (e.g., shoulder, elbow, knee, or hip). Research staff not involved in the care of the patients performed enrollment and data collection.

Interventions

During a mean postoperative hospital stay of 1 day (range, 0 to 4 days), patients followed the hospital's postoperative pain protocol, which includes acetaminophen, diclofenac, and oxycodone as needed. Patients typically use acetaminophen and diclofenac. This was not tracked or measured in detail for this study. At discharge, oral pain medication was prescribed to be taken as needed for 2 weeks. Patients received either acetaminophen with a maximum dose of 1,000 mg every 6 hours (step 1) or the same dose of acetaminophen with a separate prescription for 50 mg tramadol every 8 hours as needed (step 2). In addition to their preassigned regimen, patients were

allowed to receive rescue medication, consisting of diclofenac (maximum 50 mg every 8 hours) in the absence of contraindications for a maximum of 5 days. If a patient was not satisfied, he or she could contact the office and oxycodone could be provided as a final rescue medication.

Outcomes

At inclusion, we measured self-efficacy in response to nociception (Pain Self-Efficacy Questionnaire [PSEQ])[20], anxiety in response to nociception (validated short version of the Pain Anxiety Symptoms Scale [PASS-20])[21], and mood (Patient Health Questionnaire-2 [PHQ-2])[22]. Patients were also asked to rate pain intensity levels (i.e., pain at that moment, worst pain since injury, mean pain since injury, and level of expected pain intensity after the surgical procedure) using an 11-point ordinal scale.

Two weeks postoperatively, at the time of suture removal, all patients completed a questionnaire that included a rating of their overall satisfaction with pain relief, pain intensity level at that moment, overall worst and mean pain intensity levels, and pain intensity level that they would have considered acceptable since the surgical procedure. All were measured on 11-point ordinal scales (e.g., 0 = very unsatisfied and 10 = very satisfied). Disability was measured using the Short Musculoskeletal Function Assessment (SMFA).[23]

In addition, demographic and injury characteristics such as age, sex, work status, education level (International Standard Classification of Education)[24], anatomical site, fracture type, and type of surgical procedure were collected.

Statistical Analysis

Based on a previous study, a 2.0-point non-inferiority margin for the satisfaction score was used for sample size calculation.[10] Using a 2-group non-inferiority t test, we estimated that 23 subjects per group would yield a power of 0.90 ($1 - \beta$) with an α significance level, commonly used in non-inferiority trials, of 0.025.[25] To account for a possible loss of 10% to 15%, we planned to enroll 26 subjects in each group.

Continuous variables are presented as the mean and the standard deviation or as the median and the interquartile range, based on distribution. Distribution was tested using the Shapiro-Wilk test. Categorical variables are presented as frequencies and percentages. Baseline patient characteristics were compared between the 2 groups using the unpaired t test or the Mann-Whitney U test. Differences in categorical variables were tested using the chi-square test. Significance was set at $p < 0.05$.

The primary end point was the mean difference in satisfaction score. The mean difference and the 95% confidence interval (CI) ($[1 - 2\alpha] \times 100\%$) were calculated. Non-inferiority was declared if the upper limit of the CI did not exceed the non-inferiority margin (Δ) of 2.0. An inconclusive outcome was declared if the upper limit of the CI exceeded a Δ of 2.0. Inferiority was declared if the lower limit of the CI exceeded a Δ of 2.0.[26] Because this study was designed as a non-inferiority trial, analyses were based on both an intention-to-treat principle (once randomized, always analyzed) and a per-protocol principle (complete follow-up and no deviation from protocol). Missing data were handled using single regression imputation. The missing data in this study were

missing at random. Secondary outcomes were measured using multivariable backward linear regression analysis. Variables were entered in the regression model when their p values were < 0.10 in the bivariate analysis. This is a common cutoff value for inclusion of variables in regression modeling when the total number of study subjects is small. Factors tested for association were age, sex, treatment, fracture location, education level, PSEQ, PASS-20, and PHQ-2.

Computer randomization was performed by ALEA, validated software for randomization in clinical trials (FormsVision BV). Data were collected and were entered into an SPSS database, statistical analyses were performed using RStudio version 0.98.1103 (RStudio), R version 3.1.3 (The R Foundation).

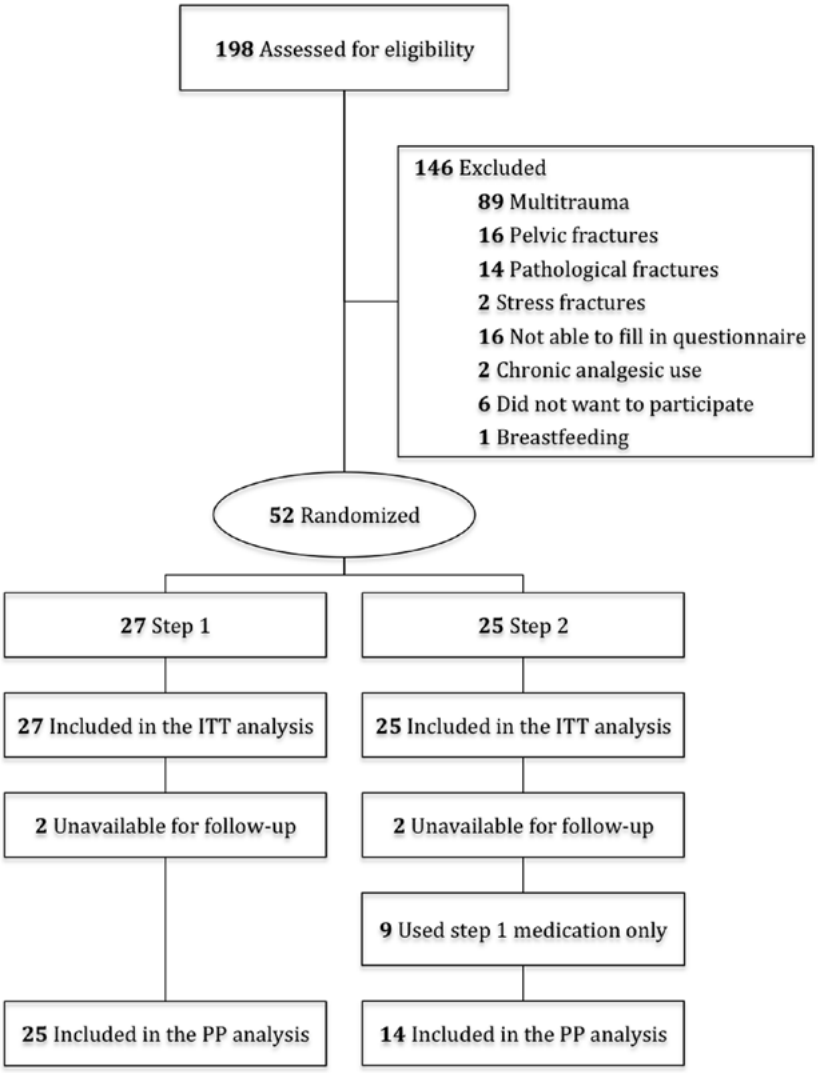

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram. ITT = intention to treat and PP = per protocol.

RESULTS

A total of 198 patients were assessed for eligibility (Fig. 1). Fifty-two patients met the criteria and were included in the intention-to-treat analysis: 27 subjects in the step 1 group and 25 subjects in the step 2 group. Four patients (2 in the step 1 group and 2 in the step 2 group) did not attend suture removal. In the step 2 group, 9 patients only used acetaminophen even though they had tramadol available. Two patients in the step 1 group received rescue medication (oxycodone according to protocol). The 9 patients in the step 2 group who only used acetaminophen and the patients with missing data were excluded in the per-protocol analysis. The fractures in the step 1 group consisted of 3 clavicles, 5 ankles, 1 hand, 5 wrists, 2 feet, 3 elbows, 2 hips, 1 humerus, 2 shoulders, and 3 tibiae. The fractures in the step 2 group consisted of 5 clavicles, 5 ankles, 3 hands, 2 wrists, 2 elbows, 2 femora, 1 hip, 1 humerus, 1 shoulder, and 3 tibiae. Baseline characteristics showed no differences between the groups (Table 1).

Table 1. Baseline Characteristics

	Step 1 Regimen (N = 27)	Step 2 Regimen (N = 25)	p Value
Age* (*yr*)	45 ± 18	42 ± 19	0.47
Male sex†	13 (48.1%)	15 (60.0%)	0.29
Fracture magnitude†			0.91
Small‡	16 (59.3%)	15 (60.0%)	
Large§	11 (40.7%)	10 (40.0%)	
Work status†			0.30
Full time	10 (37.0%)	9 (36.0%)	
Part time	3 (11.1%)	8 (32.0%)	
Retired	6 (22.2%)	3 (12.0%)	
Other	6 (22.2%)	4 (16.0%)	
Missing data	2 (7.4%)	1 (4.0%)	
Highest education level achieved†			0.75
None	1 (3.7%)	1 (4.0%)	
Primary or elementary	3 (11.1%)	3 (12.0%)	
Level 1 to 4 (lowest)	11 (40.7%)	9 (36.0%)	
Level 5 to 6	7 (25.9%)	9 (36.0%)	
Level 7 to 8 (highest)	1 (3.7%)	1 (4.0%)	
Missing data	4 (14.8%)	2 (8.0%)	
Pain at this moment# (*points*)	3 (1.0 to 5.3)	3 (1.0 to 6.0)	0.80
Worst pain# (*points*)	6 (3.0 to 8.0)	5 (4.0 to 7.8)	0.77
Mean pain# (*points*)	4.5 (3.0 to 5.0)	3.5 (2.0 to 5.0)	0.19
Expected pain intensity# (*points*)	4 (2.8 to 5.0)	4 (3.0 to 5.5)	0.65
PSEQ* (*points*)	30.1 ± 14.7	36.6 ± 11.9	0.09
PASS-20* (*points*)	46.1 ± 10.1	48.2 ± 13.3	0.53
PHQ-2# (*points*)	2.0 (2.0 to 3.0)	3.0 (2.0 to 3.8)	0.60

*The values are given as the mean and the standard deviation. †The values are given as the number of patients and the percentage. ‡This group includes hand, wrist, foot, ankle, and clavicle. §This group includes shoulder, elbow, hip, humerus, tibia, and femur. #The values are given as the median and the interquartile range.

The mean satisfaction with pain management was 8.3 for step 1 and 8.5 for step 2 medications. This mean difference of 0.2 point (95% CI, -0.78 to 1.30 points) did not exceed the non-inferiority margin of 2.0 points (Fig. 2), indicating that step 1 was non-inferior to step 2. A similar result was found in the per-protocol analysis. Step 1 medications were also non-inferior to step 2 medications on all measures of pain intensity, except for worst pain (Fig. 3). The upper limit of worst pain intensity exceeded the 2.0-point margin, whereas the lower margin did not. Therefore, this was considered inconclusive (Table 2).[26]

Variables with $p < 0.10$ in the bivariate analysis were entered in the multivariable analysis. These variables included sex ($p = 0.01$) for satisfaction with pain relief; age ($p = 0.03$) and sex ($p = 0.03$) for expected pain intensity; age ($p = 0.001$), treatment ($p = 0.06$), and education ($p = 0.06$) for worst pain intensity; and age ($p = 0.02$) and mood ($p = 0.02$) for mean pain intensity. In multivariable analysis, the only factor independently associated with greater satisfaction with pain relief was male sex. There were no factors independently associated with higher expected pain intensity after the surgical procedure. Factors independently associated with higher worst pain intensity were younger age and lower education. Factors independently associated with greater mean pain intensity were younger age and lower mood (Table 3).

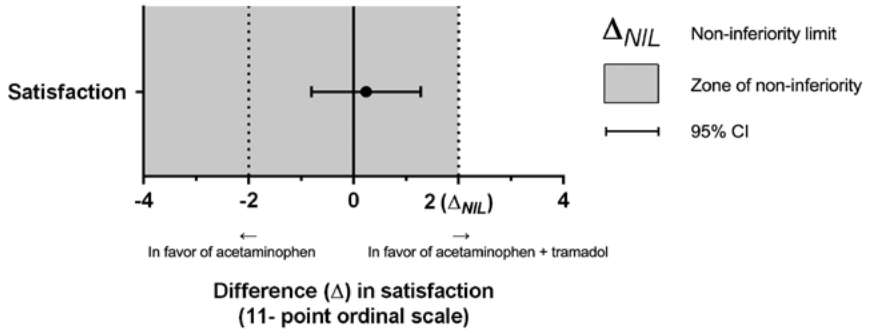

Figure 2. Satisfaction with postoperative pain management. The error bars indicate the 95% CI of the difference.

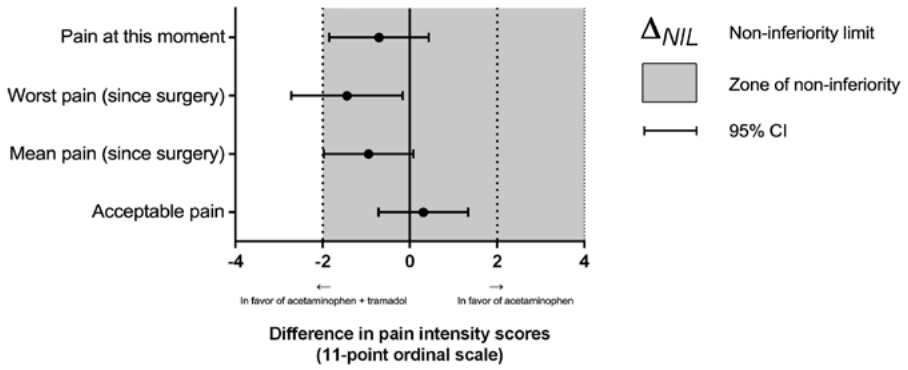

Figure 3. Pain intensity. The error bars indicate the 95% CI of the difference.

Significantly more adverse events (p = 0.006) were reported in the step 2 group (Table 2). Nausea was the most commonly reported adverse event in this group. The only 2 patients who reported nausea in the step 1 group were those who received oxycodone rescue medication.

Table 2. Primary and secondary outcome measures

	Step 1 Regimen*	Step 2 Regimen*	Difference†
Satisfaction with pain relief			
Intention-to-treat	8.3	8.5	0.2 (-0.78 - 1.30)
Per-protocol	8.2	8.4	0.2 (-1.03 - 1.57)
Pain at this moment			
Intention-to-treat	3.0	2.3	-0.7 (-1.85 - 0.43)
Per-protocol	3.2	3.0	-0.2 (-1.68 - 1.20)
Worst pain (since surgery)			
Intention-to-treat	6.9	5.5	-1.4 (-2.74 - -0.19)
Per-protocol	6.8	6.2	-0.6 (-2.12 - 1.03)
Average pain (since surgery)			
Intention-to-treat	3.9	3.0	-0.9 (-2.00 - 0.06)
Per-protocol	4.1	3.6	-0.5 (-1.83 - 0.82)
Acceptable pain			
Intention-to-treat	2.9	3.2	0.3 (-0.72 - 1.34)
Per-protocol	3.0	3.5	0.5 (-0.72 - 1.80)
SFMA			
Function index	44.7	37.7	p = 0.12
Bothersome index	44.8	35.7	p = 0.14
Adverse events	2 (7%)	10 (40%)	p = 0.006

*The values are given as the mean points, with the exception of adverse events, which are given as the number of patients, with the percentage in parentheses. †The values are given as the mean and the 95% CI, with the exception of SMFA and adverse events, which are given as the p value.

Table 3. Secondary outcome measures. Multivariable analysis.

Secondary Outcome Measures	Associated factors	Correlation coefficient	p value
Satisfaction with pain relief	Male sex	-1.5	0.01
Expected pain intensity	None		
Worst pain			
	Younger age	-0.08	< 0.01
	Lower education	-0.53	0.02
Average pain			
	Younger age	-0.03	0.046
	Lower mood	0.36	0.045

DISCUSSION

There is substantial variation in analgesia for patients recovering from a fracture surgical procedure. Opioid pain medication is commonly prescribed in the United States and Canada in spite of evidence that it does not improve satisfaction with pain relief.[9,10,27] This single-center trial examined non-inferiority in satisfaction with pain relief between step 1 and step 2 pain medications in these patients. Step 1 medications were non-inferior to step 2 medications after operative treatment of a single extremity fracture.

Our findings are in line with earlier studies that suggested that step 1 medication was not inferior to step 2 or 3 medication in patients with fracture.[9,10] In patients with hip fracture, about 80% of American patients were prescribed opioids after discharge, compared with none of the Dutch patients. A follow-up study found that all American patients used strong opioids 1 day after an ankle fracture surgical procedure, compared with only 17% of the Dutch patients. At the time of the suture removal, 63% of the American patients still used strong opioids, compared with none of the Dutch patients. Dutch patients reported less pain and equal satisfaction with pain relief. Another study found comparable analgesic effects of acetaminophen and tramadol in patients in active labor.[28] Two randomized controlled trials compared acetaminophen and ibuprofen with acetaminophen, codeine, and caffeine, 1 trial after outpatient general surgical procedures and 1 trial after outpatient breast surgical procedures, and found no differences in pain relief and pain intensity over 7 days. Furthermore, in the general surgical procedure trial, patients were more satisfied after acetaminophen and ibuprofen.[29] In the breast surgical procedure group, there were no differences in satisfaction.[30] A third randomized double-blind trial compared outpatient acetaminophen with tramadol and metamizol after a hand surgical procedure. The tramadol group reported the lowest pain scores, but almost 20% of the patients in this group withdrew from the study because of side effects. The acetaminophen group provided good analgesia and patients were more satisfied.[31] In children, there was no difference in pain scores after intravenous acetaminophen compared with intravenous tramadol after adenotonsillectomy.[32] In addition to satisfaction with pain relief, tramadol was not superior to acetaminophen in terms of pain intensity scores in our study.

Except for associations between lower education and worst pain intensity levels and between lower mood and mean pain intensity levels, we did not identify the strong associations of psychosocial factors such as self-efficacy and pain intensity or satisfaction with pain relief seen in other studies.[33-35] Perhaps culture is such a strong factor that the study was underpowered to detect these more detailed psychosocial associations.

Although opioids are considered one of the strongest pain relievers available, greater opioid intake is consistently associated with greater pain, with little relation to nociception.[27,36-39] Patients who continue to take opioid pain medication weeks to months after the surgical procedure (when nociception is largely resolved) have greater stress and distress and less effective coping strategies.[34] This suggests that opioids were used in an attempt to treat psychological distress or less effective coping strategies. Contrarily, NSAIDs are often withheld because physicians believe that they impede fracture-healing. Given the opioid crisis, it is probably wise to put these concerns aside until we obtain definitive evidence that NSAIDs impede fracture-healing in the clinical setting

or are harmful. Without such evidence, we should make good use of these medications.[40] Given the shortcomings and adverse events associated with opioid medication, greater pain and disability than expected should prompt health providers to consider the important roles of stress, lower mood, and ineffective coping strategies in human illness behavior and should be more prepared to offer a full complement of treatments to help their patients to experience less pain. It seems, at least in the United States and Canada, that both patients and surgeons may often look to opioid pain medication as standard care for the relief of postoperative pain. The evidence suggests other opportunities as well. Collectively, these findings suggest that resiliency (greater self-efficacy in response to pain) is one of the strongest pain relievers, and people may look for opioids to find relief when what they stand to benefit from more is greater resiliency.

About 25% of American adults used prescription opioids in 2013, compared with 8% in the Netherlands.[11] Therefore, some American patients might be more reluctant to consider non-opioid pain medication. Routine discussion of pain relief and standardized limits on prescription opioids can help. Practice effective communication strategies and be aware of signs of psychological distress and ineffective coping strategies. Pain is expected after an injury and a surgical procedure, and most patients worldwide get comfortable without opioids.

Our study should be considered within its limitations. First, the size of the study population provided adequate power, but was small enough to be at risk of spurious events. There were no major outliers, and we think that the people enrolled are representative of a mean patient with a single extremity fracture. Second, our study was single-blinded. Because of funding limitations, we were not able to blind patients. In addition, the purpose of this study was not to examine differences in analgesic properties, but to examine differences in overall satisfaction with pain medications. Third, a single-center study helps to reduce variability in treatment protocols, but the findings might not apply to other centers or other countries.

The results of this study should encourage physicians to be careful when considering the prescription of habit-forming and risky opioid medications. In light of the current epidemic of opioid misuse and opioid overdose deaths in the United States and Canada, the finding that step 1 pain medication is an effective pain reliever in patients discharged 1 to 2 days after a fracture surgical procedure is important. Step 2 medications caused more side effects without providing notably better satisfaction with pain relief. Step 3 medications (e.g., hydromorphone or oxycodone), the current standard in the United States and Canada, seem unnecessary. Decreasing primary prescriptions of pain medications to the first step of the WHO pain ladder seems safe and even favorable.

REFERENCES

1. Goroll AH, Mulley AG. Psychiatric problems: approach to the patient with chronic nonmalignant pain. In: Goroll AH, Mulley AG, eds. *Primary Care Medicine: Office Evaluation and Management of the Adult Patient*. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2006:1214 –1422.
2. Vranceanu AM, Barsky A, Ring D. Psychosocial aspects of disabling musculoskeletal pain. *J Bone Joint Surg Am*. 2009;91(8):2014-2018.
3. Granot M, Ferber SG. The roles of pain catastrophizing and anxiety in the prediction of postoperative pain intensity: a prospective study. *Clin J Pain*. 2005;21(5):439-445.
4. Rosenberger PH, Jokl P, Ickovics J. Psychosocial factors and surgical outcomes: an evidence-based literature review. *J Am Acad Orthop Surg*. 2006;14(7):397-405.
5. Ballantyne JC, LaForge KS. Opioid dependence and addiction during opioid treatment of chronic pain. *Pain*. 2007;129(3):235-255.
6. Bohnert AS, Valenstein M, Bair MJ, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA*. 2011;305(13):1315-1321.
7. The Pain & Policy Studies Group (PPSG). Opioid Consumption Data. 2016; http://www.painpolicy.wisc.edu/opioid-consumption-data. Accessed Juni 21, 2017.
8. Florence CS, Zhou C, Luo F, Xu L. The Economic Burden of Prescription Opioid Overdose, Abuse, and Dependence in the United States, 2013. *Med Care*. 2016;54(10):901-906.
9. Lindenhovius AL, Helmerhorst GT, Schnellen AC, Vrahas M, Ring D, Kloen P. Differences in prescription of narcotic pain medication after operative treatment of hip and ankle fractures in the United States and The Netherlands. *J Trauma*. 2009;67(1):160-164.
10. Helmerhorst GT, Lindenhovius AL, Vrahas M, Ring D, Kloen P. Satisfaction with pain relief after operative treatment of an ankle fracture. *Injury*. 2012;43(11):1958-1961.
11. van Amsterdam J, van den Brink W. The Misuse of Prescription Opioids: A Threat for Europe? *Curr Drug Abuse Rev*. 2015;8(1):3-14.
12. Schubert I, Ihle P, Sabatowski R. Increase in opiate prescription in Germany between 2000 and 2010: a study based on insurance data. *Dtsch Arztebl Int*. 2013;110(4):45-51.
13. Giraudon I, Lowitz K, Dargan PI, Wood DM, Dart RC. Prescription opioid abuse in the UK. *Br J Clin Pharmacol*. 2013;76(5):823-824.
14. Ruscitto A, Smith BH, Guthrie B. Changes in opioid and other analgesic use 1995-2010: repeated cross-sectional analysis of dispensed prescribing for a large geographical population in Scotland. *Eur J Pain*. 2015;19(1):59-66.
15. Scheck J. Tramadol: The Opioid Crisis for the Rest of the World. *The Wall Street Journal*2016.
16. World Health Organization. WHO's cancer pain ladder for adults. 2016; http://www.who.int/cancer/palliative/painladder/en/. Accessed November, 2016.
17. Hanks G, Cherny NI, Fallon M. Opioid analgesic therapy. In: Doyle D, Hanks G, Cherny N, Calman K, eds. *Oxford Textbook of Palliative Medicine*. 3rd ed. New York: Oxford United Press; 2004.
18. Savage SR, Joranson DE, Covington EC, Schnoll SH, Heit HA, Gilson AM. Definitions related to the medical use of opioids: evolution towards universal agreement. *J Pain Symptom Manage*. 2003;26(1):655-667.
19. Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. *Pain Physician*. 2008;11(2 Suppl):S105-120.
20. Nicholas MK. The pain self-efficacy questionnaire: Taking pain into account. *Eur J Pain*. 2007;11(2):153-163.
21. McCracken LM, Dhingra L. A short version of the Pain Anxiety Symptoms Scale (PASS-20): preliminary development and validity. *Pain Res Manag*. 2002;7(1):45-50.

22. Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: validity of a two-item depression screener. *Med Care*. 2003;41(11):1284-1292.

23. Swiontkowski MF, Engelberg R, Martin DP, Agel J. Short musculoskeletal function assessment questionnaire: validity, reliability, and responsiveness. *J Bone Joint Surg Am*. 1999;81(9):1245-1260.

24. UNESCO Institute for Statistics. International Standard Classification of Education ISCED 2011. 2012; http://uis.unesco.org/sites/default/files/documents/international-standard-classification-of-education-isced-2011-en.pdf. Accessed Jul 6, 2017.

25. Lewis JA, Jones DR, Rohmel J. Biostatistical methodology in clinical trials--a European guideline. *Stat Med*. 1995;14(15):1655-1657.

26. Piaggio G, Elbourne DR, Pocock SJ, Evans SJ, Altman DG, Group C. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *JAMA*. 2012;308(24):2594-2604.

27. Bot AG, Bekkers S, Arnstein PM, Smith RM, Ring D. Opioid use after fracture surgery correlates with pain intensity and satisfaction with pain relief. *Clin Orthop Relat Res*. 2014;472(8):2542-2549.

28. Kaur Makkar J, Jain K, Bhatia N, Jain V, Mal Mithrawal S. Comparison of analgesic efficacy of paracetamol and tramadol for pain relief in active labor. *J Clin Anesth*. 2015;27(2):159-163.

29. Mitchell A, van Zanten SV, Inglis K, Porter G. A randomized controlled trial comparing acetaminophen plus ibuprofen versus acetaminophen plus codeine plus caffeine after outpatient general surgery. *J Am Coll Surg*. 2008;206(3):472-479.

30. Mitchell A, McCrea P, Inglis K, Porter G. A randomized, controlled trial comparing acetaminophen plus ibuprofen versus acetaminophen plus codeine plus caffeine (Tylenol 3) after outpatient breast surgery. *Ann Surg Oncol*. 2012;19(12):3792-3800.

31. Rawal N, Allvin R, Amilon A, Ohlsson T, Hallen J. Postoperative analgesia at home after ambulatory hand surgery: a controlled comparison of tramadol, metamizol, and paracetamol. *Anesth Analg*. 2001;92(2):347-351.

32. Uysal HY, Takmaz SA, Yaman F, Baltaci B, Basar H. The efficacy of intravenous paracetamol versus tramadol for postoperative analgesia after adenotonsillectomy in children. *J Clin Anesth*. 2011;23(1):53-57.

33. Sun EC, Darnall BD, Baker LC, Mackey S. Incidence of and Risk Factors for Chronic Opioid Use Among Opioid-Naive Patients in the Postoperative Period. *JAMA Intern Med*. 2016;176(9):1286-1293.

34. Helmerhorst GT, Vranceanu AM, Vrahas M, Smith M, Ring D. Risk factors for continued opioid use one to two months after surgery for musculoskeletal trauma. *J Bone Joint Surg Am*. 2014;96(6):495-499.

35. Vranceanu AM, Jupiter JB, Mudgal CS, Ring D. Predictors of pain intensity and disability after minor hand surgery. *J Hand Surg Am*. 2010;35(6):956-960.

36. Ip HY, Abrishami A, Peng PW, Wong J, Chung F. Predictors of postoperative pain and analgesic consumption: a qualitative systematic review. *Anesthesiology*. 2009;111(3):657-677.

37. Deyo RA, Von Korff M, Duhrkoop D. Opioids for low back pain. *BMJ*. 2015;350:g6380.

38. Turk DC, Okifuji A. What factors affect physicians' decisions to prescribe opioids for chronic noncancer pain patients? *Clin J Pain*. 1997;13(4):330-336.

39. Nota SP, Spit SA, Voskuyl T, Bot AG, Hageman MG, Ring D. Opioid Use, Satisfaction, and Pain Intensity After Orthopedic Surgery. *Psychosomatics*. 2015;56(5):479-485.

40. Marquez-Lara A, Hutchinson ID, Nunez F, Jr., Smith TL, Miller AN. Nonsteroidal Anti-Inflammatory Drugs and Bone-Healing: A Systematic Review of Research Quality. *JBJS Rev*. 2016;4(3).

RISK FACTORS FOR CONTINUED OPIOID USE ONE TO TWO MONTHS AFTER SURGERY FOR MUSCULOSKELETAL TRAUMA

5

Helmerhorst GT, Vranceanu AM, Vrahas M,
Smith M, Ring D

J Bone Joint Surg Am. 2014 Mar 19;96(6):495-9.

ABSTRACT

Background

The aim of this study was to determine factors associated with self-reported ongoing use of opioid medication one to two months after operative treatment of musculoskeletal trauma.

Methods

Operatively treated patients (n = 145) with musculoskeletal trauma were evaluated one to two months after surgery. Patients indicated if they were taking opioid pain medication and completed several psychological questionnaires: the Center for Epidemiologic Studies Depression Scale, the Pain Catastrophizing Scale, the Pain Anxiety Symptoms Scale, and the Posttraumatic Stress Disorder Checklist, civilian version. The Numeric Rating Scale was used to measure pain intensity. Disability was measured with use of the Short Musculoskeletal Function Assessment Questionnaire and injury severity was measured with use of the Abbreviated Injury Scale.

Results

Patients who scored higher on the catastrophic thinking, anxiety, posttraumatic stress disorder, and depression questionnaires were significantly more likely ($p < 0.001$) to report taking opioid pain medications one to two months after surgery, regardless of injury severity, fracture site, or treating surgeon. The magnitude of disability as measured by the Short Musculoskeletal Function Assessment score was significantly higher ($p < 0.001$) in the patients who reported using opioids (40 points) compared with those who reported not using opioids (24 points). A logistic regression model not including pain intensity found that the single best predictor of reported opioid use was catastrophic thinking (odds ratio, 1.12 [95% confidence interval, 1.07 to 1.18]), which explained 23% of the variance ($p < 0.001$).

Conclusions

Patients who continue to use opioid pain medication one to two months after surgery for musculoskeletal trauma have more psychological distress, less effective coping strategies, and greater symptoms and disability than patients who do not take opioids, irrespective of injury, surgical procedure, or surgeon.

Level of Evidence

Prognostic Level III.

INTRODUCTION

Opioids are prescribed to reduce pain intensity and disability related to pain. The use of opioids for persistent or chronic non-cancer pain is debated given substantial evidence that they are associated with greater pain intensity, greater pain-related disability, and reduced quality of life.[1-3] Less is known about the effectiveness of opioids in the subacute recovery phase after operative fracture treatment.

In the United States, in contrast with many other parts of the world, most patients take opioids after fractures.[4] Opioid prescription in the United States is increasing, and it is notable that a large percentage of the world's opioid consumption is accounted for by the United States.[5,6] A study of patients recovering from operative fixation of an ankle fracture found that Dutch patients take far fewer opioids, but report similar pain intensity and satisfaction with pain relief compared with patients in the United States.[7] Considering all patients regardless of country, those who took opioids were, on average, less satisfied with pain relief than patients who took non-opioid analgesics.[7] To our knowledge, the scientific data addressing variation in opioid use and satisfaction with pain relief after orthopaedic surgery are limited largely to studies that address the ability of ancillary medical interventions to reduce opioid use.

In the original study that created the data set used in this article, pain intensity one to two months after fracture fixation was related to catastrophic thinking (irrational thinking envisioning the worst-case scenario or outcome) and the continued use of opioids rather than the bone that was fractured or injury severity. Pain intensity with activity five to eight months after fracture fixation was much more strongly associated with catastrophic thinking and continued opioid use one to two months after surgery than it was to injury severity. The use of opioids and increased catastrophic thinking early in the recovery were associated with increased pain with activity later on during recovery. Disability was also most strongly associated with catastrophic thinking, but injury severity was also a factor, particularly between five and eight months after injury.

If future studies confirm that opioids are associated with greater pain intensity and disability after fracture fixation, this will add to the already numerous reasons to be cautious with opioids. Opioids have a number of adverse effects, including nausea, vomiting, sedation, constipation, respiratory depression, and hyperalgesia.[8,9] In addition, opioids have other negative consequences including addiction, physical dependence, and tolerance. In 2008, poisoning became the leading cause of injury death in the United States. Nearly nine of ten poisoning deaths are caused by drugs and more than 40% involve opioid analgesics.[10] In one study, patients prescribed opioids for acute pain had an adjusted hazard ratio risk of 6.64 of death from an overdose of opioid pain medication.[11] Addiction is a multidimensional disease and most common in individuals who are biologically (male and younger adults) and psychosocially (stress and mental illness) vulnerable.[8,12-15] Prescription opioid analgesic abuse represents a growing and substantial economic burden and was estimated to be $8.6 billion in the United States in 2001.[16] A recent report found a correlation between sales of prescription opioids and opioid-related drug overdoses treated in emergency departments.[17]

We are looking for options to help optimize our patients' postoperative comfort and activity level. Recent studies identified that psychological factors (catastrophic thinking in particular)

are strongly associated with pain intensity and disability in patients recovering from minor hand surgery[18] and musculoskeletal trauma[19], and these studies raise promising alternatives. These studies are consistent with the findings of Ip et al., who systematically reviewed twenty-one studies of 7813 patients undergoing musculoskeletal surgery and found psychological distress to be strongly associated with postoperative analgesic consumption along with the type of surgery and patient age.[20] Moreover, catastrophic thinking was predictive of postoperative pain and analgesic use in patients undergoing lumbar fusion surgery.[21] Finally, preoperative anxiety and catastrophic thinking are associated with the development of chronic post-surgical pain.[22] With respect to persistent or chronic non-cancer pain, studies consistently find that prescription of opioid pain medication is associated more strongly with pain behaviors and mental health disorders than with pathophysiology.[23-27]

We are interested in the relationship between psychological factors and self-reported opioid use at the subacute stage between one and two months after surgery when recovery is well established. If such an association is identified and is confirmed by other studies, it raises the possibility that treatment of psychological distress and ineffective coping strategies might be additive and perhaps even more fruitful than the prescription of opioids for reducing pain intensity and disability after injury or surgery. Requests for opioids after an appropriate period of recovery might represent a helpful indicator of the potential to benefit from psychosocial interventions.

The aim of this study is to assess factors associated with self-reported continued use of opioid pain medication one to two months after musculoskeletal trauma. Our primary null hypothesis is that there will be no association among psychological factors and self-reported use of opioids one to two months after musculoskeletal trauma while accounting for demographics.

MATERIALS AND METHODS

The human research committee approved a protocol for the secondary use of data from an existing database of a previously approved prospective study regarding the relationship of psychological factors to pain intensity and disability after surgery for musculoskeletal trauma.[19] All English-speaking patients who were eighteen years of age or more with operatively treated musculoskeletal trauma were eligible. We excluded patients with pre-injury evidence of maladaptive illness behavior or greater infirmity so that we could study human illness behavior among patients with relatively untested adaptation and resiliency. The specific exclusion criteria for the initial study included: major medical comorbidities expected to worsen in the next six months such as cancer and major heart conditions; comorbid chronic pain condition; change in antidepressant medication regimen after injury; psychosis, bipolar disorder, or active substance dependence; secondary gain such as active litigation or a Workers' Compensation dispute; injury affecting cognitive and motor functions; and cognitive deficiency limiting the ability to complete questionnaires.

We used the cross-sectional data of all patients (n = 145) who completed a set of questionnaires and were asked if they were still using opioids one to two months after surgery.

The questionnaires used in this study were the following. The Center for Epidemiologic Studies Depression Scale (CES-D)[28] measured symptoms of depression and had twenty items evaluated on

a 4-point Likert scale from 0 to 3 points. A total score is obtained by adding all items, of which four are reversely scored. A score above 16 points was used as an arbitrary threshold for depressive disorder. The Pain Catastrophizing Scale (PCS)[29] measured ineffective coping strategies in response to nociception and had thirteen items evaluated on a 4-point Likert scale from 0 to 3 points. A total score is obtained by adding all items. The Pain Anxiety Symptoms Scale (PASS-20)[30] measured symptoms of anxiety and had twenty items evaluated on a 6-point Likert scale from 0 to 5 points. A total score is obtained by adding all items. The Posttraumatic Stress Disorder (PTSD) Checklist, civilian version (PCL-C)[31], measured symptoms of posttraumatic stress disorder and had seventeen items measured on a 5-point Likert scale from 1 to 5 points. A total score is obtained by adding all items. We used an arbitrary threshold of 33 points for the provisional diagnosis of posttraumatic stress disorder based on an algorithm following the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)[32] criteria. The Short Musculoskeletal Function Assessment Questionnaire (SMFA)[33] was used to measure musculoskeletal disability and had forty-six items evaluated on a 5-point Likert scale from 1 to 5 points. A total score is obtained by adding all items and then is transferred to a range from 0 to 100 points with use of the formula ([actual raw score 2 lowest possible raw score]/ possible range of raw score) x 100. A higher score indicates greater disability. The Numeric Rating Scale (NRS) for pain was used to assess pain at rest and with activity. This is an 11-point-item scale from 0 points, indicating no pain, to 10 points, indicating the worst pain ever.

Injury severity was measured with the Abbreviated Injury Scale (AIS 2005[34]). Scores range from 1 to 6 points, with the most severe fatal injuries given 6 points on the basis of severity and anatomic descriptors. Only musculoskeletal AIS scores were used in this study. When patients had multiple musculoskeletal injuries and thus multiple musculoskeletal AIS scores, the highest AIS score was used.

Statistical Analysis

A post hoc power analysis using G*Power software (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) indicated that a sample of 145 patients with forty cases would provide > 95% statistical power to detect an effect size of 0.9 (based on the means of the best predictor) and a variance inflation factor of 1.3.[35]

In a bivariate analysis, continuous explanatory variables (age, catastrophic thinking, anxiety, depression, and posttraumatic stress disorder) and response variables (pain at rest, pain with activity, and disability) were compared to determine the association with the main response variable (opioid use one to two months after injury) using an independent t test. Categorical explanatory variables (sex, fracture site [upper or lower extremity], treating surgeons, primary economic provider status, work-related injury, prior orthopaedic injuries, prior orthopaedic surgeries, injury severity according to AIS, single or multiple injuries, arbitrary threshold score for posttraumatic stress disorder on the PCL-C, arbitrary threshold score for depression on the CES-D) were compared between cohorts using the chi-square test (Fisher exact or Pearson chi-square, depending on the expected count). Significance was set at $p < 0.05$.

A multivariable backward logistic regression model was created to account for confounding between the explanatory variables. Variables with $p < 0.10$ in the bivariate analysis were entered in the model. This is a common cutoff value for inclusion of variables in regression modeling when the total number of study subjects is small. We ran two models, one that did not use response variables (e.g., pain, disability, and opioid use) as explanatory variables and one that included pain as one of the explanatory variables.

The Nagelkerke R-square and the Hosmer-Lemeshow tests were used for the overall model to assess study power and goodness of fit. Odds ratios (ORs) were calculated with the 95% confidence interval (95% CI).

RESULTS

Bivariate Analysis

Forty patients (28%) reported using opioid pain medication one to two months after injury, including twenty of seventy-six women and twenty of sixty-nine men. Thirty-five patients (24%) met our arbitrary threshold for an estimated diagnosis of major depressive disorder as measured on the CES-D and forty-two patients (29%) met our arbitrary threshold score on the PCL-C for an estimated diagnosis of posttraumatic stress disorder. The mean PCS (catastrophic thinking), mean PASS-20 (anxiety), mean PCL-C, and mean CES-D (depression) scores were significantly higher in patients using opioids ($p < 0.001$).

There was a strong significant correlation (R-square) ($p < 0.001$ for all) between PCS and CES-D (0.7), between NRS and both PCS (0.7) and CES-D (0.5), and between SFMA and both PCS (0.7) and CES-D (0.6).

Patients were more likely to report that they were still taking opioid pain medication if they met our arbitrary threshold scores on the PCL-C ($p = 0.002$) and CES-D ($p = 0.006$) one to two months after surgery. Patients still taking opioid medication one to two months after surgery had greater pain intensity (at rest and with activity) and disability ($p < 0.001$). Injury severity and fracture site were not related with continued opioid use ($p = 0.08$) (Tables 1 and 2).

Multivariable Analysis

When the four explanatory variables that met the criteria for inclusion (catastrophic thinking, symptoms of anxiety, symptoms of posttraumatic stress disorder, and symptoms of depression) were entered into a backward logistic regression model, catastrophic thinking (OR, 1.12 [95% CI, 1.07 to 1.18]) was the only factor retained and it explained 23% of the variation in opioid use ($p < 0.001$). This analysis was repeated using our arbitrary threshold values on the PCL-C and CES-D, instead of the scores, and the results were identical. A model that included pain with activity explained 34% of the variance in opioid use ($p < 0.001$).

DISCUSSION

Despite the fact that most musculoskeletal injuries are well along in the recovery process one to two months after operative treatment, 28% of our patients continued to take opioid pain medication at

Table 1. Bivariate Analysis of Opioid Medication Use One to Two Months After Surgery: Categorical Explanatory Variables

Variable	Opioid Use*	No Opioid Use*	p Value†
No. of patients	40 (28%)	105 (72%)	
Sex			0.72
Female	20 (26%)	56 (74%)	
Male	20 (29%)	49 (71%)	
Fracture site			0.55
Upper extremity	8 (21%)	30 (79%)	
Lower extremity	28 (30%)	64 (70%)	
Multiple injuries	4 (27%)	11 (73%)	
Treating surgeon			0.83
Treating surgeon 1	27 (28%)	70 (72%)	
Treating surgeon 2	12 (26%)	34 (74%)	
Treating surgeon 3‡	1 (50%)	1 (50%)	
Injury severity (AIS)§			0.08
Minor	1 (25%)	3 (75%)	
Moderate	19 (23%)	62 (77%)	
Serious	11 (24%)	35 (76%)	
Severe	7 (58%)	5 (42%)	
No. of injuries			0.69
Single	32 (27%)	87 (73%)	
Multiple	8 (31%)	18 (69%)	
Prior orthopaedic injury	23 (29%)	55 (71%)	0.58
Prior surgery	15 (33%)	30 (67%)	0.30
Primary economic provider	18 (26%)	51 (74%)	0.52
Work-related injury	1 (14%)	6 (86%)	0.59
Met threshold for posttraumatic stress disorder on PCL-C	19 (45%)	23 (55%)	0.002
Met threshold for depression on CES-D	16 (46%)	19 (54%)	0.006

*The values are given as the number of patients, with the row percentage in parentheses. Significance was set at $p < 0.05$. Treating surgeon 3 was not computed and was treated as a missing case in the final analysis. §Two AIS scores in the opioid use group are missing

Table 2. Bivariate Analysis of Opioid Medication Use One to Two Months After Surgery: Continuous Explanatory Variables

Variable	Opioid Use*	No Opioid Use*	p Value†	Difference‡
Patient age *(yr)*	47 ± 13	48 ± 19	0.81	20.7 (25.7 to 7.2)
Catastrophic thinking (PCS) *(points)*	25 ± 11	17 ± 6	<0.001	8.5 (5.6 to 11.3)
Anxiety (PASS-20) *(points)*	33 ± 27	15 ± 15	<0.001	17.8 (10.7 to 25)
Posttraumatic stress disorder (PCL-C) *(points)*	35 ± 15	25 ± 9	<0.001	9.7 (5.7 to 13.7)
Depression (CES-D) *(points)*	18 ± 11	9 ± 7	<0.001	8.8 (5.6 to 11.9)
Pain at rest (NRS) *(points)*	4.0 ± 2.4	1.3 ± 1.9	<0.001	2.6 (1.9 to 3.4)
Pain with activity (NRS) *(points)*	6.2 ± 2.0	3.1 ± 2.4	<0.001	3.1 (2.2 to 3.9)
Disability (SMFA) *(points)*	40 ± 9	24 ± 8	<0.001	28.3 (17.1 to 39.5)

*The values are given as the mean and the standard deviation. †Significance was set at $p < 0.05$. ‡The values are given as the difference, with the 95% CI in parentheses.

this time point. This rate is compared with 25% of patients three months after spine surgery[36] and 6% of patients five months after mastectomy, lumpectomy, thoracotomy, total knee replacement, or total hip replacement.[37]

The use of opioid pain medication one to two months after surgery for musculoskeletal trauma was most strongly associated with catastrophic thinking (as measured on the PCS), but also with symptoms of pain anxiety (as measured on the PASS-20), symptoms of depression (as measured on the CES-D), and symptoms of posttraumatic stress disorder (as measured on the PCL-C). Patients meeting our arbitrary threshold values on the PCL-C and CES-D were more likely to still be taking opioid pain medication one to two months after surgery. In other words, better mood and more adaptive coping strategies help patients discontinue opioids after musculoskeletal trauma surgery.

In this study, the mean disability (as measured by the SMFA) and the mean pain intensity were significantly higher in patients still using opioid pain medication one to two months after surgery ($p < 0.001$), irrespective of fracture site or injury severity. This result is consistent with evidence that variations in postoperative acute and chronic pain are best explained by preoperative psychological factors and demographics.[20-22] It is also consistent with the weight of research on persistent or chronic non-cancer pain, which has demonstrated that opioid use is associated with lower self-rated health, greater unemployment, greater use of health-care resources, lower quality of life, and more intense pain.[1,38-42]

Given the shortcomings and adverse events associated with opioid medication, greater pain and disability than expected, including requests for opioids one to two months after fracture surgery, should prompt health-care providers to consider the important roles of stress, depressed mood, and ineffective coping strategies in human illness behavior, and to be more prepared to offer a full complement of treatments to help their patients feel better and do more. It seems, at least in the United States, that both patients and surgeons may often look to opioid pain medication as the best or only hope for relief of postoperative pain. The evidence suggests otherwise. Catastrophic thinking is responsive to cognitive behavioral therapy. Providers of musculoskeletal health care, including occupational and physical therapists, can improve the situation by empathetically encouraging patients to talk about the emotional aspects of recovery and by avoiding reinforcement of ineffective coping strategies.

Our study should be considered in light of its limitations. First, this study represented secondary use of data from a prospective cohort study. Second, we used validated measures of symptoms of posttraumatic stress disorder and depression and used arbitrary cutoffs for categorization. The diagnosis of posttraumatic stress disorder or major depression would require a formal evaluation. Third, this study measured cross-sectional, self-reported opioid use as a dichotomous measure and did not address opioid intake with blood tests or other measures. Fourth, the AIS might be inadequate for discriminating injury severity. Relatively few patients had more severe injuries, and our statistical analysis of injury severity may therefore have been underpowered. Fifth, the broad areas of evaluation for enrollment and final evaluation are wide, but reflect the realities of clinical research and are necessary to avoid protocol violations and to satisfy strict human research oversight. Finally, no causal relationships could be inferred and the optimal use of opioid medication was not addressed by this study.

There is strong evidence that a biopsychosocial treatment model reduces pain.[43] This model is established for non-traumatic musculoskeletal pain[44] and, in our opinion, should now be translated to traumatic musculoskeletal pain at all phases of recovery. Addressing psychosocial factors in the early phases of recovery might reduce disability and might improve the outcome of surgical and medical procedures.[45] Interdisciplinary treatment could potentially decrease opioid use and associated adverse consequences. Future research should focus on providing surgeons with effective strategies for recognizing and addressing important psychological factors and appropriately limiting opioid pain medications. We hypothesize that screening for low pain self-efficacy (increased catastrophic thinking), feedback to the patients that improved self-efficacy will reduce pain and disability, familiarity with the basic techniques of cognitive behavioral therapy, and appropriate support from behavioral health professionals for receptive patients can ameliorate pain behavior and can reduce analgesic requirements.

REFERENCES

1. Eriksen J, Sjogren P, Bruera E, Ekholm O, Rasmussen NK. Critical issues on opioids in chronic non-cancer pain: an epidemiological study. *Pain*. 2006;125(1-2):172-179.
2. Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain*. 2004;112(3):372-380.
3. Trescot AM, Helm S, Hansen H, et al. Opioids in the management of chronic non-cancer pain: an update of American Society of the Interventional Pain Physicians' (ASIPP) Guidelines. *Pain Physician*. 2008;11(2 Suppl):S5-S62.
4. Lindenhovius AL, Helmerhorst GT, Schnellen AC, Vrahas M, Ring D, Kloen P. Differences in prescription of narcotic pain medication after operative treatment of hip and ankle fractures in the United States and The Netherlands. *J Trauma*. 2009;67(1):160-164.
5. Volkow ND, McLellan TA, Cotto JH, Karithanom M, Weiss SR. Characteristics of opioid prescriptions in 2009. *JAMA*. 2011;305(13):1299-1301.
6. Consortium DCaAtM. Opioid Consumption Maps. 2009; ppsg-production.heroku.com, 2016.
7. Helmerhorst GT, Lindenhovius AL, Vrahas M, Ring D, Kloen P. Satisfaction with pain relief after operative treatment of an ankle fracture. *Injury*. 2012;43(11):1958-1961.
8. Edlund MJ, Steffick D, Hudson T, Harris KM, Sullivan M. Risk factors for clinically recognized opioid abuse and dependence among veterans using opioids for chronic non-cancer pain. *Pain*. 2007;129(3):355-362.
9. Hanks G, Cherny NI, Fallon M. Opioid analgesic therapy. In: Doyle D, Hanks G, Cherny N, Calman K, eds. *Oxford Textbook of Palliative Medicine*. 3rd ed. New York: Oxford United Press; 2004.
10. Warner M, Chen LH, Makuc DM, Anderson RN, Minino AM. Drug poisoning deaths in the United States, 1980-2008. *NCHS Data Brief*. 2011(81):1-8.
11. Bohnert AS, Valenstein M, Bair MJ, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA*. 2011;305(13):1315-1321.
12. Ballantyne JC, LaForge KS. Opioid dependence and addiction during opioid treatment of chronic pain. *Pain*. 2007;129(3):235-255.
13. McLellan AT, Lewis DC, O'Brien CP, Kleber HD. Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. *JAMA*. 2000;284(13):1689-1695.
14. Oetting ER, Donnermeyer JF. Primary socialization theory: the etiology of drug use and deviance. I. *Subst Use Misuse*. 1998;33(4):995-1026.
15. Piazza PV, Le Moal ML. Pathophysiological basis of vulnerability to drug abuse: role of an interaction between stress, glucocorticoids, and dopaminergic neurons. *Annu Rev Pharmacol Toxicol*. 1996;36:359-378.
16. Birnbaum HG, White AG, Reynolds JL, et al. Estimated costs of prescription opioid analgesic abuse in the United States in 2001: a societal perspective. *Clin J Pain*. 2006;22(8):667-676.
17. Modarai F, Mack K, Hicks P, et al. Relationship of opioid prescription sales and overdoses, North Carolina. *Drug Alcohol Depend*. 2013;132(1-2):81-86.
18. Vranceanu AM, Jupiter JB, Mudgal CS, Ring D. Predictors of pain intensity and disability after minor hand surgery. *J Hand Surg Am*. 2010;35(6):956-960.
19. Vranceanu AM, Bachoura A, Weening A, Vrahas M, Smith RM, Ring D. Psychological factors predict disability and pain intensity after skeletal trauma. *J Bone Joint Surg Am*. 2014;96(3):e20.
20. Ip HY, Abrishami A, Peng PW, Wong J, Chung F. Predictors of postoperative pain and analgesic consumption: a qualitative systematic review. *Anesthesiology*. 2009;111(3):657-677.
21. Papaioannou M, Skapinakis P, Damigos D, Mavreas V, Broumas G, Palgimesi A. The role of catastrophizing in the prediction of postoperative pain. *Pain Med*. 2009;10(8):1452-1459.

22. Theunissen M, Peters ML, Bruce J, Gramke HF, Marcus MA. Preoperative anxiety and catastrophizing: a systematic review and meta-analysis of the association with chronic postsurgical pain. *Clin J Pain*. 2012;28(9):819-841.

23. Krebs EE, Lurie JD, Fanciullo G, et al. Predictors of long-term opioid use among patients with painful lumbar spine conditions. *J Pain*. 2010;11(1):44-52.

24. Breckenridge J, Clark JD. Patient characteristics associated with opioid versus nonsteroidal anti-inflammatory drug management of chronic low back pain. *J Pain*. 2003;4(6):344-350.

25. Sullivan MD, Edlund MJ, Steffick D, Unützer J. Regular use of prescribed opioids: association with common psychiatric disorders. *Pain*. 2005;119(1-3):95-103.

26. Turk DC, Okifuji A. What factors affect physicians' decisions to prescribe opioids for chronic noncancer pain patients? *Clin J Pain*. 1997;13(4):330-336.

27. Fillingim RB, Doleys DM, Edwards RR, Lowery D. Clinical characteristics of chronic back pain as a function of gender and oral opioid use. *Spine (Phila Pa 1976)*. 2003;28(2):143-150.

28. Radloff LS. The CES-D Scale. *Applied Psychological Measurement*. 1977;1(3):385-401.

29. Sullivan MJL, Bishop SR. The Pain Catastrophizing Scale: Development and Validation. *Psychological Assessment*. 1995;7(4):524-532.

30. McCracken LM, Dhingra L. A short version of the Pain Anxiety Symptoms Scale (PASS-20): preliminary development and validity. *Pain Res Manag*. 2002;7(1):45-50.

31. Weathers FW, Litz BT, Huska JA, Keane TM. PTSD Checklist - Civilian version. In. Boston: National Center for PTSD; 1994.

32. Association AP. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition: DSM-IV-TR®*. American Psychiatric Association; 2000.

33. Swiontkowski MF, Engelberg R, Martin DP, Agel J. Short musculoskeletal function assessment questionnaire: validity, reliability, and responsiveness. *J Bone Joint Surg Am*. 1999;81(9):1245-1260.

34. Gennarelli TA, Wodzin E, Medicine AftAoA. *Abbreviated Injury Scale 2005: Update 2008*. Association for the Advancement of Automative Medicine; 2008.

35. Hsieh FY, Bloch DA, Larsen MD. A simple method of sample size calculation for linear and logistic regression. *Stat Med*. 1998;17(14):1623-1634.

36. Mahowald ML, Singh JA, Majeski P. Opioid use by patients in an orthopedics spine clinic. *Arthritis Rheum*. 2005;52(1):312-321.

37. Carroll I, Barelka P, Wang CK, et al. A pilot cohort study of the determinants of longitudinal opioid use after surgery. *Anesth Analg*. 2012;115(3):694-702.

38. Ciccone DS, Just N, Bandilla EB, Reimer E, Ilbeigi MS, Wu W. Psychological correlates of opioid use in patients with chronic nonmalignant pain: a preliminary test of the downhill spiral hypothesis. *J Pain Symptom Manage*. 2000;20(3):180-192.

39. Kidner CL, Mayer TG, Gatchel RJ. Higher opioid doses predict poorer functional outcome in patients with chronic disabling occupational musculoskeletal disorders. *J Bone Joint Surg Am*. 2009;91(4):919-927.

40. Franklin GM, Stover BD, Turner JA, Fulton-Kehoe D, Wickizer TM, Cohort DRIS. Early opioid prescription and subsequent disability among workers with back injuries: the Disability Risk Identification Study Cohort. *Spine (Phila Pa 1976)*. 2008;33(2):199-204.

41. Webster BS, Verma SK, Gatchel RJ. Relationship between early opioid prescribing for acute occupational low back pain and disability duration, medical costs, subsequent surgery and late opioid use. *Spine (Phila Pa 1976)*. 2007;32(19):2127-2132.

42. Barth R. *Prescription narcotics: an obstacle to maximum medical improvement*. Kailua: American Medical Association;2011.

43. Hoffman BM, Papas RK, Chatkoff DK, Kerns RD. Meta-analysis of psychological interventions for chronic low back pain. *Health Psychol*. 2007;26(1):1-9.

44. Nicholas MK. Pain management in musculoskeletal conditions. *Best Pract Res Clin Rheumatol*. 2008;22(3):451-470.

45. Sharp TJ, Harvey AG. Chronic pain and posttraumatic stress disorder: mutual maintenance? *Clin Psychol Rev*. 2001;21(6):857-877.

AN EPIDEMIC OF THE USE, MISUSE AND OVERDOSE OF OPIOIDS AND DEATHS DUE TO OVERDOSE, IN THE UNITED STATES AND CANADA: IS EUROPE NEXT?

6

Helmerhorst GT, Teunis T,
Janssen SJ, Ring D

Bone Joint J. 2017 Jul;99-B (7) 856-864

ABSTRACT

The United States and Canada are in the midst of an epidemic of the use, misuse and overdose of opioids, and deaths related to overdose. This is the direct result of overstatement of the benefits and understatement of the risks of using opioids by advocates and pharmaceutical companies. Massive amounts of prescription opioids entered the community and were often diverted and misused. Most other parts of the world achieve comparable pain relief using fewer opioids.

The misconceptions about opioids that created this epidemic are finding their way around the world. There is particular evidence of the increased prescription of strong opioids in Europe.

Opioids are addictive and dangerous. Evidence is mounting that the best pain relief is obtained through resilience. Opioids are often prescribed when treatments to increase resilience would be more effective.

INTRODUCTION

Much of the world is unaware of the fact that the medical and legal professions in the United States and Canada are in the midst of an epidemic of the use, misuse and overuse of opioids, and deaths related to an overdose of these drugs. Doctors have been told by advocates backed by pharmaceutical companies that they are under-treating pain and have been overly concerned about addiction.[1-3] The large amount of opioids released into society has since been diverted and misused, leading to an epidemic of overdoses and deaths. Elsewhere it correctly remains that opioids are considered to be addictive and dangerous. The mistakes made in the United States and Canada should be generally understood around the world so that they can be avoided.

The most common reason for seeking medical care in the United States is pain and more than half of American adults (125 million) had a painful musculoskeletal disorder in 2012.[4] According to the Institute of Medicine, > 116 million Americans had persistent pain (pain that lasts longer than expected for a given nociception, i.e. after the tissues have healed, or pain that is inadequately adapted, e.g. greater than average limitations from common problems such as arthritis, tendinopathy, or backache) in 2011.[5] It is difficult to assess the financial burden of pain, but estimates range between $560 billion to $635 billion a year in the United States.[6]

Nociception is the physiology of actual or potential tissue damage. Pain is the cognitive, emotional, and behavioural response to nociception. Some people have substantial nociception and little pain such as when, for instance, a professional cyclist gets back on his bicycle after a crash which has caused a fracture of the clavicle, and finishes the race. Others have considerable pain without detectable nociception, such as those with fibromyalgia. Every orthopaedic surgeon in the United States, Canada and the rest of the world has treated patients who have undergone extensive surgery with little pain medication. This is an everyday experience. Each of us has also treated patients with intense pain after a minor procedure. The explanation for these observations lies, in part, in the evidence that the intensity of pain for a given nociception is greater when there is greater stress or distress, and that it is greater in patients with less effective coping strategies.[7-10] There is also evidence that a greater intake of opioids correlates with greater pain, irrespective of nociception, and that the continued use of opioids long after an injury has healed is associated with depression and stress.[11-14]

For some time, pain relief in the United States and Canada has focused on opioids. Common prescription opioids include oxycodone, hydrocodone, fentanyl, and morphine. Heroin, another infamous opioid, was developed by a pharmaceutical company and was once sold as a non-addictive substitute for morphine as a cough suppressant, but is now illegal in most countries.[15,16] In the last two decades the sales of prescription opioids has quadrupled in the United States and Canada, along with the rates of misuse, overdose and death.[17,18]

Opioids are used much more in the United States and Canada than elsewhere in the world.[19] They are often difficult to obtain because they are addictive and dangerous. This is the preferred strategy that has been undermined in the United States and Canada. In Europe, about two-thirds of patients with persistent pain take prescription medication, but only a third of those medications are opioids (weak opioids 23%, strong opioids 5%).[20] However, there is evidence of the increasing

prescription of strong opioids in Europe.[19,21,22] It would seem that the misconceptions about opioids that have led to the epidemic in the United States and Canada are finding their way around the world, placing other countries at risk of the same massive opioid problem involving the medical and legal professions found in the United States and Canada.

WHAT CAUSED THE OPIOID EPIDEMIC?

It is widely accepted that the increase in the misuse of opioids and deaths due to overdose in the United States were largely driven by an increase in prescriptions by healthcare providers.[23-28] Although some patients will intentionally misuse opioids for their euphoric effects and start doing so voluntarily, many subsequently change gradually from prescribed medical use to dependence, despite their intention to use these medications for pain relief as directed by their doctor. Even more important is the fact that as increasing amounts of opioids were prescribed, many were left unused in medicine cabinets where they were found by relatives, friends or acquaintances. They were also often obtained under false circumstances for the express purpose of diversion. Some were obtained illicitly, for example from "pill mills".[29-31]

Many factors have contributed to the increased use of opioids that has developed during the past two decades, including reports suggesting that they are safe, aggressive marketing of opioids by pharmaceutical companies, healthcare reform in pain management and ignorance about pain relief.

REPORTS SUGGESTING THAT OPIOIDS ARE SAFE

Several influential reports suggested a low risk of developing iatrogenic addiction among patients taking opioids for pain.[32-35] A letter to the editor of the New England Journal of Medicine in 1980 titled "Addiction rare in patients treated with narcotics" recorded only four cases of addiction among 11 882 patients who received at least one narcotic drug during hospitalisation.[32] A study by Portenoy and Foley[35] in 1986 followed 38 patients and concluded that opioid maintenance therapy can be safe in patients with persistent pain that is not related to cancer. The American Academy of Pain Medicine and the American Pain Society subsequently published a consensus statement in 1997 on the use of opioids for the treatment of persistent pain that stated: "The *de novo* development of addiction when opioids are used for the relief of pain is low".[34] A Cochrane review in 2010 by Noble et al[33] reviewed 26 studies including 4893 patients to establish the safety and effectiveness of opioids for the treatment of chronic pain which is not related to cancer. They concluded that serious adverse events such as iatrogenic opioid addiction were rare.

Many studies contradict these findings, identifying a more substantial risk, as high as 56%, of opioid misuse or iatrogenic addiction among patients who are prescribed opioids for pain relief.[23,36-38] The rise in opioid prescriptions is in a large part attributable to their increased long-term use for persistent pain not related to cancer in spite of limited or no evidence of effectiveness.[28,39-42] Examples include, but are not limited to, osteoarthritis and low back pain, both conditions for which the evidence of effectiveness and the safety of long-term opioid use is weak or nonexistent.[37,43,44]

MARKETING OF OPIOIDS BY PHARMACEUTICAL COMPANIES

Pharmaceutical companies encouraged physicians in the United States and Canada to prescribe opioids using tactics that exaggerated the potential benefits and underemphasized the risk of addiction and death.[1,3,24] For example, Purdue Pharma (Stamford, Connecticut), the manufacturer of Oxycontin, funded > 20 000 pain-related educational programmes and launched campaigns to encourage physicians to prescribe the long-term use of opioids for chronic pain not related to cancer, while downplaying the side effects and claiming that Oxycontin was less addictive and less subject to abuse than other opioids on the market.[1-3] When Purdue's patent on the opioid MS Contin was about to expire by the late 1980s, the company was looking for a new source of revenue and developed a new "controlled release oxycodone" also known as Oxycontin. Oxycontin was patented for 20 years and was said to improve the "efficiency and quality of pain management" as well as treat pain "without unacceptable side effects", according to Purdue.[45] Despite numerous attempts to modify the Oxycontin product monograph and to disclose the truthful known data on the risks of dependency, patents were protected.[46] The company used a patient starter coupon programme that provided patients with a free limited-time prescription of Oxycontin for a seven- to 30-day supply.[1] Purdue Pharma also provided financial support to the American Pain Society, The American Academy of Pain Medicine, the Joint Commission and patient societies.[1-3] In 2006, Purdue Pharma pleaded guilty in the federal court to a number of criminal charges related to the marketing of Oxycontin and paid over $600 million in fines.[47]

NEW ATTITUDES TOWARDS PAIN

Advocates with ties to the pharmaceutical industry promoted the idea that doctors under-treat pain. This led to directives based on emotion and shame that rapidly changed culture and will be difficult to undo. In 1990, state medical boards curtailed restrictions on laws governing the prescription of opioids for the treatment of chronic pain unrelated to cancer.[41,48] The treatment of pain became a human right.[49-51] In 1995, the American Pain Society introduced a campaign entitled "Pain is the Fifth Vital Sign" which urged a more aggressive use of opioids for the treatment of pain. This was included in their subsequent consensus statement that endorsed the use of opioids for persistent pain that is unrelated to cancer.[2,34,52] In 2001, the Joint Commission on Accreditation of Health Care Organisations released pain management standards for the accreditation of healthcare organisations at the height of the growing focus on opioid analgesia. Most observers feel that the measurement of care provider and hospital quality based on satisfaction with pain relief was synergistic with the promotion of opioids in leading to a greater use of opioids.[53] The Centre for Medicare and Medicaid Services incorporated pain management into patient satisfaction scores, thereby linking patient experience and pain management to reimbursement.[49,54] These pro-opioid cultural and regulatory shifts created a simple message: pain must be treated, preferably with opioids, and without the fear of iatrogenic addiction.[23]

IGNORANCE REGARDING PAIN RELIEF

Medical schools devote little time to pain relief and substance misuse.[55-58] A survey among 104 United States medical schools reported that only four have a required pain relief course and an additional 17 offered an elective course. The mean number of cumulative teaching hours spent discussing pain relief among these medical schools was 11, ranging from one to 31 hours.[57] A study among Canadian universities reported that, on average, medical students received 16 hours of education in pain relief, while veterinary students received 87 hours.[59] A recent review of Continuing Medical Education (CME) programmes in the United States showed that only five of 50 states required all or nearly all physicians to obtain CME credits on pain management.[24] As a result, physicians consistently report that their medical education does not adequately prepare them to address pain relief and substance misuse.[24]

TRENDS IN THE UNITED STATES AND CANADA

The misuse of prescription opioids continues to increase in the United States with a major impact on health, society, economy, and safety.[25,60,61] The number of prescriptions for opioids in the United States was 259 million in 2012. More than one in 20 United States citizens aged > 12 years have used prescription medication for non-medical reasons.[62,63] In 2011, the Drug Abuse Warning Network reported more than 1.2 million Emergency Department visits involving the non-medical use of prescription drugs, a third involving opioids.[64]

The most prescribed drug in the United States is an opioid: hydrocodone in combination with acetaminophen (paracetamol). There were 125.5 million prescriptions dispensed for hydrocodone/paracetamol in 2008 and 135.3 million in 2012. The next most prescribed medication (levothyroxine) had 107.5 million prescriptions in 2012. The remaining top five included lisinopril (90.8 million), simvastatine (86.1 million), and metoprolol (78.1 million).[65] The overall annual number of opioid prescriptions dispensed by retail pharmacies increased from 76 million in 1991 to 219 million in 2011.[66]

According to the three-step pain ladder of the World Health Organisation, analgesics should be prescribed in the following order: first, non-opioids (e.g. acetaminophen and nonsteroidal anti-inflammatory drugs); then, if necessary, weak opioids (e.g., tramadol and codeine); then strong opioids (e.g., oxycodone and morphine). This ladder was primarily designed for the treatment of pain in palliative cancer care, but is a framework to be considered for the treatment of acute post-operative pain.[67] Most of the world currently adheres to this step ladder. However, in the United States, 80% of patients having relatively minor surgery such as arthroscopy of the knee or carpal tunnel release had a prescription for an opioid.[68] Moreover, one third of all patients who visited an Emergency Department in the United States had opioids prescribed at discharge.[69] A total of 20% of patients with pain that was not related to cancer are prescribed opioids in office-based settings. Primary care physicians including those in internal medicine and family practice, account for about half of the prescriptions of opioids for pain. There are far fewer orthopaedic surgeons than primary care physicians, but orthopaedic surgeons are just behind primary care physicians and dentists for the total amount of opioids introduced into society in the United States.[70,71]

In 2009, drug poisoning surpassed motor vehicle collisions as the leading cause of accidental death in the United States, and the vast majority were overdoses of prescription opioids.[72] Both

prescription opioid sales and deaths due to overdose have quadrupled since 1999. More than half of all deaths due to an overdose of opioids in the United States involve a prescription drug, and at least 165 000 people have died in the United States from an overdose related to prescription opioids since the millennium. There were, for instance, 18 893 such deaths in 2014. Currently, 46 people die each day from an overdose of prescription opioids in the United States.[18,73] Thus, there has been a resurgence of heroin users and sales and deaths from overdose directly related to the prescription opioid crisis. About 80% of first time heroin users misuse prescription opioids before starting with heroin.[74,75] For every death due to a prescription opioid, there are ten inpatient admissions and 32 Emergency Department visits for misuse.[76]

COMPARISON WITH THE UNITED KINGDOM AND OTHER EUROPEAN COUNTRIES

Only a few studies about opioids have been published in Europe, and these have not often distinguished between prescribed and non-prescribed drugs.[66] There is, unfortunately, an upward

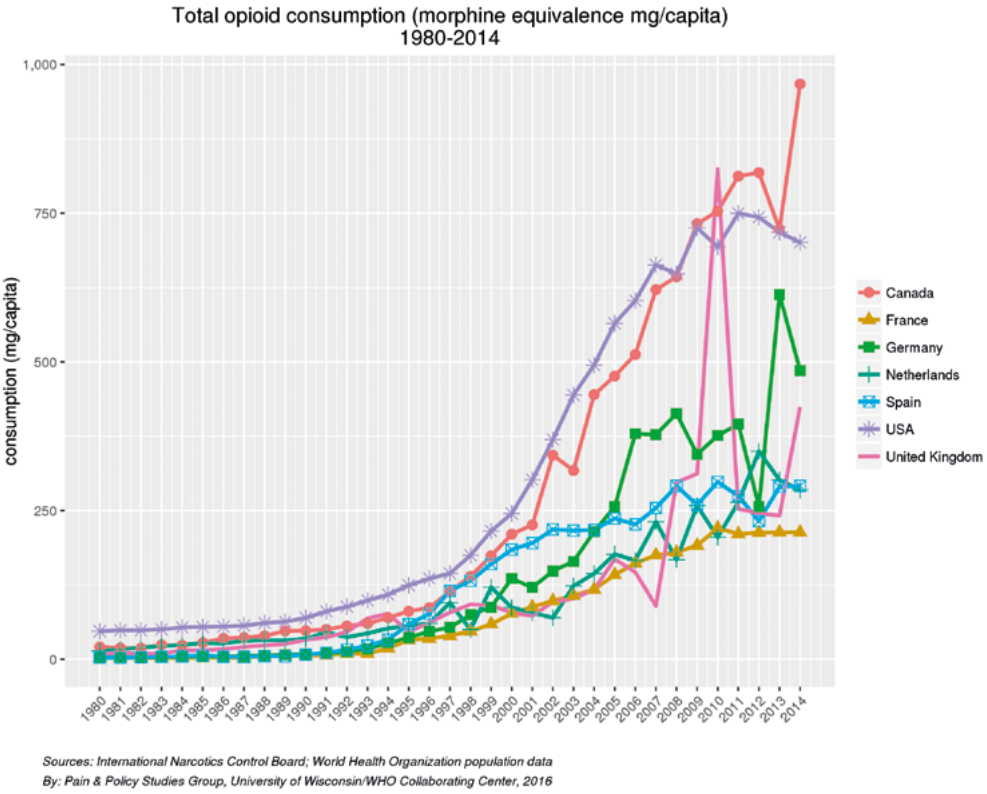

Figure 1. Graph showing total opioid consumption per country (morphine equivalence mg/capita) 1980 to 2014. Source: International Narcotics Control Board, World Health Organization (WHO) population data. Created using the Custom Consumption Graphs for Opioid Medicines[81] by: Pain and Policy Study Group, University of Wisconsin/ WHO Collaborating Center, 2016.

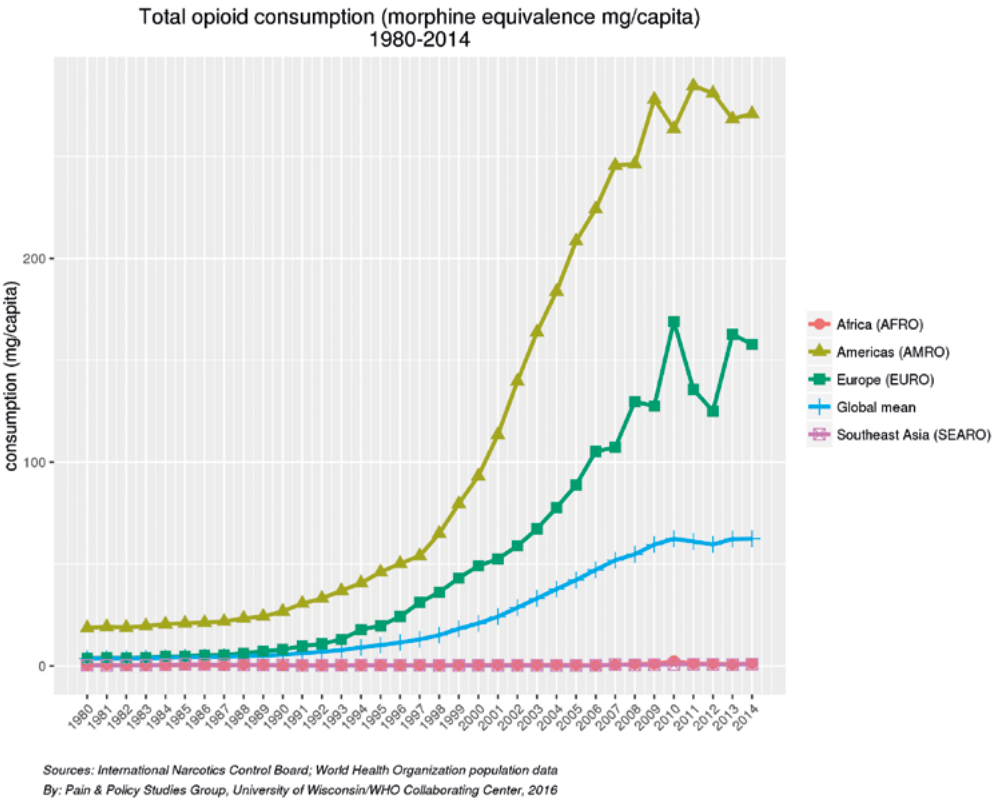

Figure 2. Graph showing total global opioid consumption (morphine equivalence mg/capita) 1980 to 2014. Source: International Narcotics Control Board, World Health Organization (WHO) population data. Created using the Custom Consumption Graphs for Opioid Medicines[81] by: Pain and Policy Study Group, University of Wisconsin/WHO Collaborating Center, 2016.

trend in the prescription of opioids and related mortality in almost all European countries, especially in the United Kingdom.[21,22,66,77] According to the International Narcotics Control Board, the consumption of prescription opioids is four times lower in Western Europe compared with the United States and Canada.[78] The European Monitoring Centre for Drugs and Drug Addiction reported 70 000 deaths due to the overdose of drugs in Europe between 2000 and 2010, and there were 6800 deaths in 2014. This is less than half of the deaths due to an overdose which were reported during this time in the United States, and the European numbers also include deaths due to overdose of a non-opioid drug and non-prescription opioids.[79] In addition, in 2014 the population of Europe was 507 million *versus* 318 million in the United States.[80] Although the general number of deaths related to prescription opioids in Europe are not known for sure, it is much lower than in the United States, but rapidly increasing in several European countries.[66] Thus, it is essential that senior members of the medical and legal professions in Europe and elsewhere learn from the mistakes made in the United States in order to avoid them.

The annual use of hydrocodone is about 60 million g in the United States compared with only 9000 g for the United Kingdom, France, Germany, Spain and the Netherlands combined.[19] The morphine equivalent for the consumption of opioids per capita in the United States was about 70 mg in 1990, 245 mg in 2000, and 701 mg in 2014. In Canada, this was 50 mg, 210 mg, and 967 mg, respectively. The equivalent numbers in the United Kingdom are lower, but increasing with concerning rapidity: 33 mg, 78 mg, and 424 mg. Germany, France, Spain and the Netherlands are experiencing similar trends in the increased consumption of opioids: between 6 mg to 34 mg (1990), 77 mg to 184 mg (2000) and 214 mg to 485 mg (2014), respectively[77] (Figs 1 and 2).[81]

The number of deaths related to drug poisoning in the United Kingdom is also far lower than in the United States, but the trends are, unfortunately, remarkably similar.[22] The total annual number of prescriptions of strong opioids (buprenorphine, fentanyl, morphine and oxycodone) for persistent pain unrelated to cancer per capita in a United Kingdom primary care setting increased by almost 60% between 2000 and 2010, with a 50% increase in mean annual days of supply per patient.[39] Nowadays, prescriptions for tramadol and oxycodone in particular are increasing in the United Kingdom.[82]

In the Netherlands, fentanyl, oxycodone and tramadol were the most commonly prescribed opioids in 2013. Nearly 8% of adults aged > 20 years, compared with about 25% in the United States used prescription opioids in 2013.[66]

As mentioned above, prescriptions of the ostensibly mild-opioid, tramadol, are increasing in Europe and it is among the most commonly prescribed opioids in the United Kingdom and the Netherlands. Deaths related to tramadol in the United Kingdom doubled between 2009 and 2012 and surpassed those related to heroin in Northern Ireland. *The Wall Street Journal* recently published a disturbing article about the ominous increase of tramadol addiction in the developing world.[66,83]

PAIN RELIEF

Nociception versus pain

The traditional biomedical model of illness assumes a direct relationship between nociception and pain. The limits of the biomedical model are consistent throughout orthopaedic surgery. There are many examples: patients with greater pain from arthritis are expected to have more degenerative changes on radiographs, but they do not. Psychosocial factors rather than pathophysiology are the major determinant of the intensity of symptoms. Increased depression prior to lumbar spinal surgery is associated with a poorer outcome three months post-operatively.[84] Increased limitation of movement of the fingers after volar plate fixation of a distal radial fracture is associated with increased catastrophic thinking.[85] Patients with greater self-efficacy (a psychological construct indicating agency and ability to adapt to adversity) are more likely to return to sports after anterior cruciate ligament reconstruction.[86] An increased intensity of pain after a steroid injection for trigger finger was associated with increased symptoms of depression.[87] In both total hip and knee arthroplasty, lower mental health status has been shown to be associated with worse outcomes.[88,89]

The shortcomings of the biomedical model and increasing evidence that psychological factors are key determinants of symptoms for a given nociception have led to the wider adoption of the biopsychosocial model of illness.[7,90] This emphasises the complex interplay of biological, psychological, cultural, and social factors on symptoms. Surgeons are familiar with some of the psychosocial mediators between nociception and pain, such as secondary gain. They may be less familiar with the influence of depression, the tendency to misinterpret or over-interpret nociception, as in catastrophic thinking, heightened concerns about illness, and social and cultural factors on behaviour in relation to an illness.

Most patients in countries other than the United States and Canada take little or no opioid analgesics after musculoskeletal trauma or surgery.[91,92] Patients in the United States take one of the strongest oral opioid analgesics available post-operatively for a fracture of the ankle. In the Netherlands, patients recovering from this form of surgery take acetaminophen, but the intensity of the pain and satisfaction with pain relief are comparable.[11] It seems that when a Dutch person breaks their ankle and has surgery, they think: "this is going to hurt", but in the United States they think: "why am I hurting?". The lesson is that resilience affords such effective pain relief that we need to make sure we do nothing to undermine or diminish it.

When we have pain, the normal response is to feel protective and prepare for the worst ("this will never go away", "it will only get worse"). This normal human thought process, called catastrophic thinking, is intended to protect us from greater damage; but most of our daily pains are not related to damage, creating a counterproductive 'false alarm'. We learn to modulate or turn off this alarm when we work out, play sports, or adapt to permanent impairment.[93] These same processes are triggered by actions intended to improve health, whether those actions address the pathophysiology or not. In research contexts this is referred to as the placebo effect and in daily life, it is labeled resilience.[9]

Opioid-centric pain management

Programmes for the management of pain which concentrated on the use of opioids represented a major step backwards. Opioids are not the most effective analgesic medication, particularly for persistent pain, and they are dangerous.[23,41,49,94-96] Patients who take more opioids have greater intensity of pain and less satisfaction with pain relief, 24 hours post-operatively for a fracture independent of nociception, and thus independent of the type or number of fractures or the days since injury or surgery.[12,13] Patients who continue to use opioids one to two months post-operatively for musculoskeletal trauma have more psychological distress, less effective coping strategies, a greater intensity of pain and a magnitude of symptoms compared with those who do not take opioids, again irrespective of nociception.[14] Another study found that opioid users were less satisfied with pain relief after various orthopaedic operations.[11]

There is much evidence of the extensive physiological and non-physiological adverse effects of taking opioids, such as hyperalgesia, hypogonadism, depression, misuse, overdose, increased risk of falls and fractures, death, and poorer quality of life.[33,95,97-100] The misuse of opioids pre-operatively is associated with considerable morbidity and mortality after orthopaedic surgery.[101]

Opioids are often prescribed when interventions to address stress and distress are more advisable. Patients still taking opioids one or two months post-operatively for trauma in the United

States have more symptoms of depression and post-traumatic stress disorder.[14] Those who report greater pain and disability are prescribed more analgesics.[100,102,103] Patients most at risk for opioid-related harm due to psychosocial issues or a previous history of substance misuse are more likely to be prescribed opioids and in dangerously high doses.[94,104] Inpatients who take more opioids have more pain.[12,13] The ultimate analgesic after musculoskeletal surgery is resilience, greater self-efficacy in response to pain; the sense that everything is on course and will turn out well. More effective coping strategies can be learned and practiced.

Effective coping strategies

The wide variation in the intensity of pain and satisfaction with pain relief for a given nociception, combined with the evidence that these variations are best accounted for by psychosocial factors, directs us to evidence-based interventions for helping patients learn and practice coping strategies, including interventions based on cognitive behavioural therapy and its derivatives. There is growing evidence that effective coping strategies, better mood, and less stress allow a more effective relief of pain than biomedical factors such as operative technique, analgesia or associated medications.[105]

In patients with a fracture of the radial head, simple coaching in the clinic addressing coping strategies immediately increased the range of movement.[106] A reduction in catastrophic thinking resulted in fewer symptoms and less disability in patients with low back pain.[107,108]

PRACTICAL STEPS

Standardised prescription protocols

The American Academy of Orthopaedic Surgeons has released a statement with strategies for the safer and more effective relief of pain in the United States.[109] This included protocols for the prescription of opioids intended to depersonalise discussions about pain relief and make it easier to limit the number of prescriptions. The upper limit of prescription in these strategies is far more than the average patient uses in the United States, let alone the rest of the world, so there can be no doubt that this is an adequate amount of opioids.[110,111] The amount of opioids in these strategies can almost certainly be reduced. An example of the potentially remarkable impact of such a departmental policy can be found in the paper by Stanek et al.[112] Surgeons elsewhere in the world who use far fewer opioids than in the United States should consider putting upper limits on opioids consistent with regional practice. They should not raise the amount of opioids prescribed to the levels used in the United States strategies which are intended to diminish opioid use to pre-epidemic levels or lower.

General principles

Only one doctor should provide opioids. The care of patients who take opioids prior to surgery, including methadone or buprenorphine/naloxone (Suboxone; Indivior Inc., Richmond, Virginia), should be coordinated by both the primary doctor and the doctor prescribing opioids. Patients should be weaned off opioids and have all psychosocial stress factors identified and treated prior to surgery. Orthopaedic surgeons should not treat persistent pain. Disproportionate pain (too much

or too long) suggests unaddressed stress, distress or less effective coping strategies. Orthopaedic surgeons treat acute pain that is expected to improve over hours and should not use extended release opioids.

Continuing education

Doctors should understand the risks of addiction and death when prescribing opioids. With the exception of those dying of cancer, patients should use as few opioids as possible for as short a time as possible. All doctors should be familiar with the verbal and non-verbal signs of psychological distress and ineffective coping strategies; and with tools that screen for risk for substance misuse, stress, distress, and less effective coping strategies and they should be familiar with the available treatments and have experts readily available for referral.

Communication strategies

The foundation of the effective relief of pain is expert communication. There is much evidence about the best verbal and non-verbal techniques for relieving stress and bolstering resilience. Surgeons and their team would benefit from efforts to prescribe, practice, and continuously improve these strategies. Since the communication strategies of surgeons are usually not as well honed as their technical skills, this will take time, practice, and persistence. We surgeons need to do our part, but we might consider adding highly effective communicators to our team so as not to rely on our own less effective communication strategies.

Make sure that patients know you care about their comfort. A simple question like: "What did you take for pain relief after your surgery?" can get the conversation started. Answers that indicate strong resilience can be reinforced. When patients are upset by the realisation that surgery will cause pain or if it prompts the memory of a difficult recovery from another operation or injury, it is time to consider the psychosocial factors.

A phone call to patients post-operatively can put them at ease. For patients having trouble with pain relief, consider asking: "Does the surgery hurt more than you expected?". Be silent while he or she gathers her thoughts, as a way to demonstrate care and concern while reminding them why they have pain, which relieves the sense that something is wrong.

In conclusion, the general public and the medical and legal professions in Europe and the rest of the world need to be careful not to make the same mistakes made in the United States and Canada. Opioids relieve pain, but they are addictive and dangerous and do not provide peace of mind. Resilience is the best form of pain relief. Pain is generally managed in the rest of the world without the use of opioids. That is a much better strategy and worth preserving.

REFERENCES

1. Van Zee A. The promotion and marketing of oxycontin: commercial triumph, public health tragedy. *Am J Public Health*. 2009;99(2):221-227.
2. Kolodny A, Courtwright DT, Hwang CS, et al. The prescription opioid and heroin crisis: a public health approach to an epidemic of addiction. *Annual review of public health*. 2015;36:559-574.
3. US General Accounting Office. Prescription Drugs: OxyContin Abuse and Diversion and Efforts to Address the Problem. 2003; http://www.gao.gov/new.items/d04110.pdf. Accessed March 21, 2017.
4. Clarke TC, Nahin RL, Barnes PM, Stussman BJ. Use of Complementary Health Approaches for Musculoskeletal Pain Disorders Among Adults: United States, 2012. *Natl Health Stat Report*. 2016(98):1-12.
5. Institute of Medicine (US) Committee on Advancing Pain Research C, and Education. In: *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*. Washington (DC)2011.
6. Pizzo PA, Clark NM. Alleviating suffering 101--pain relief in the United States. *N Engl J Med*. 2012;366(3):197-199.
7. Vranceanu AM, Bachoura A, Weening A, Vrahas M, Smith RM, Ring D. Psychological factors predict disability and pain intensity after skeletal trauma. *J Bone Joint Surg Am*. 2014;96(3):e20.
8. Severeijns R, Vlaeyen JW, van den Hout MA, Weber WE. Pain catastrophizing predicts pain intensity, disability, and psychological distress independent of the level of physical impairment. *Clin J Pain*. 2001;17(2):165-172.
9. Menendez ME, Ring D. Factors Associated with Greater Pain Intensity. *Hand Clin*. 2016;32(1):27-31.
10. Veehof MM, Trompetter HR, Bohlmeijer ET, Schreurs KM. Acceptance- and mindfulness-based interventions for the treatment of chronic pain: a meta-analytic review. *Cogn Behav Ther*. 2016;45(1):5-31.
11. Helmerhorst GT, Lindenhovius AL, Vrahas M, Ring D, Kloen P. Satisfaction with pain relief after operative treatment of an ankle fracture. *Injury*. 2012;43(11):1958-1961.
12. Bot AG, Bekkers S, Arnstein PM, Smith RM, Ring D. Opioid use after fracture surgery correlates with pain intensity and satisfaction with pain relief. *Clin Orthop Relat Res*. 2014;472(8):2542-2549.
13. Nota SP, Spit SA, Voskuyl T, Bot AG, Hageman MG, Ring D. Opioid Use, Satisfaction, and Pain Intensity After Orthopedic Surgery. *Psychosomatics*. 2015;56(5):479-485.
14. Helmerhorst GT, Vranceanu AM, Vrahas M, Smith M, Ring D. Risk factors for continued opioid use one to two months after surgery for musculoskeletal trauma. *J Bone Joint Surg Am*. 2014;96(6):495-499.
15. Moore D. Heroin: A brief history of unintended consequences. *Times Union*2014.
16. MacLaren E. Heroin History and Statistics. 2015;2017. http://drugabuse.com/library/heroin-history-and-statistics/.
17. Rudd RA, Seth P, David F, Scholl L. Increases in Drug and Opioid-Involved Overdose Deaths - United States, 2010-2015. *MMWR Morb Mortal Wkly Rep*. 2016;65(5051):1445-1452.
18. Centers for Disease Control and Prevention (CDC). Wide-ranging online data for epidemiologic research (WONDER). 2016; https://wonder.cdc.gov/. Accessed March 21, 2017.
19. International Narcotics Control Board (INCB). Estimated world requirements of narcotic drugs in grams for 2016; October update. 2016; http://www.incb.org/documents/Narcotic-Drugs/Status-of-Estimates/2016/EstOct16.pdf. Accessed March 21, 2017.
20. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain*. 2006;10(4):287-333.
21. Schubert I, Ihle P, Sabatowski R. Increase in opiate prescription in Germany between 2000 and 2010: a study based on insurance data. *Dtsch Arztebl Int*. 2013;110(4):45-51.
22. Giraudon I, Lowitz K, Dargan PI, Wood DM, Dart RC. Prescription opioid abuse in the UK. *Br J Clin Pharmacol*. 2013;76(5):823-824.

23. Beauchamp GA, Winstanley EL, Ryan SA, Lyons MS. Moving beyond misuse and diversion: the urgent need to consider the role of iatrogenic addiction in the current opioid epidemic. *Am J Public Health*. 2014;104(11):2023-2029.

24. Davis CS, Carr D. Physician continuing education to reduce opioid misuse, abuse, and overdose: Many opportunities, few requirements. *Drug Alcohol Depend*. 2016;163:100-107.

25. Bohnert AS, Valenstein M, Bair MJ, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA*. 2011;305(13):1315-1321.

26. Wisniewski AM, Purdy CH, Blondell RD. The epidemiologic association between opioid prescribing, non-medical use, and emergency department visits. *Journal of addictive diseases*. 2008;27(1):1-11.

27. The National Center on Addiction and Substance Abuse at Columbia University (CASA). Under the counter. The diversion and abuse of controlled prescription drugs in the U.S. 2005; https://www.centeronaddiction.org/sites/default/files/Under-the-counter-the-diversion-and-abuse-of-controlled-prescription-drugs-in-the-us_0.pdf. Accessed December 4, 2017.

28. Chapman CR, Lipschitz DL, Angst MS, et al. Opioid pharmacotherapy for chronic non-cancer pain in the United States: a research guideline for developing an evidence-base. *The journal of pain : official journal of the American Pain Society*. 2010;11(9):807-829.

29. Inciardi JA, Surratt HL, Cicero TJ, Beard RA. Prescription opioid abuse and diversion in an urban community: the results of an ultrarapid assessment. *Pain Med*. 2009;10(3):537-548.

30. Inciardi JA, Surratt HL, Lugo Y, Cicero TJ. The Diversion of Prescription Opioid Analgesics. *Law Enforc Exec Forum*. 2007;7(7):127-141.

31. Cicero TJ, Kurtz SP, Surratt HL, et al. Multiple Determinants of Specific Modes of Prescription Opioid Diversion. *J Drug Issues*. 2011;41(2):283-304.

32. Porter J, Jick H. Addiction rare in patients treated with narcotics. *N Engl J Med*. 1980;302(2):123.

33. Noble M, Treadwell JR, Tregear SJ, et al. Long-term opioid management for chronic noncancer pain. *Cochrane Database Syst Rev*. 2010(1):CD006605.

34. The American Academy of Pain Medicine and the American Pain Society. The use of opioids for the treatment of chronic pain. A consensus statement from the American Academy of Pain Medicine and the American Pain Society. *Clin J Pain*. 1997;13(1):6-8.

35. Portenoy RK, Foley KM. Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. *Pain*. 1986;25(2):171-186.

36. Fishbain DA, Cole B, Lewis J, Rosomoff HL, Rosomoff RS. What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant drug-related behaviors? A structured evidence-based review. *Pain medicine (Malden, Mass)*. 2008;9(4):444-459.

37. Martell BA, O'Connor PG, Kerns RD, et al. Systematic review: opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction. *Annals of internal medicine*. 2007;146(2):116-127.

38. Boscarino JA, Rukstalis MR, Hoffman SN, et al. Prevalence of prescription opioid-use disorder among chronic pain patients: comparison of the DSM-5 vs. DSM-4 diagnostic criteria. *Journal of addictive diseases*. 2011;30(3):185-194.

39. Zin CS, Chen LC, Knaggs RD. Changes in trends and pattern of strong opioid prescribing in primary care. *Eur J Pain*. 2014;18(9):1343-1351.

40. Boudreau D, Von Korff M, Rutter CM, et al. Trends in long-term opioid therapy for chronic non-cancer pain. *Pharmacoepidemiology and drug safety*. 2009;18(12):1166-1175.

41. Manchikanti L, Helm S, 2nd, Fellows B, et al. Opioid epidemic in the United States. *Pain Physician*. 2012;15(3 Suppl):ES9-38.

42. Chou R, Turner JA, Devine EB, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Annals of internal medicine*. 2015;162(4):276-286.

43. da Costa BR, Nuesch E, Kasteler R, et al. Oral or transdermal opioids for osteoarthritis of the knee or hip. *Cochrane Database Syst Rev*. 2014(9):CD003115.

44. Chaparro LE, Furlan AD, Deshpande A, Mailis-Gagnon A, Atlas S, Turk DC. Opioids compared with placebo or other treatments for chronic low back pain: an update of the Cochrane Review. *Spine (Phila Pa 1976)*. 2014;39(7):556-563.

45. Oshlack B, Chasin M, Minogue JJ, Kaiko RF. Controlled release oxycodone compositions. In: Google Patents; 1999.

46. Ausness RC. Role of Litigation in the Fight against Prescription Drug Abuse. *W Va L Rev*. 2013;116:1117.

47. Meier B. In Guilty Plea, OxyContin Maker to Pay $600 Million. *The New York Times*2007.

48. Federation of State Medical Boards of the US. Model guidelines for the use of controlled substances for the treatment of pain: A policy document of the Federation of State Medical Boards of the United States. 1998; http://www.painpolicy.wisc.edu/sites/www.painpolicy.wisc.edu/files/model_0.pdf. Accessed December 4, 2017.

49. Kotecha MK, Sites BD. Pain policy and abuse of prescription opioids in the USA: a cautionary tale for Europe. *Anaesthesia*. 2013;68(12):1210-1215.

50. Brennan F, Carr DB, Cousins M. Pain management: a fundamental human right. *Anesthesia and analgesia*. 2007;105(1):205-221.

51. Cousins MJ, Lynch ME. The Declaration Montreal: access to pain management is a fundamental human right. *Pain*. 2011;152(12):2673-2674.

52. Campbell JN. APS 1995 presidential address. Pain Forum 5:85–88; 1996.

53. Phillips DM. JCAHO pain management standards are unveiled. Joint Commission on Accreditation of Healthcare Organizations. *JAMA*. 2000;284(4):428-429.

54. Wallace AS, Freburger JK, Darter JD, Jackman AM, Carey TS. Comfortably numb? Exploring satisfaction with chronic back pain visits. *Spine J*. 2009;9(9):721-728.

55. Yanni LM, McKinney-Ketchum JL, Harrington SB, et al. Preparation, confidence, and attitudes about chronic noncancer pain in graduate medical education. *Journal of graduate medical education*. 2010;2(2):260-268.

56. The National Center on Substance Abuse at Columbia University. *Missed Opportunity: National Survey Of Primary Care Physicians And Patients On Substance Abuse*. National Center on Substance Abuse at Columbia University, New York;2000.

57. Mezei L, Murinson BB. Pain education in North American medical schools. *The journal of pain : official journal of the American Pain Society*. 2011;12(12):1199-1208.

58. Keller CE, Ashrafioun L, Neumann AM, Van Klein J, Fox CH, Blondell RD. Practices, perceptions, and concerns of primary care physicians about opioid dependence associated with the treatment of chronic pain. *Substance abuse*. 2012;33(2):103-113.

59. Watt-Watson J, McGillion M, Hunter J, et al. A survey of prelicensure pain curricula in health science faculties in Canadian universities. *Pain research & management*. 2009;14(6):439-444.

60. International Narcotics Control Board (INCB). Opioid Consumption Maps. 2009-2016; https://ppsg.medicine.wisc.edu/. Accessed November 2016, 2016.

61. Florence CS, Zhou C, Luo F, Xu L. The Economic Burden of Prescription Opioid Overdose, Abuse, and Dependence in the United States, 2013. *Med Care*. 2016;54(10):901-906.

62. Centers for Disease Control and Prevention (CDC). Opioid Painkiller Prescribing. 2014; http://www.cdc.gov/vitalsigns/opioid-prescribing/. Accessed November, 2016.

63. Substance Abuse and Mental Health Services Administration. Results from the 2012 National Survey on Drug Use and Health: Summary of National Findings and Detailed Tables. 2013; http://archive.samhsa.gov/data/NSDUH/2012SummNatFindDetTables/Index.aspx. Accessed March 21, 2017.

64. Crane EH. Emergency Department Visits Involving Narcotic Pain Relievers. In: *The CBHSQ Report*. Rockville (MD)2013-2015.

65. IMS Health. National Prescription Audit; Top 25 Medicines by Dispensed Prescriptions (U.S.). 2012; https://www.imshealth.com/files/web/Corporate/News/Top-Line Market Data/US_Top_25_Medicines_Dispensed_Prescriptions.pdf. Accessed November, 2016.

66. van Amsterdam J, van den Brink W. The Misuse of Prescription Opioids: A Threat for Europe? *Curr Drug Abuse Rev*. 2015;8(1):3-14.

67. World Health Organization (WHO). WHO's cancer pain ladder for adults. 2016; http://www.who.int/cancer/palliative/painladder/en/. Accessed November, 2016.

68. Wunsch H, Wijeysundera DN, Passarella MA, Neuman MD. Opioids Prescribed After Low-Risk Surgical Procedures in the United States, 2004-2012. *JAMA*. 2016;315(15):1654-1657.

69. Mazer-Amirshahi M, Mullins PM, Rasooly I, van den Anker J, Pines JM. Rising opioid prescribing in adult U.S. emergency department visits: 2001-2010. *Acad Emerg Med*. 2014;21(3):236-243.

70. Daubresse M, Chang HY, Yu Y, et al. Ambulatory diagnosis and treatment of nonmalignant pain in the United States, 2000-2010. *Med Care*. 2013;51(10):870-878.

71. Centers for Disease Control and Prevention (CDC). Opioid Overdose; Prescribing Data. 2016; http://www.cdc.gov/drugoverdose/data/prescribing.html. Accessed November, 2016.

72. Paulozzi LJ. Prescription drug overdoses: a review. *J Safety Res*. 2012;43(4):283-289.

73. Centers for Disease Control and Prevention (CDC) NVSS, Mortality File. Number and age-adjusted rates of drug-poisoning deaths involving opioid analgesics and heroin: United States, 2000–2014. 2014; http://www.cdc.gov/nchs/data/health_policy/AADR_drug_poisoning_involving_OA_Heroin_US_2000-2014.pdf. Accessed March 21, 2017.

74. Jones CM. Heroin use and heroin use risk behaviors among nonmedical users of prescription opioid pain relievers - United States, 2002-2004 and 2008-2010. *Drug Alcohol Depend*. 2013;132(1-2):95-100.

75. Centers for Disease Control and Prevention (CDC). Vital signs: overdoses of prescription opioid pain relievers, United States, 1999–2008. *MMWR Morbidity and Mortality Weekly Report* 2011; http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6043a4.htm. Accessed November, 2016.

76. Centers for Disease Control and Prevention (CDC). Opioid Overdose; Data. 2016; http://www.cdc.gov/drugoverdose/data/index.html. Accessed November, 2016.

77. The Pain & Policy Studies Group (PPSG). Opioid Consumption Data. 2016; http://www.painpolicy.wisc.edu/opioid-consumption-data. Accessed November, 2016.

78. International Narcotics Control Board (INCB). *Narcotic drugs technical report: Estimated world requirements for 2015 - statistics for 2013.* New York: United Nations;2015.

79. European Monitoring Centre for Drugs and Drug Addiction. Perspectives on drugs; Preventing overdose deaths in Europe. 2016; http://www.emcdda.europa.eu/topics/pods/preventing-overdose-deaths. Accessed November, 2016.

80. Population Reference Bureau (PRB). 2014 World Population Data Sheet. 2016; http://www.prb.org/pdf14/2014-world-population-data-sheet_eng.pdf. Accessed November, 2016.

81. The Pain & Policy Studies Group (PPSG). Custom Consumption Graphs for Opioid Medicines. 2017; https://ppsg-chart.medicine.wisc.edu/. Accessed March 21, 2017.

82. Ruscitto A, Smith BH, Guthrie B. Changes in opioid and other analgesic use 1995-2010: repeated cross-sectional analysis of dispensed prescribing for a large geographical population in Scotland. *Eur J Pain*. 2015;19(1):59-66.

83. Scheck J. Tramadol: The Opioid Crisis for the Rest of the World. *The Wall Street Journal*2016.

84. Sinikallio S, Aalto T, Airaksinen O, et al. Depression is associated with poorer outcome of lumbar spinal stenosis surgery. *Eur Spine J*. 2007;16(7):905-912.

85. Teunis T, Bot AG, Thornton ER, Ring D. Catastrophic Thinking Is Associated With Finger Stiffness After Distal Radius Fracture Surgery. *J Orthop Trauma*. 2015;29(10):e414-420.

86. Webster KE, Feller JA, Lambros C. Development and preliminary validation of a scale to measure the psychological impact of returning to sport following anterior cruciate ligament reconstruction surgery. *Phys Ther Sport*. 2008;9(1):9-15.

87. Julka A, Vranceanu AM, Shah AS, Peters F, Ring D. Predictors of pain during and the day after corticosteroid injection for idiopathic trigger finger. *J Hand Surg Am*. 2012;37(2):237-242.

88. Anakwe RE, Jenkins PJ, Moran M. Predicting dissatisfaction after total hip arthroplasty: a study of 850 patients. *J Arthroplasty*. 2011;26(2):209-213.

89. Heck DA, Robinson RL, Partridge CM, Lubitz RM, Freund DA. Patient outcomes after knee replacement. *Clin Orthop Relat Res*. 1998(356):93-110.

90. Vranceanu AM, Barsky A, Ring D. Psychosocial aspects of disabling musculoskeletal pain. *J Bone Joint Surg Am*. 2009;91(8):2014-2018.

91. Lindenhovius AL, Helmerhorst GT, Schnellen AC, Vrahas M, Ring D, Kloen P. Differences in prescription of narcotic pain medication after operative treatment of hip and ankle fractures in the United States and The Netherlands. *J Trauma*. 2009;67(1):160-164.

92. Carragee EJ, Vittum D, Truong TP, Burton D. Pain control and cultural norms and expectations after closed femoral shaft fractures. *Am J Orthop (Belle Mead NJ)*. 1999;28(2):97-102.

93. Sullivan MJL. The Pain Catastrophizing Scale. 2009. http://sullivan-painresearch.mcgill.ca/pdf/pcs/PCSManual_English.pdf.

94. Weisberg D, Stannard C. Lost in translation? Learning from the opioid epidemic in the USA. *Anaesthesia*. 2013;68(12):1215-1219.

95. Eriksen J, Sjogren P, Bruera E, Ekholm O, Rasmussen NK. Critical issues on opioids in chronic non-cancer pain: an epidemiological study. *Pain*. 2006;125(1-2):172-179.

96. Dhalla IA, Persaud N, Juurlink DN. Facing up to the prescription opioid crisis. *BMJ*. 2011;343:d5142.

97. Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. *Pain Physician*. 2011;14(2):145-161.

98. Angst MS, Clark JD. Opioid-induced hyperalgesia: a qualitative systematic review. *Anesthesiology*. 2006;104(3):570-587.

99. Manchikanti L, Vallejo R, Manchikanti KN, Benyamin RM, Datta S, Christo PJ. Effectiveness of long-term opioid therapy for chronic non-cancer pain. *Pain Physician*. 2011;14(2):E133-156.

100. Deyo RA, Von Korff M, Duhrkoop D. Opioids for low back pain. *BMJ*. 2015;350:g6380.

101. Menendez ME, Ring D, Bateman BT. Preoperative Opioid Misuse is Associated With Increased Morbidity and Mortality After Elective Orthopaedic Surgery. *Clin Orthop Relat Res*. 2015;473(7):2402-2412.

102. Ip HY, Abrishami A, Peng PW, Wong J, Chung F. Predictors of postoperative pain and analgesic consumption: a qualitative systematic review. *Anesthesiology*. 2009;111(3):657-677.

103. Turk DC, Okifuji A. What factors affect physicians' decisions to prescribe opioids for chronic noncancer pain patients? *Clin J Pain*. 1997;13(4):330-336.

104. Sullivan MD, Howe CQ. Opioid therapy for chronic pain in the United States: promises and perils. *Pain*. 2013;154 Suppl 1:S94-100.

105. Vranceanu AM, Jupiter JB, Mudgal CS, Ring D. Predictors of pain intensity and disability after minor hand surgery. *J Hand Surg Am*. 2010;35(6):956-960.

106. Teunis T, Thornton ER, Guitton TG, Vranceanu AM, Ring D. Coaching of patients with an isolated minimally displaced fracture of the radial head immediately increases range of motion. *J Hand Ther*. 2016;29(3):314-319.

107. Wertli MM, Burgstaller JM, Weiser S, Steurer J, Kofmehl R, Held U. Influence of catastrophizing on treatment outcome in patients with nonspecific low back pain: a systematic review. *Spine (Phila Pa 1976)*. 2014;39(3):263-273.

108. Wertli MM, Eugster R, Held U, Steurer J, Kofmehl R, Weiser S. Catastrophizing-a prognostic factor for outcome in patients with low back pain: a systematic review. *Spine J*. 2014;14(11):2639-2657.

109. American Academy of Orthopaedic Surgeons (AAOS). Opioid Use, Misuse, and Abuse in Orthopaedic Practice. 2015; http://www.aaos.org/uploadedFiles/PreProduction/About/Opinion_Statements/advistmt/1045 Opioid Use, Misuse, and Abuse in Practice.pdf. Accessed November, 2016.

110. Rodgers J, Cunningham K, Fitzgerald K, Finnerty E. Opioid consumption following outpatient upper extremity surgery. *J Hand Surg Am*. 2012;37(4):645-650.

111. Kim N, Matzon JL, Abboudi J, et al. A Prospective Evaluation of Opioid Utilization After Upper-Extremity Surgical Procedures: Identifying Consumption Patterns and Determining Prescribing Guidelines. *J Bone Joint Surg Am*. 2016;98(20):e89.

112. Stanek JJ, Renslow MA, Kalliainen LK. The effect of an educational program on opioid prescription patterns in hand surgery: a quality improvement program. *J Hand Surg Am*. 2015;40(2):341-346.

7

GENERAL DISCUSSION
CONCLUSIONS
SUMMARY

GENERAL DISCUSSION

People can rapidly adapt to their environment.[1-3] Yet, the power of mutual ideas or customs (culture) in a society can be so binding, that unfamiliar behaviors seem peculiar, even when they are favorable. Some cultural differences in the world are obvious, others are obscure or concealed on the subculture level. For example, it was difficult to build a habit of seat-belt use in the 1980s, while nowadays it would feel strange to go without one.[4,5] This thesis identified opportunities to learn from cultural differences (e.g. prescription habits or satisfaction with pain relief), even when cultures appear rather similar at first hand.

Effective pain relief is complex. Individuals experience different pain intensity for similar nociception, and react differently to analgesics. There is currently no perfect instrument to measure nociception (the pathophysiology of actual or potential tissue damage). Nor is there an ideal medication that can treat every pain effectively without unwanted side-effects, and development of such a pill is unlikely. The experience in the US and Canada confirms that over-reliance on opioids for pain relief can lead to misuse and overdose deaths. It is often difficult to change existing practice patterns. Scientific research is key in changing or avoiding disadvantageous practices. We should develop pain relief strategies that use as few opioids as possible and appropriately dispose of unused opioids.

Cultural differences in the prescription of opioid pain medications

Chapter 2 documented dramatic differences in prescription habits between the United States of America and the Netherlands. These cultural differences can help us optimize pain relief. Among patients with hip fractures, 85% of American and 58% of Dutch patients were prescribed opioids during hospitalization ($p < 0.001$). After discharge, 77% of American and none of the Dutch patients were prescribed opioids ($p < 0.001$). Among patients with ankle fracture, 98% of American and 64% of Dutch patients were prescribed opioids during hospitalization ($p < 0.001$). After discharge, 82% of American patients and 6% of Dutch patients were prescribed opioids ($p < 0.001$). This suggests that non-opioid pain medications, such as paracetamol (acetaminophen) and NSAIDs provide adequate pain relief for most patients.

We found that country was the strongest predictor for the prescription of opioids in both in- and outpatient setting. Therefore culture (or at least "accepted attitudes") seems to have substantial influence on prescribing habits. The Netherlands have an unfitting reputation regarding (recreational) drug use (even though the prevalence of cannabis use is twice as high in America[6]), but these findings seem to adhere to the idea that American people are more receptive to opioids. This secondary objective was not the main focus in this study, but it provides us an opportunity to understand the origin of the differences.

These results are consistent with other studies of cultural or ethnic differences in pain relief.[7-11] Eighty percent of American patients were dissatisfied with pain control after intramedullary rod fixation of a femoral shaft fracture, compared to 8% of Vietnamese patients, despite the fact that American patients received much more narcotic analgesia (30 mg/kg vs. 1 mg/kg). Only 4% of American patients felt they had an accurate impression of how much a femur fracture would hurt,

compared to 76% of the Vietnamese patients. More than half of the American patients felt there had to be some other explanation than the fracture to explain the severity of their pain.[9] Another study found that American women expected labor to be more painful than Dutch women, and received significantly greater amounts of pain medication.[8] These dramatic cultural differences in opioid use and pain experience raise important opportunities for helping people get and stay comfortable.

In future studies, it would be useful to measure differences in opioid prescription habits in more countries. This way more robust conclusions can be drawn. Especially including countries in different cultures would gain insight in the amount of prescriptions, and how patients manage their pain. For instance, comparing oriental countries with western countries might show even greater differences. Although we think our results are representative of the prescriptions habits in the US and the Netherlands, a multi-centered study per country would provide us with greater uniformity, and a better way to compare countries, instead of hospitals.

Satisfaction with pain relief

Chapter 2 could not address whether Dutch patients (or patients using fewer opioids) suffer more than American patients (or patients using more opioids). In Chapter 3 we prospectively studied pain intensity and satisfaction with pain relief between Dutch and American patients on the first postoperative day and at the time of suture removal after surgical treatment of an ankle fracture. Dutch patients were as satisfied with tramadol or paracetamol alone after ankle fracture surgery compared to oxycodone for American patients. One day after surgery, 17% of Dutch patients used strong opioids and 33% used no opioids at all while 100% of American patients (100%) used strong opioid pain medication. At the time of suture removal (about two weeks after surgery), only 13% of Dutch patients were taking a weak opioid (tramadol) and 50% were taking no medication, compared to 63% of American patients who were still taking strong opioids. Patients that did not use opioids and Dutch patients had lower pain intensity and equivalent satisfaction with pain relief compared to patients that used opioids and American patients respectively. Nationality was the best predictor of pain intensity the day after surgery (Americans had higher pain intensity).

Some studies document the effectiveness of non-opioid analgesia after surgery, but very few compared this with opioid pain medications. In the US, a prospective study of patients undergoing primary total hip arthroplasty showed lower mean pain intensity during the first 24 hours among patients using non-opioid compared to opioid analgesia.[12] A 2015 Cochrane review compared NSAIDs, among other combinations, to opioids after acute soft tissue injury (i.e. sprains). They concluded that, although quality of evidence was low, there were no differences in pain scores between the groups. Return to function and adverse events were in favor of the NSAIDs group.[13]

There is also evidence that intake of more opioids correlates with greater pain irrespective of the degree of nociception, and that self-efficacy and better mood are the most effective pain relievers.[14,15] Opioids may be stronger pain relievers than NSAIDs or paracetamol, but they might cloud the mind and hinder effective coping strategies, and they seem to be frequently misused to treat stress, distress, and less effective coping strategies with techniques based on cognitive behavioral therapy would be more effective.

Clinicians and researchers in the US might find the idea of treating major injuries or surgeries without opioids difficult to comprehend, while in the rest of the world (especially in the Netherlands) a comparison between non-opioids and strong opioids might seem like an unnecessary hazard. The next step would seem to initiate quality improvement initiatives or prospective studies, preferably randomized trials, that evaluate the ability of compassion, planning, strategies based on optimizing self-efficacy and resiliency after injury or surgery, to determine the effect on opioid intake, pain intensity, and satisfaction with pain relief. Our sense is that opioids should be used more sparingly in the United States and Canada and that the rest of the world should stick with their current strategies that make minimal use of opioids. This is important as it seems that advocates and pharmaceutical marketing are starting to have the same deleterious influence on clinicians in Europe that lead to the current crisis of opioid misuse and overdose deaths in the United States and Canada. We must avoid repeating their mistakes at all costs.

In Chapter 3, patients that did not use opioids had equivalent satisfaction with pain relief compared to patients that used opioids. In addition, half of Dutch patients were not taking pain medications two weeks after surgery and were very satisfied. In Chapter 4 we studied this in more detail. In the Netherlands, we had the opportunity to compare paracetamol with tramadol in a randomized clinical trial. We determined that satisfaction with pain relief and pain intensity with prescription of step 1 (paracetamol) was non-inferior to step 2 (paracetamol and tramadol) pain medications after extremity fracture surgery.

These results are consistent with studies of patients after general surgery or in labor.[16-18] In a Swiss cardiac surgery study, NSAIDs provided better postoperative pain relief with less side-effects compared to tramadol.[19] In India, NSAIDs are associated with lower pain intensity and reduced use of analgesics compared to tramadol in the first 24 hours after dental surgery.[20,21] Turkish children have no difference in pain scores after intravenous acetaminophen versus intravenous tramadol after adenotonsillectomy.[22] A Swedish study compared paracetamol with tramadol after hand surgery in a randomized double blind trial and found the tramadol group to report lower pain scores, but almost 20% of the patients in this group withdrew from the study due to side effects (i.e. nausea and dizziness). Paracetamol provided good analgesia and patients were more satisfied.[23] These studies support our idea that opioid pain medication is often not needed in acute pain management, and many patients (at least outside the US) can satisfactorily manage without them.

In line with others, we found associations for worst pain intensity levels and lower education, and average pain with lower mood. A systematic review found strong evidence for the association between fewer years of education and persistent pain after orthopaedic trauma.[24] We know that education on pain helps reduce pain in patients with chronic musculoskeletal pain.[25] This will probably also be beneficial in the acute pain setting. We should learn to understand patients at risk and take extra care in clear communication and anticipations. We specifically measured self-efficacy and pain-anxiety, since this was seen in other studies.[26-30] Our study was probably underpowered to detect these explicit associations, in which culture is conceivably such a strong factor. We hypothesize that baseline self-efficacy may be higher (and/or pain-anxiety lower) in Dutch patients compared to American patients. To our knowledge this has not been studied before in this setting, and here lie opportunities for future research.

Opioids are generally considered one of the strongest pain relievers available, but our results support the idea that they are often not needed. Nonsteroidal anti-inflammatory drugs (NSAIDs) are often withheld in the US, because physicians think they impede fracture healing, even though solid evidence is lacking. A recent systematic review concluded again that there is currently no solid evidence and that denying patients NSAIDs is even harmful by increasing narcotic requirements.[31] Until proven otherwise, NSAIDs should not be left aside in the management of fracture pain, especially in times of an opioid crisis.

All types of scientific research have their limitations, and even though a randomized trial is considered a strong indication of evidence, this study is no exception. Our findings may not be applicable in every setting. Patients were not blinded, and this was a single center study. Still, the purpose of this study was not to examine differences in analgesic properties, but in overall satisfaction with pain medications. Its results should encourage surgeons (and other health care providers) to pay careful attention when considering the prescription of habit forming and risky pain medications. It would be better to booster patient characteristics that help them to tolerate pain. Fracture patients are very satisfied with step 1 medications, and step 2 medications caused more side effects without providing notably better satisfaction with pain relief. The current standard in the US of step 3 medications (e.g. oxycodone) seems excessive.

Pain and pain relief are strongly psychosocially mediated.[32-35] The cultural differences documented in Chapter 2 and 3 support the idea that psychosocial factors create important opportunities for people to be more comfortable after injury or surgery. Cognitive and behavioral strategies in particular merit attention. As in other studies, people that took more opioids had more pain in the previous chapters[14,36], seemingly related to less effective coping skills and more symptoms of depression and anxiety. It might be that these patients seek relieve in the medications as a resolution for their distress. Earlier studies already confirmed that psychological distress (e.g. anxiety and/or depression), less effective coping strategies and secondary gain (e.g. injury compensation) influence pain intensity and pain-related disability.[27,37-40]

Risk factors for continued opioid use

It would be useful to determine the characteristics of patients that can enhance comfort and reduce opioid intake after surgery. For instance, the influence of psychological distress, coping mechanisms, heightened illness concern, pain anxiety, etc. Efforts to enhance those characteristics in our patients would be expected to both decrease suffering, limit opioid related problems and might improve pain management beyond what is possible using medications.

Chapter 5 sought risk factors for continued use of opioid pain medications in patients one to two months after musculoskeletal trauma surgery. The strongest factor associated with continued opioid use was catastrophic thinking. Other factors associated were symptoms of pain anxiety, symptoms of depression, and symptoms of posttraumatic stress disorder. These are all signs of psychological distress. Injury or surgery related factors were not associated with continued use. Meaning, better mood and more adaptive coping strategies are helpful characteristics for patients to discontinue opioids after musculoskeletal trauma surgery. This is consistent with other studies,

showing that postoperative pain differences are best explained by preoperative psychological factors and demographics.[28,30,41]

More than a quarter of the studied patients still continued opioid intake at follow up, at which tissue healing is expected to be mostly complete. While these high numbers are known for patients after spine surgery (25% continued opioid intake at three months)[42], this amount is especially disturbing in our (acute) patient group. Requests for ongoing use of opioids, greater pain and disability than expected, and psychological distress should alert physicians to consider other aspects of pain-management, such as enhancing effective coping approaches or resiliency. Patients and surgeons may often reach for opioid pain medications as an attempt to treat (ongoing) postoperative pain, often unaware that they are actually addressing psychological distress with opioids. While instead psychological distress is more receptive to forms of psychological treatment (e.g. cognitive behavioral therapy, mindfulness, encouragement), which can even reduce opioid use.[43-47] A recent meta-analysis also found other forms of non-pharmaceutical therapies to be effective in reducing opioid consumption after total knee arthroplasty.[48]

The study comes with some limitations. First, the data used was originally collected for the purpose of another prospective study. Second, we used (validated) questionnaires for evaluation of psychological factors, but not a definite (clinically evaluated) diagnosis. Third, opioid use was self-reported and we did not measure amount of intake. Optimal use of opioid medication was therefore not addressed in this study.

Given the limitations and adverse events associated with opioid medication (and other analgesics, we should also consider other possibilities. When patients take more opioids, it is associated with greater pain, with little relation to nociception.[14,36,41,49] Patients that continue opioid intake after nociception is mostly resolved (weeks to months after surgery) have less effective coping strategies and more stress, as found in Chapter 5. This strengthens the hypothesis that opioids might be used in an attempt to treat psychological stress or less effective coping strategies. Bearing in mind that about a quarter of all the American adults used prescription opioids in 2013, compared to only 8% in the Netherlands[50], we should be more attentive to psychological stress, lower mood and less effective coping strategies, and consider these opportunities to booster resiliency as management for pain.

Some coping strategies or mindsets are better at relieving pain than others. We know that psychosocial treatment models can reduce pain and opioid use.[47,51-53] However, there is currently no model for the treatment of traumatic musculoskeletal pain other than pharmaceutical, and herein lies an opportunity to improve post-operative pain and disability (and therefore surgical outcome). Early recognition of risk factors can improve treatment safety and efficacy by decreasing opioid use, and bolstering active pain relief. Future research is needed to address the effects of using a biopsychosocial treatment model in musculoskeletal trauma patients.

Epidemic Prescription Opioid Misuse and Overdose Deaths

Chapter 2 to 5 showed apparent differences in prescription of opioid medications in musculoskeletal trauma between two western cultures, but also risk factors for its use. Chapter 6 reviewed how and

why opioid prescriptions led to an epidemic use of prescription opioids that developed in the US and Canada, and how to stop or prevent this from happening in Europe. Most European surgeons (and other physicians) are not aware of this opioid epidemic and its subsequent consequences. Ask your colleagues and chances are they are not even aware that most fracture patients in the US and Canada are prescribed opioids. In the US, it is now recognized that the opioid epidemic (with its misuse and overdose deaths) was driven largely by the increase in prescriptions by healthcare providers.[54-59] We are dealing with patients and handling their pain every day, yet most colleagues in Europe seem oblivious to the fact that sales, rates of misuse, overdose, and death of prescription opioids quadrupled since the millennium, and people die on a daily basis because of prescription opioids in the US.[60-62]

As described in Chapter 6, opioid consumption is still four times lower in Western Europe compared to the US, but the overall trend (including mortality) is alarmingly similar and almost all European countries are following in the footsteps of the US and Canada.[50,63-66] Nowadays, especially tramadol and oxycodone prescriptions are increasing in Europe, and tramadol related mortality is becoming a serious problem.[50,67,68]

Treatment of pain became a human right.[69-71] Patients deserve effective attention to pain, but care should be taken as to how this is implemented. Pursuing testimonies of advocates, industries, commissions and organizations that pain must be treated, preferably with opioids and without the fear iatrogenic addiction, proved dangerous. Nowadays, we are unfortunately relying too much on opioids and the biomedical model as the mainstay for pain management.[55] The limits of the biomedical model (assuming a direct correspondence between nociception and pain) can be found consistently throughout orthopaedic surgery: Patients with minimal pain but extensible pathophysiology, and on the other side of the spectrum patients with unexpected amounts of pain. Evidence that psychological factors are crucial elements for pain intensity and magnitude of limitations for a given nociception, is continuously gaining and have led to the acceptance of the biopsychosocial model.[35,72] This thesis contributes to this adaptation as well. There is growing evidence that effective coping strategies, better mood, and less stress are more effective pain relievers than biomedical factors such as operative technique, analgesia, or medications.[27] Things that surgeons can do to help patients in this should not be underestimated; bonding with patients, taking a genuine interest in them and convey empathy and compassion. The things we say and do are powerful and can enhance resiliency. Practical steps to reduce opioid prescriptions should focus on effective communication strategies, standardized prescription protocols, adequate education and ongoing pain should be treated by experienced teams. In some countries, surgeons are not responsible for the prescription of outpatient pain medications. Regardless, it is important for surgeons in all countries to help improve the safety and efficacy of pain relief. How we discuss pain and who we choose to offer surgery for pain are key elements of our culture's pain relief strategy.

Europe and the rest of the world need to be careful not to make the same mistakes made in the US and Canada. Most of the world effectively relieves pain using very few opioids. We should learn from errors and success. Opioids relieve nociception, but they do not offer the most effective pain reliever: peace of mind.

CONCLUSIONS

Pain is an expected aspect of recovery from fracture and surgery. Yet, differences in the perception of pain, prescriptions of pain medications, response to pain medication, and satisfaction with pain relief confront us with an enormous challenge in managing pain. There is no perfect approach. Every form of pain management has its advantages and disadvantages. The optimal form of analgesic treatment available should reduce pain with the least amount of harm. The differences between cultures in managing pain can be used to our advantage and we should learn from best practices. This thesis showed that opioids are used frequently in fracture patients after surgery in the United States. It also showed effective pain relief is achieved without opioids, particularly outside of the United States and Canada, and patients are satisfied with safer pain medications such as acetaminophen. Greater opioid intake is continuously associated with greater pain. In addition, ongoing use of opioid pain medication after established healing of musculoskeletal trauma are signs of psychological distress (e.g. depression, post-traumatic stress, and catastrophic thinking) rather than injury or surgery related factors. We seem to be misdiagnosing and mistreating the psychosocial aspects of recovery. Prescription opioid consumption and misuse took on epidemical proportions in the US and Canada, and although Europe is at risk of making the same mistakes, it is not too late. Errors are nutrition for progress. Pain-management can benefit especially from enhancing effective coping strategies.

Opioids are habit forming and deadly. Most patients don't need opioids or are equally satisfied with safer medications after surgery for an extremity fracture. When opioids are used, it should be in the weakest form for the shortest time possible, and mostly for sleep. People need to know how to safely dispose of unused pills so they are not diverted and misused. We often think we need to treat pain with pills, but culture has proved we can do better than that.

REFERENCES

1. Field Y, Boyle EA, Telis N, et al. Detection of human adaptation during the past 2000 years. *Science*. 2016;354(6313):760-764.
2. Sabeti PC, Schaffner SF, Fry B, et al. Positive natural selection in the human lineage. *Science*. 2006;312(5780):1614-1620.
3. Max DT. How Humans Are Shaping Our Own Evolution. In. *National Geographic*. Vol April. Washington, D.C.2017.
4. Leichter H. Saving lives and protecting liberty: a comparative study of the seat-belt debate. *J Health Polit Policy Law*. 1986;11(2):323-344.
5. Kidd DG, McCartt AT, Oesch NJ. Attitudes toward seat belt use and in-vehicle technologies for encouraging belt use. *Traffic Inj Prev*. 2014;15(1):10-17.
6. UNODC Statistics. Annual prevalence, Cannabis. 2017; https://data.unodc.org/, 2017.
7. Green CR, Anderson KO, Baker TA, et al. The unequal burden of pain: confronting racial and ethnic disparities in pain. *Pain Med*. 2003;4(3):277-294.
8. Senden IP, van du Wetering MD, Eskes TK, Bierkens PB, Laube DW, Pitkin RM. Labor pain: a comparison of parturients in a Dutch and an American teaching hospital. *Obstet Gynecol*. 1988;71(4):541-544.
9. Carragee EJ, Vittum D, Truong TP, Burton D. Pain control and cultural norms and expectations after closed femoral shaft fractures. *Am J Orthop (Belle Mead NJ)*. 1999;28(2):97-102.
10. Meints SM, Miller MM, Hirsh AT. Differences in Pain Coping Between Black and White Americans: A Meta-Analysis. *J Pain*. 2016;17(6):642-653.
11. Mossey JM. Defining racial and ethnic disparities in pain management. *Clin Orthop Relat Res*. 2011;469(7):1859-1870.
12. Post ZD, Restrepo C, Kahl LK, van de Leur T, Purtill JJ, Hozack WJ. A prospective evaluation of 2 different pain management protocols for total hip arthroplasty. *J Arthroplasty*. 2010;25(3):410-415.
13. Jones P, Dalziel SR, Lamdin R, Miles-Chan JL, Frampton C. Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury. *Cochrane Database Syst Rev*. 2015(7):CD007789.
14. Bot AG, Bekkers S, Arnstein PM, Smith RM, Ring D. Opioid use after fracture surgery correlates with pain intensity and satisfaction with pain relief. *Clin Orthop Relat Res*. 2014;472(8):2542-2549.
15. Menendez ME, Ring D. Factors Associated with Greater Pain Intensity. *Hand Clin*. 2016;32(1):27-31.
16. Kaur Makkar J, Jain K, Bhatia N, Jain V, Mal Mithrawal S. Comparison of analgesic efficacy of paracetamol and tramadol for pain relief in active labor. *J Clin Anesth*. 2015;27(2):159-163.
17. Mitchell A, van Zanten SV, Inglis K, Porter G. A randomized controlled trial comparing acetaminophen plus ibuprofen versus acetaminophen plus codeine plus caffeine after outpatient general surgery. *J Am Coll Surg*. 2008;206(3):472-479.
18. Mitchell A, McCrea P, Inglis K, Porter G. A randomized, controlled trial comparing acetaminophen plus ibuprofen versus acetaminophen plus codeine plus caffeine (Tylenol 3) after outpatient breast surgery. *Ann Surg Oncol*. 2012;19(12):3792-3800.
19. Immer FF, Immer-Bansi AS, Trachsel N, et al. Pain treatment with a COX-2 inhibitor after coronary artery bypass operation: a randomized trial. *Ann Thorac Surg*. 2003;75(2):490-495.
20. Gopalraju P, Lalitha RM, Prasad K, Ranganath K. Comparative study of intravenous Tramadol versus Ketorolac for preventing postoperative pain after third molar surgery--a prospective randomized study. *J Craniomaxillofac Surg*. 2014;42(5):629-633.

21. Jain AD, Vsm R, Ksn SB, Km S, Tewathia N. A Comparative Assessment of Postoperative Analgesic Efficacy of Lornoxicam versus Tramadol after Open Reduction and Internal Fixation of Mandibular Fractures. *Craniomaxillofac Trauma Reconstr*. 2017;10(3):171-174.

22. Uysal HY, Takmaz SA, Yaman F, Baltaci B, Basar H. The efficacy of intravenous paracetamol versus tramadol for postoperative analgesia after adenotonsillectomy in children. *J Clin Anesth*. 2011;23(1):53-57.

23. Rawal N, Allvin R, Amilon A, Ohlsson T, Hallen J. Postoperative analgesia at home after ambulatory hand surgery: a controlled comparison of tramadol, metamizol, and paracetamol. *Anesth Analg*. 2001;92(2):347-351.

24. Clay FJ, Watson WL, Newstead SV, McClure RJ. A systematic review of early prognostic factors for persisting pain following acute orthopedic trauma. *Pain Res Manag*. 2012;17(1):35-44.

25. Louw A, Diener I, Butler DS, Puentedura EJ. The effect of neuroscience education on pain, disability, anxiety, and stress in chronic musculoskeletal pain. *Arch Phys Med Rehabil*. 2011;92(12):2041-2056.

26. Sun EC, Darnall BD, Baker LC, Mackey S. Incidence of and Risk Factors for Chronic Opioid Use Among Opioid-Naive Patients in the Postoperative Period. *JAMA Intern Med*. 2016;176(9):1286-1293.

27. Vranceanu AM, Jupiter JB, Mudgal CS, Ring D. Predictors of pain intensity and disability after minor hand surgery. *J Hand Surg Am*. 2010;35(6):956-960.

28. Papaioannou M, Skapinakis P, Damigos D, Mavreas V, Broumas G, Palgimesi A. The role of catastrophizing in the prediction of postoperative pain. *Pain Med*. 2009;10(8):1452-1459.

29. Khan RS, Ahmed K, Blakeway E, et al. Catastrophizing: a predictive factor for postoperative pain. *Am J Surg*. 2011;201(1):122-131.

30. Theunissen M, Peters ML, Bruce J, Gramke HF, Marcus MA. Preoperative anxiety and catastrophizing: a systematic review and meta-analysis of the association with chronic postsurgical pain. *Clin J Pain*. 2012;28(9):819-841.

31. Marquez-Lara A, Hutchinson ID, Nunez F, Jr., Smith TL, Miller AN. Nonsteroidal Anti-Inflammatory Drugs and Bone-Healing: A Systematic Review of Research Quality. *JBJS Rev*. 2016;4(3).

32. Wiech K. Deconstructing the sensation of pain: The influence of cognitive processes on pain perception. *Science*. 2016;354(6312):584-587.

33. Johnson AC, Greenwood-Van Meerveld B. Stress-induced pain: a target for the development of novel therapeutics. *J Pharmacol Exp Ther*. 2014;351(2):327-335.

34. Carlino E, Benedetti F. Different contexts, different pains, different experiences. *Neuroscience*. 2016;338:19-26.

35. Vranceanu AM, Barsky A, Ring D. Psychosocial aspects of disabling musculoskeletal pain. *J Bone Joint Surg Am*. 2009;91(8):2014-2018.

36. Nota SP, Spit SA, Voskuyl T, Bot AG, Hageman MG, Ring D. Opioid Use, Satisfaction, and Pain Intensity After Orthopedic Surgery. *Psychosomatics*. 2015;56(5):479-485.

37. Meredith P, Strong J, Feeney JA. Adult attachment, anxiety, and pain self-efficacy as predictors of pain intensity and disability. *Pain*. 2006;123(1-2):146-154.

38. Meredith PJ, Strong J, Feeney JA. The relationship of adult attachment to emotion, catastrophizing, control, threshold and tolerance, in experimentally-induced pain. *Pain*. 2006;120(1-2):44-52.

39. Severeijns R, Vlaeyen JW, van den Hout MA, Weber WE. Pain catastrophizing predicts pain intensity, disability, and psychological distress independent of the level of physical impairment. *Clin J Pain*. 2001;17(2):165-172.

40. MacDermid JC, Donner A, Richards RS, Roth JH. Patient versus injury factors as predictors of pain and disability six months after a distal radius fracture. *J Clin Epidemiol*. 2002;55(9):849-854.

41. Ip HY, Abrishami A, Peng PW, Wong J, Chung F. Predictors of postoperative pain and analgesic consumption: a qualitative systematic review. *Anesthesiology*. 2009;111(3):657-677.

42. Mahowald ML, Singh JA, Majeski P. Opioid use by patients in an orthopedics spine clinic. *Arthritis Rheum*. 2005;52(1):312-321.

43. Williams AC, Eccleston C, Morley S. Psychological therapies for the management of chronic pain (excluding headache) in adults. *Cochrane Database Syst Rev*. 2012;11:CD007407.

44. Anheyer D, Haller H, Barth J, Lauche R, Dobos G, Cramer H. Mindfulness-Based Stress Reduction for Treating Low Back Pain: A Systematic Review and Meta-analysis. *Ann Intern Med*. 2017;166(11):799-807.

45. van Dessel N, den Boeft M, van der Wouden JC, et al. Non-pharmacological interventions for somatoform disorders and medically unexplained physical symptoms (MUPS) in adults. *Cochrane Database Syst Rev*. 2014(11):CD011142.

46. Rolving N, Nielsen CV, Christensen FB, Holm R, Bünger CE, Oestergaard LG. Preoperative cognitive-behavioural intervention improves in-hospital mobilisation and analgesic use for lumbar spinal fusion patients. *BMC Musculoskelet Disord*. 2016;17:217.

47. Windmill J, Fisher E, Eccleston C, et al. Interventions for the reduction of prescribed opioid use in chronic non-cancer pain. *Cochrane Database Syst Rev*. 2013(9):CD010323.

48. Tedesco D, Gori D, Desai KR, et al. Drug-Free Interventions to Reduce Pain or Opioid Consumption After Total Knee Arthroplasty: A Systematic Review and Meta-analysis. *JAMA Surg*. 2017:e172872.

49. Deyo RA, Von Korff M, Duhrkoop D. Opioids for low back pain. *BMJ*. 2015;350:g6380.

50. van Amsterdam J, van den Brink W. The Misuse of Prescription Opioids: A Threat for Europe? *Curr Drug Abuse Rev*. 2015;8(1):3-14.

51. Monticone M, Cedraschi C, Ambrosini E, et al. Cognitive-behavioural treatment for subacute and chronic neck pain. *Cochrane Database Syst Rev*. 2015(5):CD010664.

52. Chou R, Deyo R, Friedly J, et al. Nonpharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline. *Ann Intern Med*. 2017;166(7):493-505.

53. Laird KT, Tanner-Smith EE, Russell AC, Hollon SD, Walker LS. Short-term and Long-term Efficacy of Psychological Therapies for Irritable Bowel Syndrome: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol*. 2016;14(7):937-947.e934.

54. Davis CS, Carr D. Physician continuing education to reduce opioid misuse, abuse, and overdose: Many opportunities, few requirements. *Drug Alcohol Depend*. 2016;163:100-107.

55. Beauchamp GA, Winstanley EL, Ryan SA, Lyons MS. Moving beyond misuse and diversion: the urgent need to consider the role of iatrogenic addiction in the current opioid epidemic. *Am J Public Health*. 2014;104(11):2023-2029.

56. Bohnert AS, Valenstein M, Bair MJ, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA*. 2011;305(13):1315-1321.

57. Wisniewski AM, Purdy CH, Blondell RD. The epidemiologic association between opioid prescribing, non-medical use, and emergency department visits. *J Addict Dis*. 2008;27(1):1-11.

58. The National Center on Addiction and Substance Abuse at Columbia University (CASA). Under the counter. The diversion and abuse of controlled prescription drugs in the U.S. 2005; https://www.centeronaddiction.org/sites/default/files/Under-the-counter-the-diversion-and-abuse-of-controlled-prescription-drugs-in-the-us_0.pdf. Accessed December 4, 2017.

59. Chapman CR, Lipschitz DL, Angst MS, et al. Opioid pharmacotherapy for chronic non-cancer pain in the United States: a research guideline for developing an evidence-base. *J Pain*. 2010;11(9):807-829.

60. Rudd RA, Seth P, David F, Scholl L. Increases in Drug and Opioid-Involved Overdose Deaths - United States, 2010-2015. *MMWR Morb Mortal Wkly Rep*. 2016;65(5051):1445-1452.

61. Centers for Disease Control and Prevention (CDC). Wide-ranging online data for epidemiologic research (WONDER). 2016; https://wonder.cdc.gov/. Accessed March 21, 2017.

62. Centers for Disease Control and Prevention NVSS, Mortality File. Number and age-adjusted rates of drug-poisoning deaths involving opioid analgesics and heroin: United States, 2000–2014. 2014; http://www.cdc.gov/nchs/data/health_policy/AADR_drug_poisoning_involving_OA_Heroin_US_2000-2014.pdf, 2016.

63. Schubert I, Ihle P, Sabatowski R. Increase in opiate prescription in Germany between 2000 and 2010: a study based on insurance data. *Dtsch Arztebl Int*. 2013;110(4):45-51.

64. Giraudon I, Lowitz K, Dargan PI, Wood DM, Dart RC. Prescription opioid abuse in the UK. *Br J Clin Pharmacol*. 2013;76(5):823-824.

65. The Pain & Policy Studies Group (PPSG). Opioid Consumption Data. 2016; http://www.painpolicy.wisc.edu/opioid-consumption-data. Accessed Juni 21, 2017.

66. International Narcotics Control Board. *Narcotic drugs technical report: Estimated world requirements for 2015 - statistics for 2013*. New York: United Nations;2015.

67. Ruscitto A, Smith BH, Guthrie B. Changes in opioid and other analgesic use 1995-2010: repeated cross-sectional analysis of dispensed prescribing for a large geographical population in Scotland. *Eur J Pain*. 2015;19(1):59-66.

68. Erasmus D, Scheck TP. *Erasmus's life of Origen : a new annotated translation of the prefaces to Erasmus of Rotterdam's edition of Origen's writings (1536)*. Washington, D.C.: The Catholic University of America Press; 2016.

69. Kotecha MK, Sites BD. Pain policy and abuse of prescription opioids in the USA: a cautionary tale for Europe. *Anaesthesia*. 2013;68(12):1210-1215.

70. Brennan F, Carr DB, Cousins M. Pain management: a fundamental human right. *Anesth Analg*. 2007;105(1):205-221.

71. Cousins MJ, Lynch ME. The Declaration Montreal: access to pain management is a fundamental human right. *Pain*. 2011;152(12):2673-2674.

72. Vranceanu AM, Bachoura A, Weening A, Vrahas M, Smith RM, Ring D. Psychological factors predict disability and pain intensity after skeletal trauma. *J Bone Joint Surg Am*. 2014;96(3):e20.

SUMMARY

There is substantial variation among physicians, hospitals, communities and cultures in the management of pain relief for patients after skeletal trauma. In the United States, most patients are given opioids. This thesis investigates the effects of various pain management strategies on pain relief, satisfaction with pain relief, and disability after musculoskeletal trauma. The main objectives are to 1) evaluate the differences in pain management after skeletal trauma in the Netherlands and the US, 2) test if current analgesic prescription in fracture patients is suitable, 3) find factors associated with continued use of opioids after surgery for skeletal trauma in the United States.

Chapter 2

The aim of this chapter is to determine if orthopaedic surgeons in different cultures have different prescription habits of opioids after operative treatment of skeletal trauma.

Study question: Is opioid pain medication prescribed more frequently in the United States as compared with the Netherlands after operative treatment of hip and ankle fractures?

Substantially more American than Dutch patients were prescribed opioids during hospitalization (85% versus 58% among patients with a hip fracture, and 98% versus 64% among patients with an ankle fracture). After discharge, these differences were even more striking. About 80% of all the American patients were prescribed opioids compared to none of the Dutch patients with a hip fracture and only 6% of the Dutch patients with an ankle fracture. This seems to suggests that non-opioid pain medications, such as paracetamol (acetaminophen) and NSAIDs might provide adequate pain relief for most patients. These dramatic cultural differences in opioid use and pain experience raise important opportunities for helping people get and stay comfortable.

Chapter 3

The aim of this chapter is to determine if Dutch patients and patients that do not take opioid pain medications after operative treatment of an ankle fracture are undertreated.

Study question: Is there a difference in pain and satisfaction with pain relief between American and Dutch patients after surgical treatment of an ankle fracture?

Dutch patients were as satisfied with tramadol or paracetamol alone compared to oxycodone for American patients. In addition, one day after surgery, all American patients used strong opioids, compared to 17% of Dutch patients. Two weeks after surgery, 63% of American patients were still taking strong opioids, compared to none of the Dutch. Patients that did not use opioids had lower pain intensity and equivalent satisfaction with pain relief, compared to the opioid users.

Chapter 4

The aim of this chapter is to determine if patients recovering from extremity fracture surgery are less satisfied after receiving step 1 (paracetamol) pain medication compared to step 2 (paracetamol + tramadol) pain medication.

Study question: Is patient satisfaction after prescription of step 1 pain medications non-inferior to step 2 pain medications after operative treatment of an extremity fracture?

In this randomized trial, patients in the paracetamol group (step 1) had a mean pain satisfaction score of 8.3, compared to 8.5 for the paracetamol + tramadol group (step 2), with significantly more patients experiencing adverse events in the paracetamol + tramadol group. This mean difference did not exceed the non-inferiority margin of 2.0 points, indicating that prescription of step 1 (paracetamol) was non-inferior to step 2 (paracetamol and tramadol) pain medications after extremity fracture surgery. This supports our idea that many patients (at least outside the US) can satisfactorily manage acute pain without opioids. Given that tramadol has more side effects and is potentially habit-forming, acetaminophen should be considered the mainstay for pain relief in patients recovering from extremity fracture surgery. These results should encourage surgeons to pay careful attention when considering the prescription of habit forming and risky pain medications. It would be better to bolster patient characteristics (e.g. less depression, more self-efficacy) that help them get comfortable.

Chapter 5

The aim of this chapter is to identify factors associated with ongoing use of opioid medications one to two months after operative treatment of musculoskeletal trauma.

Study question: Do psychosocial factors contribute to the use of opioid medication one to two months after operative treatment of musculoskeletal trauma to a higher extent than trauma related factors?

Risk factors associated with continued use of opioids after surgery were all signs of psychological distress: catastrophic thinking, symptoms of pain anxiety, symptoms of depression, and symptoms of posttraumatic stress disorder. Injury or surgery related factors were not associated with continued opioid use. This suggests that continued use of opioids after injury and surgery are well along in the healing process is likely a misdiagnosis and mistreatment of psychological distress and less effective coping strategies.

Chapter 6

The aim of this chapter is to determine to what extent opioid medications are prescribed in recent years in European countries, and compare this to the North American opioid crisis. European countries should learn from the mistakes made in North America and avoid repeating them.

Study question: Are European countries following the trend of the crisis of opioid misuse, overdoses, and overdose deaths in the United States and Canada and how do we prevent it?

Opioid consumption is still four times lower in Western Europe compared to the US, but the overall trend (including mortality) is alarmingly similar and almost all European countries are following in the footsteps of the US and Canada. Nowadays, especially tramadol and oxycodone prescriptions are increasing in Europe, and tramadol related mortality is becoming a serious problem. The misconceptions about opioids that created the North American opioid crisis are finding their way around the world. Evidence is mounting that the best pain relief is obtained through resilience. Opioids are often prescribed when treatments to increase resilience would be more effective. Effective communication strategies and standardized prescription protocols are key elements in reducing opioid use.

Conclusions

This thesis showed that, in spite of seemingly similar nociception (pathophysiology), there are substantial cultural differences in experiencing and managing pain after surgery of musculoskeletal trauma. The United States and Canada are in the midst of a crisis of opioid use, misuse, overdose, and deaths related to overdose. Driven largely by the increase in prescriptions by healthcare providers starting in the 1980s, this was a direct effect of overstatement of the benefits and understatement of the risks of using opioids by advocates and pharmaceutical companies. Patients and surgeons often look for opioid pain medications as a solution to treat (ongoing) postoperative pain, perhaps unaware that they are actually addressing psychological distress or less effective coping strategies with opioids. In fact, many patients (at least in the Netherlands) are equally satisfied with much safer and non-addictive pain medications after surgical treatment of musculoskeletal trauma. Evidence is gaining that effective coping strategies, better mood, and less stress are more effective pain relievers than biomedical factors such as operative technique or medications. We should make good use of these opportunities to provide better and much safer treatment options to handle pain relief.

NEDERLANDSE SAMENVATTING

PORTFOLIO

LIST OF PUBLICATIONS

DANKWOORD

CURRICULUM VITAE

NEDERLANDSE SAMENVATTING

Er bestaat een aanzienlijke variatie in de behandeling van pijn voor patiënten die een traumatisch letsel van het bewegingsapparaat hebben opgelopen tussen verschillende artsen, ziekenhuizen, samenlevingen en culturen. In de Verenigde Staten (VS) krijgen de meeste van deze patiënten opioïden ter verlichting van de pijn, terwijl in Nederland deze middelen veel minder worden voorgeschreven. Dit proefschrift onderzoekt de effecten van verschillende pijnbehandelstrategieën op de verlichting van pijn, tevredenheid met de pijnverlichting en mate van invaliditeit na trauma van het bewegingsapparaat. De belangrijkste doelstellingen hiervan zijn 1) het evalueren van de verschillen tussen Nederland en de VS in de behandeling van pijn na trauma van het bewegingsapparaat, 2) het beoordelen of de huidige, voorgeschreven pijnmedicatie geschikt is voor patiënten met fracturen, 3) het opsporen van factoren die samenhangen met aanhoudend gebruik van opioïden in de VS, nadat een operatieve behandeling van trauma van het bewegingsapparaat heeft plaatsgevonden.

Hoofdstuk 2

In dit hoofdstuk wordt onderzocht of orthopaedisch chirurgen uit verschillende culturen verschillend voorschrijfgedrag vertonen ten aanzien van patiënten die operatief behandeld worden aan een traumatisch letsel van het bewegingsapparaat. De onderzoeksvraag is: wordt in de VS vaker opioïde pijnmedicatie voorgeschreven dan in Nederland na operatieve behandeling van heup- en enkelfracturen?

Aanzienlijk meer Amerikaanse dan Nederlandse patiënten bleken opioïde pijnmedicatie voorgeschreven te hebben gekregen tijdens hun ziekenhuisopname (85% vergeleken met 58% bij patiënten met een heupfractuur en 98% vergeleken met 64% bij patiënten met een enkelfractuur). Na ontslag waren deze verschillen nog veel groter. Zo'n 80% van de Amerikaanse patiënten met een heup- of enkelfractuur kreeg opioïden voorgeschreven, vergeleken met geen van de Nederlandse patiënten met een heupfractuur en slechts 6% van de Nederlandse patiënten met een enkelfractuur. Dit lijkt te suggereren dat niet-opioïde pijnmedicatie, zoals paracetamol en NSAID's, bij de meeste patiënten voor adequate pijnstilling kan zorgen. Deze culturele verschillen in het gebruik van opioïden en de mogelijke beleving van pijn, verschaffen mogelijkheden om patiënten beter te helpen om zich comfortabel te (blijven) voelen.

Hoofdstuk 3

Om te onderzoeken of Nederlandse patiënten of patiënten die geen opioïde pijnmedicatie nemen worden onderbehandeld, wordt in dit hoofdstuk het verschil in pijn en tevredenheid met pijnstilling bestudeerd tussen Amerikaanse en Nederlandse patiënten na operatieve behandeling van een enkelfractuur.

Nederlandse patiënten waren even tevreden met het zwakwerkende opioïd tramadol of zelfs met alleen paracetamol als Amerikaanse patiënten waren met het sterkwerkende opioïd oxycodon. Eén dag na operatie gebruikten alle Amerikaanse patiënten sterke opioïde pijnstillers, vergeleken met slechts 17% van de Nederlandse patiënten. Twee weken na de operatie gebruikten 63% van

de Amerikaanse patiënten nog sterke opioïde pijnstillers, terwijl geen van de Nederlandse patiënten een opioïde pijnstiller gebruikten. Patiënten die geen opioïden gebruikten hadden een lagere pijnintensiteit en waren even tevreden met de pijnstilling als patiënten die wel opioïden gebruikten.

Hoofdstuk 4

In dit hoofdstuk onderzoeken we of patiënten die herstellen van een operatieve behandeling van een botbreuk van een ledemaat minder tevreden zijn na het krijgen van stap 1 pijnmedicatie (paracetamol) of van stap 2 pijnmedicatie (paracetamol + tramadol). De onderzoeksvraag is: Is de tevredenheid bij patiënten die herstellen van een operatie van een botbreuk van een ledemaat na het voorschrijven van stap 1 pijnmedicatie hetzelfde ('niet-inferieur') als na het voorschrijven van stap 2 pijnmedicatie?

Patiënten in de paracetamol groep (stap 1) hadden in dit gerandomiseerde onderzoek een gemiddelde pijntevredenheidscore van 8.3 vergeleken met 8.5 in de paracetamol + tramadol groep (stap 2), waarbij significant meer bijwerkingen voorkwamen in de paracetamol + tramadol groep. Dit verschil overschreed de 'niet-inferieur' grens van 2.0 punten niet, wat betekent dat het voorschrijven van stap 1 pijnmedicatie (paracetamol) niet voor minder tevredenheid zorgt dan stap 2 pijnmedicatie (paracetamol + tramadol) na operatieve behandeling van een botbreuk (van een ledemaat). Dit ondersteunt ons idee dat veel patiënten (in ieder geval buiten de VS) dit soort pijn naar tevredenheid kunnen verdragen zonder het gebruik van opioïde pijnstillers. Aangezien tramadol meer bijwerkingen had en potentieel verslavend is, zou paracetamol de voornaamste pijnstiller moeten zijn in de behandeling van pijn bij patiënten die herstellen van een operatie van een botbreuk van een ledemaat. De gevonden resultaten zouden chirurgen moeten aansporen om alert en voorzichtig te zijn als ze overwegen verslavende en risicovollere pijnmedicatie voor te schrijven. Het zou beter zijn om versterkende karaktereigenschappen van patiënten aan te moedigen, die ervoor zorgen dat ze zich comfortabeler voelen (minder somberheid, betere zelfredzaamheid).

Hoofdstuk 5

Het doel van dit hoofdstuk is om factoren te identificeren die geassocieerd zijn met aanhoudend gebruik van opioïde pijnmedicatie, één tot twee maanden na operatieve behandeling van trauma van het bewegingsapparaat. De onderzoeksvraag is: dragen psychosociale factoren, meer dan trauma-gerelateerde factoren bij aan het gebruik van opioïde pijnmedicatie één tot twee maanden na operatieve behandeling van trauma van het bewegingsapparaat?

Risicofactoren die geassocieerd zijn met aanhoudend gebruik van opioïde pijnmedicatie na operatie waren allen tekenen van psychische stress: catastrofaal denken, symptomen van pijnvrees, symptomen van depressie en symptomen van posttraumatische stress. Letsel of chirurgie-gerelateerde factoren waren niet geassocieerd met aanhoudend gebruik van opioïden. Het lijkt erop dat aanhoudend gebruik van opioïden, nadat herstel van het letsel en de operatie in de meeste gevallen al is opgetreden, wijst op de onjuiste diagnose en behandeling van psychische stress en minder effectieve coping strategieën.

Hoofdstuk 6

In dit hoofdstuk onderzoeken we in welke mate opioïde pijnstillers de afgelopen jaren in Europese landen worden voorgeschreven en of dat te vergelijken is met de Noord-Amerikaanse opioïden-crisis. Europese landen kunnen leren van de fouten die in Noord-Amerika zijn gemaakt en dit voorschrijfgedrag trachten te voorkomen.

De onderzoeksvraag in dit hoofdstuk luidt: bestaat er in Europese landen eenzelfde tendens van gebruik en misbruik van opioïden, overdoseringen en aan overdosis gerelateerde mortaliteit zoals dit in de Verenigde Staten en Canada bestaat en hoe kan dat worden voorkomen?

In West-Europa is het gebruik van opioïden vier keer lager dan in de VS en Canada, maar de algemene tendens (inclusief de mortaliteit) is verontrustend gelijkwaardig en in bijna alle Europese landen volgen de grafieken die van de VS en Canada. In Europa neemt met name het gebruik van tramadol en oxycodon toe, waarbij tramadol gerelateerde mortaliteit een serieus probleem aan het worden is. De misvattingen over opioïden die er zorg voor hebben gedragen dat in Noord-Amerika een opioïden-crisis is ontstaan, vinden inmiddels hun weg over de hele wereld. Er zijn echter aanwijzingen dat de beste vorm van pijnverlichting wordt verkregen door (psychische) weerbaarheid en veerkracht. Opioïde pijnstillers worden frequent voorgeschreven, terwijl behandelingen om deze weerbaarheid en veerkracht te vergroten effectiever zouden zijn. Effectieve communicatiestrategieën en gestandaardiseerde voorschrijf-protocollen zijn sleutelelementen voor de vermindering van het gebruik van opioïde pijnstillers.

Conclusie

Dit proefschrift laat zien dat er aanzienlijke culturele verschillen zijn in het ervaren van en omgaan met pijn na operatieve behandeling van trauma van het bewegingsapparaat, ondanks een ogenschijnlijk vergelijkbare nociceptie (pathofysiologie). De Verenigde Staten en Canada bevinden zich in een crisis van gebruik, misbruik, overdosering en overdosis gerelateerde mortaliteit van opioïde pijnmedicatie. Dit is ontstaan door toename vanaf de jaren tachtig van het aantal voorschriften door zorgverleners ten gevolge van uitlatingen van advocaten en lobbyisten van farmaceutische bedrijven, die de voordelen van het gebruik van opioïden overschatten en de risico s onderschatten. Patiënten en artsen (waaronder orthopaedisch chirurgen) grijpen vaak naar opioïde pijnstillers als oplossing voor (aanhoudende) postoperatieve pijn, terwijl ze mogelijk niet beseffen dat ze in feite een vorm van psychische stress of minder effectieve 'coping strategieën' proberen te behandelen met deze middelen. Veel patiënten (althans in Nederland) blijken net zo tevreden met veel veiligere en niet-verslavende pijnstillers na operatieve behandeling van trauma van het bewegingsapparaat. Er komt steeds meer bewijs dat effectieve coping strategieën, betere psychische gesteldheid en minder stress effectievere pijnstillers zijn dan biomedische factoren als operatietechniek of geneesmiddelen. Het zou verstandig zijn om goed gebruik te maken van de mogelijkheden die hier liggen, zodat we betere en veiligere behandelingsopties kunnen bieden voor de verlichting van pijn bij onze patiënten.

PORTFOLIO

Courses		Year
Knee, multi-ligament course	München, Germany	2018
Anterior Hip Approach	Rotterdam	2018
Advanced Trauma Life Support, refresher	Harlem Hospital Center, NYC	2017
Osteotomy course	ViaSana	2017
Hip arthroplasty	York, United Kingdom	2016
Hip arthroplasty	Radboud Ziekenhuis	2016
Medical Business Masterclass	MBM, Amsterdam	2016
AO Spine, principles	St Maartenskliniek	2015
Knee arthroscopy	UMCU	2015
Radiation/radiology course	Boerhaave	2015
Knee arthroplasty	AMC	2015
AO fracture management, principles	Davos, Switzerland	2012
Advanced Trauma Life Support	Harlem Hospital Center, NYC	2012
Laparoscopy	VuMC	2012
Good Clinical Practice (BROK)	AMC	2012
Entrepreneurship in Health and Life Sciences	AMC	2012
Acute Life support training	St. Anthonius Hospital	2011
Amsterdam Foot and Ankle Course	Participation organization, AMC	2009
Human subject protection	MGH, Boston	2007
Research Integrity and Data Management	MGH, Boston	2007
Fundamentals of Biostatistics	MGH, Boston	2007
Good Clinical Practice	MGH, Boston	2007

Presentations	
What's New in Orthopaedic Trauma. *AMC Symposium.*	2016
Stabilization of distal radius fractures with an associated comminuted radial styloid fracture via a single volar approach. *NOV Congress Annual Meeting.*	2011
Differences in prescription of narcotic pain medication after operative treatment of hip and ankle fractures in the United States and the Netherlands. Poster presentation. *Nordic Orthopaedic Federation international congress.*	2008

Review activities	
Injury	2017-18

Parameters of Esteem	
Stichting de Merel Grant *Project: Pain management after Skeletal Trauma.*	2012
NAF (The Netherland – America Foundation) Grant *Project: Harvard Medical School research internship.*	2008

Portfolio. (Continued)

Lectures	**Year**
Ankle Arthroplasty vs. Arthrodesis, AMC residency program	2017
Mortality after Hip Fractures, AMC residency program	2016
Pain Management after Extremity Fractures, Tergooi general surgery residents	2015
Proximal Humerus Fractures, AMC residency program	2015
Scaphoid Fractures, Slotervaart general surgery residents	2014
Hip Fracture Surgical Management, Slotervaart general surgery residents	2013
Tutoring	
Medical Interns and Students, AMC	2012-18
Ankle fractures, North-Holland general surgery residents	2016-17
Media mentions	
Voorwoord. *NTVO*. 2017 Dec; Vol. 24, Nr. 4.	2017
Can It Be Done—Opioid-Free Recovery? *J Bone Joint Surg Am*. 2017 Nov; 15;99(22):e123.	2017
Overmatig gebruik van opioïden. Rubriek: Let op! *Geneesmiddelenbulletin*. 2017 Oct; Jaargang 51, Nr. 10.	2017

LIST OF PUBLICATIONS

Pain Relief After Operative Treatment of an Extremity Fracture: A Noninferiority Randomized Controlled Trial
Helmerhorst GT, Zwiers R, Ring D, Kloen P.
J Bone Joint Surg Am. 2017 Nov; 99(22):1908-1915

An epidemic of the use, misuse and overdose of opioids and deaths due to overdose, in the United States and Canada: is Europe next?
Helmerhorst GT, Teunis T, Janssen SJ, Ring D.
Bone Joint J. 2017 Jul; *99-B(7):856-864*

Risk Factors for Continued Opioid Use 1 to 2 Months after Surgery for Musculoskeletal Trauma.
Helmerhorst GT, Vranceanu AM, Vrahas M, Smith M, Ring D.
J Bone Joint Surg Am. 2014 Mar; 96(6):495-9

Injury Complexity Factors Predict Heterotopic Ossification Restricting Motion after Elbow Trauma.
Wiggers JK, Helmerhorst GT, Brouwer KM, Niekel MC, Nunez F, Ring D.
Clin Orthop Relat Res. 2013 Sep; 427(7):2162-*7*

Satisfaction with Pain Relief after Operative Treatment of an Ankle Fracture.
Helmerhorst GT, Lindenhovius AL, Vrahas M, Ring D, Kloen P.
Injury. 2012 Nov; 43(11):1958-61

Orthogonal plating of intra-articular distal radius fractures with an associated comminuted radial styloid fracture via a single volar approach
Helmerhorst GT, Kloen P.
Injury. 2012 Aug; 43(8):1307-12

Predictors of diagnosis of ulnar neuropathy after surgically treated distal humerus fractures.
Wiggers JK, Brouwer KM, Helmerhorst GT, Ring D.
J Hand Surg Am. 2012 Jun; 37(6):1168-72

Differences in prescription of narcotic pain medication after operative treatment of hip and ankle fractures in the United States and the Netherlands.
Lindenhovius AL*, Helmerhorst GT*, Schnellen AC, Vrahas M, Ring D, Kloen P.
J Trauma. 2009 Jul; 67(1):160-4
**contributed equally*

Subtle Essex-Lopresti lesions: report of 2 cases.
Helmerhorst GT, Ring D.
J Hand Surg Am. 2009 Mar;34(3):436-8.

DANKWOORD

Aan de totstandkoming van dit proefschrift hebben meerderen bijgedragen en mijn dank gaat uit naar hun allen. Naast mijn dank aan alle patiënten die in de onderzoekingen hebben geparticipeerd, wil ik in het bijzonder graag de volgende personen bedanken.

Allereerst mijn promotores en co-promotor.

Promotor, prof. dr. D.C. Ring:
Dear David, thank you so much for your inspiration and your faith to look across (the) borders. Your vision, devotion and thoughtfulness encourage many, and your drive and passion are truly catching. You have the exceptional gift of pointing out the essence in the shortest amount of time. You're a great teacher and outstanding motivator. I'm sincerely grateful for your entrustment, confidence and support.

Promotor en opleider, prof. dr. G.M.M.J. Kerkhoffs:
Beste Gino, fantastische teamspeler. Dank voor je vertrouwen in mij. Dank ook voor de vrijheid en het optimisme dat je geeft. Je levert uitstekende patiëntenzorg en vervult daarin de rol van een ware pater familias. Jij geeft a.i.o's vertrouwen en ontketent gedrevenheid, bezieling en het gevoel dat ze meedoen aan de top. Ik wil je zeer hartelijk danken dat jij mijn promotor wilde zijn, maar bovenal dat ik jou als opleider heb mogen hebben. Ik zie dat als een grote eer.

Co-promotor, dr. P. Kloen:
Beste Peter, bij jou startte mijn interesse in orthopedie en trauma. Je bent daarin onmiskenbaar van grote waarde en hebt mij bijzonder veel geleerd. Van het doorploegen van de eerste klinische-status in het archief, de eerste K-draad boren op de OK, tot grote traumatologische operaties. Daarnaast ben ik door jouw connectie met David op zijn afdeling in Boston terecht gekomen. Zowel wetenschappelijk als klinisch ben ik je zeer erkentelijk voor je mentorschap. Je bent vastberaden en secuur, maar geeft tegelijkertijd ruimte en motivatie om zelf te ontwikkelen en ik wil je daarvoor zeer danken.

Overige leden van de promotiecommissie; prof. dr. D. Eygendaal, prof. dr. dr. M.W. Hollmann, prof. dr. A. van Kampen, prof. dr. M.J.M.H. Lombarts en prof. dr. M.H.J. Verhofstad: dank voor de interesse in en beoordeling van het proefschrift.

Beste co-auteurs, ik ben jullie enorm dankbaar voor de vruchtbare en zeer lonende samenwerking. Ruben Zwiers, dank voor je toewijding en je input. Zelfs invoeren van gegevens wordt leuk als je de grootste tafel van het café vol paperassen gooit en er twee bier naast zet. Een van de leukste momenten was het resultaat te zien ontstaan, waar we stiekem al van durfden te dromen. Anneluuk Lindenhovius, dank voor je medewerking en supervisie van de eigenlijke start van het project. Dank ook Teun en Stein, bijzonder interessant wat we te weten zijn gekomen door naar het grote

plaatje te kijken. Jullie waren van enorme waarde hierin. Ook Ana-Maria Vranceanu en de overige co-auteurs wil ik hartelijk danken.

Rosalie, Veerle en secretariaat orthopedie AMC, dank voor jullie administratieve hulp.

Ongelofelijk fijne collegae, ik wil jullie heel erg bedanken voor onze fijne samenwerking. AMC, Boston, Tergooi, Slotervaart en TWG. Ik prijs mijzelf zeer fortuinlijk met collegae waar ik zo goed mee kan samenwerken, maar vooral ook zoveel plezier mee heb.

Vanzelfsprekend ben ik al mijn vrienden en (schoon)familie zeer dankbaar voor de rol die jullie spelen in mijn leven. Jullie warmte, liefde en vertrouwen zijn onmisbaar en maken van het leven een feest.

Ten slotte dank ik hen die mij het meest nabij zijn en aan wie mijn dankbaarheid nooit genoeg omschreven zal kunnen worden. Lieve Theo en Moniek, paps en mams, bedankt voor jullie onzegbare liefde. In de veiligste en warmste haven opgroeien, met zo'n immense hoeveelheid aan liefde en vertrouwen is iets wat nauwelijks te bevatten is en waar ik jullie permanent dankbaar voor ben. Dank dat jullie ons alle kansen hebben geboden om op jullie schouders te staan. Katrien, grote zus; Hendrik, kleine broer; in jullie midden staan is zo ongehoord leuk. Elkaars voorbeeld zijn op zoveel manieren is werkelijk schitterend. En voorbeeld doet volgen. Wat een geluk dat jullie weer om mij heen staan, nu als paranimfen, en we gedrieën verder lopen.

Allerliefste Ruth, prachtige vrolijkerd, bedankt dat je zoveel liefde geeft en me zo aan het lachen maakt. Dank je wel voor al je steun en bemoedigingen. Samen met jou zijn is waanzinnig en schitterend.

CURRICULUM VITAE

Gijs Helmerhorst was born in Amsterdam, on the 31st of July, 1984. In 2002, he graduated from Grammar School at the St. Ignatius Gymnasium in Amsterdam. Subsequently he studied Medical Informatics until 2003, when he was admitted to Medical School at the Academic Medical Center, University of Amsterdam. During his studies, he started a research fellowship at the Department of Orthopaedic Surgery at the Academic Medical Center (supervision: dr. P. Kloen) and at Massachusetts General Hospital - Harvard Medical School, Boston, United States of America (supervision: prof. dr. D.C. Ring). The foundations of his PhD research were laid here, and in 2008 he received a NAF grant to support his research collaboration. After his graduation in 2010, he started working as a resident at the General and Orthopaedic Surgery Department at the BovenIJ hospital, Amsterdam. He completed the Good Clinical Practice course at MGH (2007) and the AMC (2012). In 2012, he was rewarded a grant from Stichting de Merel to pursue a PhD for his thesis proposal and he started his orthopaedic surgery residency in that same year. His general surgery training was completed at the Department of General Surgery at MC Slotervaart (supervision: dr. B. J. Dwars†). His orthopaedic residency commenced at the Department of Orthopaedic Surgery at the Academic Medical Center (supervision: prof. dr. C.N. van Dijk), and was continued at Tergooi Hospitals (supervision: dr. A.M.J.S. Vervest), the Academic Medical Center (supervision: prof. dr. G.M.M.J. Kerkhoffs) and MC Slotervaart (supervision: dr. H.M. van der Vis). Much of the research described in this thesis was performed during his residency, which is due to be completed by August 2018.

Gijs T.T. Helmerhorst

Pain Relief after Musculoskeletal Trauma