Head and neck muscles are the source of pain in TENSION-TYPE HEADACHES.\textsuperscript{1,2} Ibuprofen is an effective treatment.\textsuperscript{3}

Ibuprofen is an effective treatment.\textsuperscript{3}

Adults and children over 12 years of age:
Nurofen\textsuperscript{\textregistered} 200–400 mg every 4 hours to a maximum of 1200 mg/day.

Reasons for discontinuation of long-term opioid therapy in patients with and without substance use disorders
Risk factors for neuropathic pain in diabetes mellitus
Intraoperative ketamine reduces immediate postoperative opioid consumption after spinal fusion surgery in chronic pain patients with opioid dependency: a randomized, blinded trial
Acute pain management in patients with drug dependence syndrome
Management of postsurgical pain in patients treated preoperatively with opioids

Volume 12 Number 2
2017
Total Pain Solution

Moderate to moderately severe pain in adults:
- Rapid-acting, longer duration analgesia
- Acute pain
- Subacute pain
- Chronic pain

Severe, chronic intractable pain:
- Once-daily, 24-hr pain control
- Chronic non-cancer pain
- Chronic cancer pain
- Chronic non-cancer pain

Chronic intractable pain:
- Continuous 72-hour analgesia
- Chronic cancer pain
- Chronic non-cancer pain

An affordable pain portfolio, quality assured

Reference: [Insert reference text here]

Fendermal
TramHexal
TramHexal Co
Ibuprofen Forte

When acute and chronic pain present
Editorial

During my time as a “pain enthusiast” I have worked with many dedicated people who have had one simple goal: to raise the awareness and management of pain in South Africa.

The first person to “believe” was Prof Lombie Odendaal who established a small entity known as the Pain Management Society of South Africa (PMSSA). He managed to start regional discussions and meetings as well as to encourage new “converts” Prof Helgaard Meyer then took charge of what we now know as PainSA with the first annual Congress held at Mount Grace under his watch. Since then we have seen a growth in member numbers, an increase in Annual Congress attendance and an increase in the duration of the Congress from 2 to 3 days.

Following in from the “old school” including Dr Johan Smuts and myself the “new generation of enthusiasts are at the helm. Dr Sean Chetty is the 2017 Annual PainSA Congress organiser. I wish Sean, the President, and the Congress Organising Committee much success with 2017 at Century City. I hope to meet and speak to many of you at the Congress.

Dr. Milton Raff
BSc MB ChB FFA(SA)

Dear Readers

We are proud to contribute to the pursuit of knowledge in the field of pain medicine by bringing together experts in the field to share their expertise with you. The mission of the Society is: ‘To improve the management of pain in all its aspects in Southern Africa’, and through this annual congress we facilitate the sharing of knowledge, skills, and experiences of our understanding of pain, its assessment, and its management.

The annual Pain SA Congress creates a collegiate environment for this sharing to occur within, and more importantly, between the various clinical, academic, social, and spiritual domains that encompass effective pain management. The Congress is the Society’s premier educational event, and we have seen it grow in attendance annually, which is an encouraging sign to us as a Society, that we are addressing a need in the healthcare space. Together with the regional pain academy meetings, Pain SA is leading the charge to improve access to quality education in pain management in South Africa.

The Society also is actively looking at ways to promote original research in the field of pain. In 2017 the society awarded its first research scholarship for post-graduate research in pain. In addition, together with our sponsors, we are also launching research prizes for the best oral research presentation and the best poster presentation at the 2017 congress.

The organizing committee has been working hard over the past 14 months to develop a congress programme that will be both stimulating and enjoyable for all our participants. We hope you are attending the congress and use the opportunity to network with like-minded individuals in South Africa.

Best regards
Sean Chetty

All correspondence to the editor should be addressed to: raffs@iafrica.com
9 RESEARCH PAPER
Reasons for discontinuation of long-term opioid therapy in patients with and without substance use disorders
Travis I. Lovejoy, Benjamin J. Morasco, Michael I. Demidenko, Thomas H.A. Meath, Joseph W. Frank, Steven K. Dobscha

18 TOPICAL REVIEW
Risk factors for neuropathic pain in diabetes mellitus
Harry L. Hébert, Abirami Veluchamy, Nicola Torrance, Blair H. Smith

27 RESEARCH PAPER
Intraoperative ketamine reduces immediate postoperative opioid consumption after spinal fusion surgery in chronic pain patients with opioid dependency: a randomized, blinded trial
Rikke Vibeke Nielsen, Jonna Storm Fomsgaard, Hanna Siegel, Robertas Martusevicius, Lone Nikolajsen, Jørgen Berg Dahl, Ole Mathiesen

35 PAIN CLINICAL UPDATES
Acute pain management in patients with drug dependence syndrome
Jane Quinlan, Felicia Cox

43 2017 GLOBAL YEAR AGAINST PAIN AFTER SURGERY
Management of postsurgical pain in patients treated preoperatively with opioids
Hazem A. Ashmawi
TarginAct®
oxycodone HCl / naloxone HCl

CHANGING THE FACE OF PAIN

Unique ORAL combination for acute and chronic pain 1,2

Effective analgesia with improved tolerability profile 1,3


For full prescribing information refer to the package insert approved by the medicines regulatory authority.

Mundipharma (PTY) LTD, PO BOX 23162 CLAREMONT, 7705. TEL: 021 671 5251 FAX: 021 671 5256
www.mundipharma.co.za


56 TarginAct® 5 mg/2.5 mg Prolonged Release Tablets. Each tablet contains 5 mg oxycodone hydrochloride and 2.5 mg naloxone hydrochloride. Registration No: 403.9/0045
56 TarginAct® 10 mg/5 mg Prolonged Release Tablets. Each tablet contains 10 mg oxycodone hydrochloride and 5 mg naloxone hydrochloride. Registration No: 402.8/0046
56 TarginAct® 20 mg/10 mg Prolonged Release Tablets. Each tablet contains 20 mg oxycodone hydrochloride and 10 mg naloxone hydrochloride. Registration No: 402.8/0047
56 TarginAct® 40 mg/20 mg Prolonged Release Tablets. Each tablet contains 40 mg oxycodone hydrochloride and 20 mg naloxone hydrochloride. Registration No: 402.8/0048
When science and technology meet.

Xefo®rapid is a tablet with a delivery method that has comparable pharmacokinetics to an intramuscular injection, resulting in rapid relief from pain and inflammation.  

- Effective relief of pain and inflammation  
- Rapid onset of action for effective pain relief  
- Good tolerability and safety profile  
- Balanced COX-1 and COX-2


**Pain Relief**

**Bridging the gap from pain to relief**

---

### Workshop 1

**Venue:** Hall C  

**09h00 – 12h30**  
**Multimodal approach for the treatment of neck and shoulder pain**  

- **Participants:** Pauline du Plessis, Latifa Firrifay  

**SESSION**

- **PART 1:**  
  - **10h30 – 11h00**  
  - **Tea Break**  

**SESSION**

- **PART 2:**  
  - **11h00 – 12h30**  
  - **Lunch**

---

### Workshop 2

**Venue:** Hall D  

**09h00 – 12h30**  
**Ultrasound Workshop for Acute Pain**

- **Co-Ordinators:** Pauline du Plessis, Latifa Firrifay  

**SESSION**

- **PART 1:**
  - **09h00 – 12h30**
- **200 Places are limited and always fill quickly. Please register early and join us for this interactive day.**

---

### Workshop 3

**Venue:** MR 11  

**09h00 – 12h30**  
**Clinical Assessment and reasoning for complex pain**

- **Co-Ordinators:** Romy Parker, Tony Madden, Tarin Penberthy  

**SESSION**

- **PART 1:**  
  - **10h30 – 11h00**  
  - **Tea Break**  

**SESSION**

- **PART 2:**  
  - **11h00 – 12h30**  
  - **Lunch**

---

**Friday 12 May 2017**

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
<th>Workshop 1</th>
<th>Workshop 2</th>
<th>Workshop 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>09h00 – 17h00</td>
<td>Registration &amp; Arrival Tea/Coffee</td>
<td>Multimodal approach for the treatment of neck and shoulder pain</td>
<td>Ultrasound Workshop for Acute Pain</td>
<td>Clinical Assessment and reasoning for complex pain</td>
</tr>
<tr>
<td>09h00 – 12h30</td>
<td><strong>Co-Ordinators</strong></td>
<td>Co-Ordinators Pauline du Plessis, Latifa Firrifay</td>
<td>Co-Ordinators Pauline du Plessis, Latifa Firrifay</td>
<td>Co-Ordinators Romy Parker, Tony Madden, Tarin Penberthy</td>
</tr>
<tr>
<td>09h00 – 12h30</td>
<td><strong>Venue:</strong> Hall C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>09h00 – 12h30</td>
<td><strong>Participants:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10h30 – 11h00</td>
<td><strong>Tea Break</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11h00 – 13h00</td>
<td><strong>Lunch</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Scientific Programme continued
#### Friday 12 May 2017

<table>
<thead>
<tr>
<th>Workshop 1</th>
<th>Workshop 2</th>
<th>Workshop 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Venue</strong></td>
<td><strong>Hall C</strong></td>
<td><strong>Hall D</strong></td>
</tr>
<tr>
<td><strong>Time</strong></td>
<td><strong>Event</strong></td>
<td><strong>Event</strong></td>
</tr>
<tr>
<td>13h30 – 15h00</td>
<td>Multimodal approach for the treatment of neck and shoulder pain</td>
<td>Co-Ordinators Pauline du Plessis Latifa Firifray</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Time</strong></th>
<th><strong>Event</strong></th>
<th><strong>Venue</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>15h00 – 15h30</td>
<td>REFRESHMENTS</td>
<td><strong>VENUE</strong> <strong>HALL C</strong></td>
</tr>
<tr>
<td>15h30 – 17h30</td>
<td>Plenary Session 1 Chair: Romy Parker</td>
<td><strong>VENUE</strong> <strong>HALL C</strong></td>
</tr>
<tr>
<td>15h30 – 16h00</td>
<td>Opening Welcome</td>
<td>Sean Chetty</td>
</tr>
<tr>
<td>16h00 – 16h30</td>
<td>Chronic widespread pain</td>
<td>Helgard Meyer</td>
</tr>
<tr>
<td>16h30 – 17h30</td>
<td>Mindfulness in general</td>
<td>Danielle Klemp</td>
</tr>
<tr>
<td>16h30 – 17h30</td>
<td>Consent in the mentally ill patient (E)</td>
<td>Kerry-Ann Louw</td>
</tr>
<tr>
<td>17h30 – 18h30</td>
<td>Evening Symposium sponsored by Takeda No Pain. No Gain. Use and Misuse of NSAIDS in sports injuries</td>
<td>Wayne Derman The Institute of Sport and Exercise Medicine (Stellenbosch University)</td>
</tr>
</tbody>
</table>

### Saturday 13 May 2017

<table>
<thead>
<tr>
<th><strong>Time</strong></th>
<th><strong>Event</strong></th>
<th><strong>Venue</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>07h00 – 08h30</td>
<td>REGISTRATION &amp; ARRIVAL TEA/COFFEE</td>
<td><strong>VENUE</strong> <strong>MR 11</strong></td>
</tr>
<tr>
<td>07h30 – 08h20</td>
<td>Breakfast Symposium sponsored by Sandoz Combination analgesics in the treatment of Pain</td>
<td>Milton Raff</td>
</tr>
<tr>
<td>08h30 – 09h00</td>
<td>Transition from acute to chronic pain after surgery</td>
<td>Ruben Naidoo</td>
</tr>
<tr>
<td>09h00 – 09h30</td>
<td>How to make pain management part of hospital culture and practice</td>
<td>Janieke van Nugteren</td>
</tr>
<tr>
<td>09h30 – 10h00</td>
<td>Placebo</td>
<td>Antonia Wadley</td>
</tr>
<tr>
<td>10h00 – 10h30</td>
<td>REFRESHMENTS</td>
<td></td>
</tr>
</tbody>
</table>
**Scientific Programme continued**

**Saturday 13 May 2017**

<table>
<thead>
<tr>
<th>VENUE</th>
<th>MR 11</th>
<th>Chair: Liz Gwyther</th>
<th>VENUE</th>
<th>HALL C</th>
</tr>
</thead>
<tbody>
<tr>
<td>10h30 – 13h00</td>
<td>Parallel Session 1</td>
<td></td>
<td>10h30 – 13h00</td>
<td>Parallel Session 2</td>
</tr>
<tr>
<td>10h30 – 11h00</td>
<td>Pain and malingering</td>
<td>Karen Theunissen</td>
<td>10h30 – 11h00</td>
<td>Post-stroke pain</td>
</tr>
<tr>
<td>11h00 – 11h30</td>
<td>Trigger what?</td>
<td>Romy Parker</td>
<td>11h00 – 11h30</td>
<td>Neuromodulation and pain</td>
</tr>
<tr>
<td>11h30 – 12h00</td>
<td>Return to work and the chronic pain patient</td>
<td>Carollyn Stirrat</td>
<td>11h30 – 12h00</td>
<td>Vitamin D deficiency – a painful reality</td>
</tr>
<tr>
<td>12h00 – 12h30</td>
<td>When nociception is not enough: What we know and what we don’t</td>
<td>Tony Madden</td>
<td>12h00 – 12h30</td>
<td>Acceptance and commitment therapy for chronic pain: Recent empirical development</td>
</tr>
<tr>
<td>12h30 – 13h00</td>
<td>CBT - How does this help the patient in pain?</td>
<td>Bernice du Plessis</td>
<td>12h30 – 13h00</td>
<td>New developments in migraine</td>
</tr>
<tr>
<td>13h00 – 14h00</td>
<td>LUNCH</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Poster presentations next to the Janssen Stand. Prize sponsored by Dr Reddy’s

<table>
<thead>
<tr>
<th>VENUE</th>
<th>MR 11</th>
<th>Chair: Tarin Penberthy</th>
<th>VENUE</th>
<th>HALL C</th>
</tr>
</thead>
<tbody>
<tr>
<td>14h00 – 14h15</td>
<td>Lumbar radiculopathy patients – One &amp; three-year results of a randomised controlled trial</td>
<td>Ina Diener</td>
<td>14h00 – 14h30</td>
<td>Pain from the joint: more than just structural damage</td>
</tr>
<tr>
<td>14h15 – 14h30</td>
<td>Neuropathic pain is common in acute/sub-acute cervico-brachial pain and can be treated effectively with neural mobilisation</td>
<td>Annalie Basson</td>
<td>14h30 – 15h00</td>
<td>Cannabinoids and pain management: The South African perspective</td>
</tr>
<tr>
<td>14h30 – 14h45</td>
<td>Pain Intensity and Depression: A Cross Sectional Descriptive study Among Women in a Developing Country</td>
<td>Vincent Adzika</td>
<td>15h00 – 15h30</td>
<td>Pain management for sports injuries in elite athletes</td>
</tr>
<tr>
<td>14h45 – 15h00</td>
<td>Poor post-operative pain management in breast surgery patients in South Africa</td>
<td>Alexa Buck</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15h00 – 15h15</td>
<td>Women’s knowledge, awareness and experience of labour epidurals in Gauteng</td>
<td>Janine Wagner</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15h15 – 15h30</td>
<td>Dispensing patterns of meprobamate-containing combination analgesics in community pharmacies in South Africa</td>
<td>Ilse Truter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15h30 – 16h00</td>
<td>REFRESHMENTS</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Scientific Programme continued
#### Saturday 13 May 2017

<table>
<thead>
<tr>
<th>VENUE</th>
<th>MR 11</th>
<th>VENUE</th>
<th>HALL C</th>
</tr>
</thead>
<tbody>
<tr>
<td>16h00 – 17h00</td>
<td>Parallel Session 3 - Free communications (continued)</td>
<td>Chair: Tarin Penberthy</td>
<td>Parallel Session 5 - Topical Symposium Sponsored by Pfizer OTC</td>
</tr>
<tr>
<td></td>
<td>The effects of graded motor imagery and its components on phantom limb pain in upper and lower limb amputees</td>
<td>Katleho Limakatso</td>
<td>Chair: Sudha Bechan</td>
</tr>
<tr>
<td>16h00 – 16h15</td>
<td>A lower than expected prevalence of pain in HIV positive patients receiving modern antiretroviral treatment</td>
<td>Guillaume Muller</td>
<td>Pauline Du Plessis</td>
</tr>
<tr>
<td>16h15 – 16h30</td>
<td>Lessons learnt: The contextual challenges of rural research</td>
<td>Cameron Reardon</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VENUE</th>
<th>HALL C</th>
</tr>
</thead>
<tbody>
<tr>
<td>17h00 – 18h00</td>
<td>Is pain management necessary and sufficient to ensure death with dignity (E)</td>
</tr>
<tr>
<td>18h00 – 18h30</td>
<td>AGM</td>
</tr>
</tbody>
</table>

- Networking dinner

### Sunday 14 May 2017

<table>
<thead>
<tr>
<th>VENUE</th>
<th>MR 11</th>
<th>VENUE</th>
<th>HALL C</th>
</tr>
</thead>
<tbody>
<tr>
<td>09h00 – 11h00</td>
<td>Parallel Session 6</td>
<td>Chair: Janieke van Nugteren</td>
<td>Parallel Session 7</td>
</tr>
<tr>
<td>09h00 – 09h30</td>
<td>Pain and sleep</td>
<td>Stella lacovides</td>
<td>Chair: Pauline du Plessis</td>
</tr>
<tr>
<td>09h30 – 10h00</td>
<td>Pain in pregnancy</td>
<td>Sudha Bechan</td>
<td>Christianne Bowens</td>
</tr>
<tr>
<td>10h00 – 10h30</td>
<td>Pain management in children</td>
<td>Michelle Meiring</td>
<td>Clint Cupido</td>
</tr>
<tr>
<td>10h30 – 11h00</td>
<td>Anxiety and post-op pain in children</td>
<td>Anusha Lachman</td>
<td>Eric Hodgson</td>
</tr>
<tr>
<td>11h00 – 11h30</td>
<td>REFRESHMENTS</td>
<td></td>
<td>Liz Gwyther</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VENUE</th>
<th>HALL C</th>
</tr>
</thead>
<tbody>
<tr>
<td>11h30 – 12h00</td>
<td>Psychiatry of pain sufferers</td>
</tr>
<tr>
<td>12h00 – 12h30</td>
<td>Social media for improved pain research dissemination and practice</td>
</tr>
<tr>
<td>12h30 – 13h00</td>
<td>Plenary Ethics Lecture: Societal impact of pain (E)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VENUE</th>
<th>HALL C</th>
</tr>
</thead>
<tbody>
<tr>
<td>13h30</td>
<td>CLOSING</td>
</tr>
<tr>
<td>12h00 – 12h30</td>
<td>Social media for improved pain research dissemination and practice</td>
</tr>
<tr>
<td>12h30 – 13h00</td>
<td>Plenary Ethics Lecture: Societal impact of pain (E)</td>
</tr>
</tbody>
</table>

- Closing
Reasons for discontinuation of long-term opioid therapy in patients with and without substance use disorders

Travis I. Lovejoy\textsuperscript{a,b,c,*}, Benjamin J. Morasco\textsuperscript{a,b}, Michael I. Demidenko\textsuperscript{a}, Thomas H.A. Meath\textsuperscript{a,d}, Joseph W. Frank\textsuperscript{e,f}, Steven K. Dobscha\textsuperscript{a,b}

Abstract
Several factors may accelerate opioid discontinuation rates, including lack of information about the long-term effectiveness of opioids for chronic pain, heightened awareness about opioid-related adverse events, closer monitoring of patients for opioid-related aberrant behaviors, and greater restrictions around opioid prescribing. Rates of discontinuation may be most pronounced in patients deemed to be “high risk.” The purpose of this study was to compare reasons for discontinuation of long-term opioid therapy (LTOT) between patients with and without substance use disorder (SUD) diagnoses receiving care within a major U.S. health care system. This retrospective cohort study assembled a cohort of Veterans Health Administration patients prescribed opioid therapy for at least 12 consecutive months who subsequently discontinued opioid therapy for at least 12 months. From this cohort, we randomly selected 300 patients with SUD diagnoses and propensity score–matched 300 patients without SUD diagnoses. A comprehensive manual review of patients’ medical records ascertained reasons for LTOT discontinuation. Most patients (85%) were discontinued as a result of clinician, rather than patient, decisions. For patients whose clinicians initiated discontinuation, 75% were discontinued because of opioid-related aberrant behaviors. Relative to patients without SUD diagnoses, those with SUD diagnoses were more likely to discontinue LTOT because of aberrant behaviors (81% vs 68%), most notably abuse of alcohol or other substances. This is the first study to document reasons for discontinuation of LTOT in a sample of patients with and without SUD diagnoses. Treatments that concurrently address SUD and chronic pain are needed for this high-risk population.

Keywords: Opioid, Chronic opioid therapy, Long-term opioid therapy, Opioid discontinuation, Substance use disorder

1. Introduction
Opioid therapy for chronic pain is common,\textsuperscript{12,17} although recent data suggest plateauing\textsuperscript{30,31} or even declining\textsuperscript{11} opioid-prescribing rates. Reduced opioid prescribing for chronic pain may be due to a combination of factors including heightened awareness of increases in opioid-related adverse events,\textsuperscript{11} lack of information on the effectiveness of long-term opioid therapy (LTOT),\textsuperscript{7} and availability of state Prescription Drug Monitoring Programs (PDMPs) to ascertain concurrent prescribing of controlled substances.\textsuperscript{51} These factors may also contribute to opioid therapy discontinuation.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

\textsuperscript{a} Center to Improve Veteran Involvement in Care, VA Portland Health Care System, Portland, OR, USA.\textsuperscript{b} Department of Psychiatry, Oregon Health & Science University, Portland, OR, USA.\textsuperscript{c} School of Public Health, Oregon Health & Science University, Portland, OR, USA.\textsuperscript{d} Center for Health System Effectiveness, Oregon Health & Science University, Portland, OR, USA.\textsuperscript{e} Center of Innovation for Veteran-Centered and Value-Driven Care, VA Eastern Colorado Health Care System, Denver, CO, USA.\textsuperscript{f} Division of General Internal Medicine, University of Colorado School of Medicine, Aurora, CO, USA

*Corresponding author. Address: Center to Improve Veteran Involvement in Care, VA Portland Health Care System, 3770 SW U.S. Veterans Hospital Rd, Mail Code: R&D 66, Portland, OR 97239, USA. Tel.: 503-220-8262 x57744; fax: 503-402-2952. E-mail address: travis.lovejoy@va.gov (T. I. Lovejoy).

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal’s Web site (www.painjournalonline.com).

PAIN 158 (2017) 526–534
© 2016 International Association for the Study of Pain
http://dx.doi.org/10.1097/j.pain.0000000000000796

526 T.I. Lovejoy et al. • 158 (2017) 526–534
was associated with longer duration on opioid therapy, higher daily doses of opioids, greater number of pain diagnoses, and tobacco use disorder diagnosis. A study of patients from a national private health network and state Medicaid found similar results, although patients who engaged in opioid misuse behaviors were less likely to discontinue LTOT.33 Despite these robust descriptions of demographic and clinical correlates of LTOT discontinuation, little is known about reasons for discontinuation of LTOT, particularly in patients at “high risk” for opioid-related adverse events.

The aim of this study was to compare reasons for discontinuation of LTOT between patients with and without SUD receiving care within a major U.S. health care system in the years after release of the 2009 and 2010 opioid therapy clinical practice guidelines. We hypothesized that patients with SUD would be more likely to discontinue LTOT because of aberrant behaviors, including illicit substance use, aberrant urine drug tests, opioid misuse, and diversion.

2. Methods

This study was approved by the Veterans Health Administration (VHA) Portland Health Care System Institutional Review Board.

2.1. Data source and sample selection

We used the VHA Corporate Data Warehouse (CDW) to identify a national cohort of VHA patients prescribed opioid therapy for all of 2011. The CDW provides comprehensive information contained in electronic medical records for all VHA patients. We defined LTOT as having been prescribed opioid therapy for the entirety of 2011, allowing prescription opioid refill gaps of no more than 30 days between the completion of an opioid prescription and a refill of the next opioid prescription. Allowing 30-day gaps accounted for delayed scheduled refills due to travel, prescription mail order delays, or other circumstances. The allowance of 30-day gaps has been used in previous studies examining discontinuation of LTOT in the VHA.1868 The mean number of days prescribed opioids in 2011 for this cohort was 351 of 365 days (SD = 17 days). From this cohort, we identified patients who discontinued LTOT—ie, had no VHA opioid prescriptions—for at least 12 consecutive months starting some time in 2012. We chose a 12-month discontinuation interval to ensure discontinuation was an intended treatment decision and not due to geographic relocation, switching care to another VHA facility, extended inpatient hospitalizations, or other reasons that may result in failure to renew an active opioid prescription. The date of the last opioid refill was used as an index date for each patient to ascertain patient sociodemographic and clinical characteristics before discontinuation. Because this study focused on discontinuation of LTOT in the context of chronic noncancer pain, we excluded patients with the following characteristics in the year before the index date: (1) the only opioid therapy prescribed was through a VHA opioid substitution program (ie, buprenorphine or methadone maintenance therapy), (2) a diagnosis of cancer, (3) enrollment in hospice or long-term care, or (4) having received surgery for which opioids may have been prescribed. We also excluded patients with no VHA contact (ie, no VHA clinical encounters or medications prescribed) or who died in the year after discontinuation, as well as nonveterans or veteran patients whose only medical care was obtained at a facility located in a U.S. territory. Figure 1 details sample selection and the number of patients meeting each exclusion criterion.

2.2. Propensity score matching

The aim of this study was to compare reasons for opioid discontinuation between patients with and without SUDs. From the cohort of 7247 patients who discontinued LTOT in 2012, 1868 (26%) had an SUD diagnosis based on ICD-9-CM codes in the year before the index date. These included diagnoses of abuse or dependence for alcohol, amphetamines, cannabis, cocaine, hallucinogens, opioids, sedatives/hypnotics, polysubstance use, or other/unknown substances. For the purpose of this study, an SUD diagnosis was defined as having an ICD-9-CM code for an SUD diagnosis linked to a medical visit encounter. A medical visit encounter included encounters with any treating clinician—physician, physician assistant, nurse, psychologist, social worker, or other clinical provider—and could be for the purpose of medical, mental health, or other health care needs. We randomly sampled 300 patients with an SUD diagnosis for subsequent chart review. An additional 300 patients without an SUD diagnosis were matched as controls using propensity score matching procedures to ensure a similar distribution of sociodemographic and clinical characteristics to the sample of patients with an SUD diagnosis. We used this matching procedure to lessen the likelihood of confounding biases that may arise due to underlying differences between patients with and without SUD diagnoses. We first modeled the probability that a patient would receive an SUD diagnosis in the year before the index date using logistic regression that included sociodemographic and clinical characteristics before discontinuation. Because this study focused on discontinuation of LTOT in the context of chronic noncancer pain, we excluded patients with the following characteristics in the year before the index date: (1) the only opioid therapy prescribed was through a VHA opioid substitution program (ie, buprenorphine or methadone maintenance therapy), (2) a diagnosis of cancer, (3) enrollment in hospice or long-term care, or (4) having received surgery for which opioids may have been prescribed. We also excluded patients with no VHA contact (ie, no VHA clinical encounters or medications prescribed) or who died in the year after discontinuation, as well as nonveterans or veteran patients whose only medical care was obtained at a facility located in a U.S. territory. Figure 1 details sample selection and the number of patients meeting each exclusion criterion.
receiving an SUD diagnosis in the year before the index date. Matching was conducted using a nearest neighbor matching algorithm.\textsuperscript{44} For each patient with an SUD diagnosis, this procedure selects the non-SUD diagnosis patient with the smallest absolute difference in propensity score. Standardized differences were then used to assess covariate balance between the matched groups.\textsuperscript{40} and kernel density plots of propensity scores were used to test for sufficient overlap.\textsuperscript{21} The online Supplemental Digital Content lists, for each variable in the propensity model, the standardized differences between patients with and without an SUD diagnosis in the full sample of \(N = 7247\), and the matched sample of \(N = 600\) (available online at http://links.lww.com/PAIN/A370).

2.3. Chart review tool development, pilot testing, and coding fidelity

After sample selection, 4 experienced chart reviewers (one internist, one psychiatrist, and 2 psychologists) with expertise treating SUD and non-SUD VHA patients receiving LTOT for chronic noncancer pain developed a chart review coding tool using group consensus procedures that identified reasons for LTOT discontinuation (see Supplemental Digital Content for the chart review tool, available online at http://links.lww.com/PAIN/A371). To refine the content of the chart review tool and review process, the developers pilot tested the tool on a randomly selected sample of 60 patients from the cohort of patients who discontinued LTOT who were not included in the analytic sample. A research associate (RA) experienced with reviewing and coding VHA medical charts for opioid-related studies was trained in coding procedures for this study. After training, the RA and study principal investigator double-coded 25 randomly selected medical charts of patients not included in the analytic sample. We used a benchmark of kappa \(>0.70\) or simple agreement \(>95\%) for binary variables as measures of adequate intercoder agreement.\textsuperscript{29} The average kappa across all study variables was 0.88 (average percent simple agreement = 97\%) and all study variables met our a priori standard of acceptable reliability.

The RA subsequently reviewed and coded the 600 charts from the analytic patient sample over a 4-month period. To ensure ongoing fidelity to the coding scheme, the study principal investigator double-coded 60 randomly selected charts (10\%). The average kappa across all variables in the study phase was 0.85 (average percent simple agreement = 98\%) and all study variables met our standard of acceptable reliability.

2.4. Variables

2.4.1. Administrative data abstraction

Data abstracted from the CDW included demographic characteristics (age, sex, race/ethnicity) and rurality of a patient’s place of residence based on rural–urban commuting area codes.\textsuperscript{37} Medical comorbidities were assessed with the Elkhaurer Comorbidity Measure,\textsuperscript{18} where higher scores indicate a greater number of comorbidities. Veterans Health Administration service-connected disability status, which is disability granted to veteran patients as a result of military service–related injuries or traumas, was obtained. Data did not permit ascertainment of specific medical conditions for which patients were service connected. Diagnoses of SUDs, mental health disorders, and chronic pain conditions were obtained for the 12 months before discontinuation of LTOT. Opioid-related variables assessed over the 12 months before discontinuation included type(s) of opioid(s) prescribed, average daily dose of opioids in morphine equivalents, and number of opioid prescribers in the 12 months before discontinuation. Finally, we identified patients prescribed benzo diazepines in the 12 months before discontinuation.

2.4.2. Chart review

Review of patients’ electronic medical records identified reasons for discontinuation of LTOT. Reasons were grouped by patient- and clinician-initiated reason (see Table 1 for discontinuation reasons listed in the chart review coding tool). Clinician-initiated reasons were grouped into 3 categories to further assess discontinuation themes. The first, “Aberrant Behaviors,” included aberrant urine drug test results, suspected use of alcohol or other substances, opioid misuse, opioid diversion, and nonadherence to plan of care (eg, failing to present for a urine drug test when asked). The second, “Patient Safety Concerns,” included previous opioid overdose, high risk for an opioid-related adverse event, and contraindication with other prescribed medication. The final category, “Lack of Efficacy,” included opioids not indicated for type of chronic pain, opioids not decreasing pain, and opioids not improving functioning.

Patients could be coded as having multiple patient- or clinician-initiated discontinuation reasons (eg, a patient may have tested positive for an illicit substance and have been suspected of diverting opioid medication). However, all reasons were either patient initiated or clinician initiated in this sample. Opioid discontinuation reasons did not span both categories.

2.5. Statistical analysis

We utilized \(\chi^2\) tests of association for categorical variables and independent sample \(t\) tests for continuous variables to compare demographic and clinical characteristics between patients with and without SUD diagnoses. We next used binary logistic regression to examine associations of SUD status with reasons for opioid discontinuation. Adjusted models controlled for variables associated with opioid discontinuation in previous studies.\textsuperscript{49} These included sociodemographic characteristics (age, sex, race/ethnicity, and rurality), mental health diagnoses (depressive disorders, bipolar disorders, post-traumatic stress disorder (PTSD) other anxiety disorders, and psychotic disorders), tobacco use disorder diagnosis, Elkhaurer Comorbidity score, number of pain diagnoses, type of opioid prescribed, average daily dose of opioids in morphine equivalents in the year before the index date, benzodiazepine prescription in the year before the index date, and number of opioid prescribers in the year before the index date. The combination of both propensity score matching and covariate regression techniques is commonly used and provides estimates that are generally more robust to model misspecification and residual confounding when compared with either method in isolation.\textsuperscript{42,44}

3. Results

The study sample comprised 300 patients with an SUD diagnosis in the year before opioid therapy discontinuation and 300 propensity score–matched patients without an SUD diagnosis. Similar to the population of veterans prescribed opioid therapy through VHA,\textsuperscript{38,49} the study sample had a mean age of 55 years, was predominantly male (95\%), non-Hispanic white (72\%), and resided in urban locations (73\%). High proportions of patients in this sample received diagnoses for mental health disorders in the year before discontinuation of LTOT, including PTSD (31\%), anxiety disorders other than PTSD (25\%), and depressive disorders (25\%). Nearly half (45\%) of patients had been diagnosed with tobacco use disorder.

Nearly all patients (86\%) had been diagnosed with musculoskeletal pain, with smaller proportions having been diagnosed...
with headaches (including migraine; 11%) or neuropathic pain (6%). Hydrocodone, oxycodone, methadone, and morphine were the most commonly prescribed opioid medications in the year before discontinuation, with 57%, 38%, 29%, and 26% of patients being prescribed these medications, respectively. Forty-five percent of patients were prescribed 2 or more opioids concurrently in the year before discontinuation. The average morphine equivalent daily dose (MEDD) of prescribed opioids in the year before discontinuation was 76 mg. Fifty-six percent of patients had nearly 3 different VHA opioid prescribers in the year before discontinuation.

Among the sample of 300 patients with an SUD diagnosis, alcohol use disorder was the most common SUD (52%), followed by opioid use disorder (29%), cocaine use disorder (14%), cannabis use disorder (11%), sedative/hypnotic/anxiolytic use disorder (5%), amphetamine use disorder (4%), and other SUDs (12%; eg, hallucinogen, polysubstance, and unspecified SUD).

Table 2 provides descriptive statistics for patient sociodemographic and clinical characteristics, as well as bivariate comparisons between patients with and without SUD.

3.1. Reasons for discontinuation of long-term opioid therapy

For most patients (85%), discontinuation of LTOT was initiated by a clinician, rather than patient, decision. Clinician-initiated discontinuation reasons included aberrant behaviors (64%), which comprised suspected substance abuse (44%), aberrant urine drug test results (37%), opioid misuse behaviors (15%), nonadherence to the pain plan of care (11%—eg, failing to present for urine drug tests or primary care appointments when asked), and concerns about opioid diversion (4%). Of the 223 patients whose clinician-initiated discontinuation reasons included aberrant urine drug tests, results of urine drug tests included negative for prescribed opioid(s) (26%), positive for cannabis (47%), positive for cocaine (22%), positive for a nonprescribed opioid (11%), positive for amphetamines (10%), positive for a nonprescribed sedative/hypnotic/anxiolytic (6%), and positive for alcohol (4%). Some patients had multiple aberrant urine drug test results that led to discontinuation. Few patients were discontinued by their clinicians because of aberrant behaviors, or nonadherence to their pain plan of care. Patients with SUD were less likely to discontinue opioids for reasons that were not documented in the electronic medical record, and this was true for both patient (OR = 0.23, 95% CI = 0.07-0.78) and clinician-initiated (OR = 0.40, 95% CI = 0.20-0.80) discontinuation. Patients with and without SUD did not significantly differ on any other patient- or clinician-initiated discontinuation reasons in unadjusted models (Table 3).

In unadjusted models, patients with SUD were more likely to have opioids discontinued by clinicians because of aberrant behaviors (odds ratio [OR] = 1.79, 95% confidence interval [CI] = 1.28-2.51), most notably known or suspected abuse of illicit substances (OR = 2.04, 95% CI = 1.47-2.83). However, they were no more likely than patients without SUD to be discontinued because of aberrant urine drug test results, opioid diversion, opioid misuse behaviors, or nonadherence to their pain plan of care. Patients with SUD were less likely to discontinue opioids for reasons that were not documented in the electronic medical record, and this was true for both patient (OR = 0.24, 95% CI = 0.08-0.56) and clinician-initiated (OR = 0.40, 95% CI = 0.24-0.68) discontinuation. Patients with and without SUD did not significantly differ on any other patient- or clinician-initiated discontinuation reasons in unadjusted models (Table 3).

Results of covariate-adjusted models were consistent with those of unadjusted models. Namely, patients with SUD were more likely to discontinue LTOT because of aberrant behaviors, known or suspected substance abuse, and for reasons not documented in the medical record. Effect size magnitudes as measured by the OR were equivalent or slightly greater in covariate-adjusted models. Similar to unadjusted models, patients with SUD did not differ from patients without SUD on any other patient- or clinician-initiated opioid discontinuation reasons (see Table 3 for results of multivariable models).

4. Discussion

In a sample of 600 VHA patients with and without SUD who discontinued LTOT, an overwhelming majority (85%) of discontinuations were initiated by clinicians rather than patients. Of
patients whose clinicians initiated the discontinuation, 75% were due to an aberrant behavior, including substance abuse, aberrant urine drug tests, other opioid misuse behaviors, opioid diversion, and nonadherence to the chronic pain plan of care. Clinician-initiated discontinuations in response to patients’ aberrant and potentially high-risk behaviors are recommended by the 2009 American Pain Society and 2010 VA/DoD clinical practice guidelines that were in place at the time patients in this study discontinued LTOT. The 2016 CDC clinical practice guidelines recommend ongoing evaluation of clinical outcomes of opioid

<table>
<thead>
<tr>
<th>Variable</th>
<th>Full sample N = 600, % (n) or M ± SD</th>
<th>SUD n = 300, % (n) or M ± SD</th>
<th>No SUD n = 300, % (n) or M ± SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sociodemographic characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>54.5 ± 11.0</td>
<td>55.3 ± 10.7</td>
<td>53.8 ± 11.3</td>
<td>0.095</td>
</tr>
<tr>
<td>Male sex</td>
<td>94.5 (567)</td>
<td>93.7 (281)</td>
<td>95.3 (286)</td>
<td>0.371</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td>0.721</td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>71.5 (429)</td>
<td>71.3 (214)</td>
<td>71.7 (215)</td>
<td></td>
</tr>
<tr>
<td>Black, non-Hispanic</td>
<td>15.3 (92)</td>
<td>16.0 (48)</td>
<td>14.7 (44)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>2.3 (14)</td>
<td>1.7 (5)</td>
<td>3.0 (1)</td>
<td></td>
</tr>
<tr>
<td>Other/unknown</td>
<td>10.8 (65)</td>
<td>11.0 (33)</td>
<td>10.7 (32)</td>
<td></td>
</tr>
<tr>
<td><strong>Rural–urban continuum</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.877</td>
</tr>
<tr>
<td>Isolated</td>
<td>5.5 (33)</td>
<td>5.7 (17)</td>
<td>5.3 (16)</td>
<td></td>
</tr>
<tr>
<td>Small rural</td>
<td>8.3 (50)</td>
<td>7.3 (22)</td>
<td>9.3 (28)</td>
<td></td>
</tr>
<tr>
<td>Large rural</td>
<td>12.8 (77)</td>
<td>12.7 (38)</td>
<td>13.0 (39)</td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>72.8 (437)</td>
<td>74.0 (222)</td>
<td>71.7 (215)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0.5 (3)</td>
<td>0.3 (1)</td>
<td>0.7 (2)</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elixhauser Comorbidity Measure</td>
<td>1.6 ± 1.4</td>
<td>1.8 ± 1.3</td>
<td>1.4 ± 1.4</td>
<td>0.002</td>
</tr>
<tr>
<td>Any VHA–service connected disability</td>
<td>57.5 (345)</td>
<td>54.7 (164)</td>
<td>60.3 (181)</td>
<td>0.160</td>
</tr>
<tr>
<td><strong>Mental health diagnoses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive disorder</td>
<td>25.3 (152)</td>
<td>32.0 (96)</td>
<td>18.7 (56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>7.8 (47)</td>
<td>9.7 (29)</td>
<td>6.0 (18)</td>
<td>0.085</td>
</tr>
<tr>
<td>PTSD</td>
<td>31.3 (188)</td>
<td>35.3 (106)</td>
<td>27.3 (82)</td>
<td>0.055</td>
</tr>
<tr>
<td>Other anxiety disorders</td>
<td>25.3 (152)</td>
<td>30.9 (90)</td>
<td>20.7 (62)</td>
<td>0.009</td>
</tr>
<tr>
<td>Psychotic disorder</td>
<td>7.5 (45)</td>
<td>8.7 (26)</td>
<td>6.3 (19)</td>
<td>0.278</td>
</tr>
<tr>
<td><strong>Substance use disorder</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>—</td>
<td>52.0 (156)</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Amphetamine</td>
<td>—</td>
<td>4.0 (12)</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Cannabis</td>
<td>—</td>
<td>11.3 (34)</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td>—</td>
<td>13.7 (41)</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Opioid</td>
<td>—</td>
<td>29.3 (88)</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Sedative</td>
<td>—</td>
<td>4.7 (14)</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>—</td>
<td>12.3 (37)</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td><strong>Tobacco use disorder</strong></td>
<td>44.5 (267)</td>
<td>52.3 (157)</td>
<td>36.7 (110)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Pain and opioid characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pain diagnoses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>86.0 (516)</td>
<td>90.3 (271)</td>
<td>81.7 (245)</td>
<td>0.002</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>5.8 (35)</td>
<td>6.3 (19)</td>
<td>5.3 (16)</td>
<td>0.601</td>
</tr>
<tr>
<td>Migraine headache</td>
<td>10.5 (63)</td>
<td>13.0 (39)</td>
<td>8.0 (24)</td>
<td>0.046</td>
</tr>
<tr>
<td><strong>Type of opioid prescribed</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>56.8 (341)</td>
<td>54.3 (163)</td>
<td>59.3 (178)</td>
<td>0.216</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>37.7 (226)</td>
<td>39.0 (117)</td>
<td>36.3 (109)</td>
<td>0.500</td>
</tr>
<tr>
<td>Methadone</td>
<td>29.2 (175)</td>
<td>31.7 (95)</td>
<td>26.7 (80)</td>
<td>0.176</td>
</tr>
<tr>
<td>Morphine</td>
<td>25.5 (153)</td>
<td>20.7 (69)</td>
<td>21.3 (64)</td>
<td>0.019</td>
</tr>
<tr>
<td>Codeine</td>
<td>3.3 (20)</td>
<td>3.3 (10)</td>
<td>3.3 (10)</td>
<td>1.000</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>2.8 (17)</td>
<td>3.3 (10)</td>
<td>2.3 (7)</td>
<td>0.460</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>2.0 (12)</td>
<td>2.0 (6)</td>
<td>2.0 (6)</td>
<td>1.000</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>0.2 (1)</td>
<td>0.3 (1)</td>
<td>0.0 (0)</td>
<td>0.317</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>0.2 (1)</td>
<td>0.3 (1)</td>
<td>0.3 (1)</td>
<td>0.317</td>
</tr>
<tr>
<td><strong>Average morphine equivalent daily dose</strong></td>
<td>76.2 ± 88.6</td>
<td>82.2 ± 92.7</td>
<td>70.1 ± 84.0</td>
<td>0.096</td>
</tr>
<tr>
<td><strong>(MEDD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEDD categories</td>
<td></td>
<td></td>
<td></td>
<td>0.140</td>
</tr>
<tr>
<td>&lt;50 mg MEDD</td>
<td>56.2 (337)</td>
<td>52.7 (158)</td>
<td>59.7 (179)</td>
<td></td>
</tr>
<tr>
<td>50 mg to &lt;90 mg MEDD</td>
<td>20.0 (120)</td>
<td>19.7 (59)</td>
<td>20.3 (61)</td>
<td></td>
</tr>
<tr>
<td>90 mg to &lt;120 mg MEDD</td>
<td>6.7 (40)</td>
<td>8.3 (25)</td>
<td>5.0 (15)</td>
<td></td>
</tr>
<tr>
<td>120 mg or greater MEDD</td>
<td>17.2 (103)</td>
<td>19.3 (58)</td>
<td>15.0 (45)</td>
<td></td>
</tr>
<tr>
<td>Number of opioid prescribers</td>
<td>2.6 ± 1.6</td>
<td>2.7 ± 1.7</td>
<td>2.5 ± 1.5</td>
<td>0.023</td>
</tr>
<tr>
<td>Prescribed benzodiazepine</td>
<td>13.3 (80)</td>
<td>14.3 (43)</td>
<td>12.3 (37)</td>
<td>0.471</td>
</tr>
</tbody>
</table>

MEDD, morphine equivalent daily dose; PTSD, post-traumatic stress disorder; SUD, substance use disorder; VHA, Veterans Health Administration.
therapy for each patient and to taper or discontinue opioid therapy if harms outweigh benefits. Coupled with CDC recommendations for clinicians to review PDMP data quarterly and perform annual urine drug testing, rates of LTOT discontinuation due to aberrant behaviors may increase as CDC guidelines are adopted by clinicians and health care systems.

Clinicians face challenges when discontinuing LTOT for patients who engage in behaviors that heighten risk of opioid-related adverse events. Continuing to prescribe opioids to patients who are misusing, abusing, or diverting medication could result in significant harm to individual patients and society. Conversely, discontinuing LTOT when aberrant behaviors are identified, even when these actions represent good clinical practice, may erode the patient–provider relationship. Patient-centered models of care may be difficult to use in situations when patients perceive punitive action as being directed toward them. The ways in which clinicians communicate with patients before, during, and after discontinuation of LTOT are paramount to ensuring patients continue to receive pain care and other needed services rather than disengaging from a clinic or health care system entirely. If mishandled, patients may be at increased risk of engaging in illicit behaviors to obtain opioids, attempt to obtain opioids from other clinics or the emergency room, or resort to street drugs such as heroin.8,32

In this study, patients with an SUD diagnosis were more likely than those without to be discontinued for aberrant behaviors, specifically substance abuse. Previous data indicate patients with SUD are more likely to misuse opioids46 and experience adverse opioid-related events such as overdose and death.3 Data from this study indicate that these patients are also more likely to be discontinued from LTOT for substance-related reasons. For many patients with comorbid chronic pain and SUD, pain predicates SUD and inadequately treated pain may lead to increased substance use.24 Treating chronic pain in SUD patients is further complicated by high rates of medical and psychiatric comorbidities.25 The complexity of this patient population points to the need for comprehensive, multidisciplinary care that, at a minimum, concurrently addresses substance use and pain, as well as other psychiatric and medical conditions that exacerbate pain and SUD symptoms. Indeed, patients with SUD are less likely than their non-SUD counterparts to experience improvements in pain-related functioning when receiving standard pain care,34 pointing to the fact that these patients often require a higher level of care. Cognitive behavioral therapy for co-occurring pain and SUD delivered in specialty SUD treatment settings has demonstrated efficacy in improving pain and SUD outcomes.10,22,23 For most patients with SUD who are unwilling……
or otherwise unable to engage in specialty SUD treatment, the primary care medical home may be an alternative treatment setting for meeting these patients’ pain and SUD needs. Although many health systems currently lack capacity for such integrated models of care, others (eg, Veterans Health Administration, Kaiser Permanente) have integrated primary medical and mental health across their health care systems. Behavioral approaches to pain management administered through telehealth also show promise for expanding the reach of services to underserved rural areas. As capacity for behavioral health specialists in primary care continues to grow, incorporating specialists with backgrounds in treating both chronic pain and SUD or providing training to specialists already working in these clinical settings will be paramount.

Notably, 37% of patients in this study discontinued LTOT because of aberrant urine drug tests, and results did not differ between those with and without SUD diagnoses. A previous study found that 21% of patients on LTOT with no opioid-related behavioral issues tested positive for one or more nonprescribed controlled or illicit substances. These findings combined with those of this study suggest a guideline-concordant universal precautions approach to urine drug testing, in which all patients are randomly tested, may be necessary to accurately identify patients who misuse or abuse prescription medications, and illicit substances. Targeting urine drug testing to high-risk patients only, such as those with SUD diagnoses or other behaviors indicative of opioid misuse, will miss a substantial proportion of patients using substances.

Nearly half of aberrant urine drug tests that resulted in discontinuation of LTOT included a positive test for cannabis. Although we were unable to ascertain from the medical record the reasons for cannabis use, cannabis may be used by some patients to treat chronic pain. Currently, 29 states and the District of Columbia have passed legislation allowing the use of cannabis for medical purposes. Eight states—Alaska, California, Colorado, Maine, Massachusetts, Nevada, Oregon, and Washington—and the District of Columbia allow recreational use of cannabis. As the medicinal and recreational use of cannabis becomes legal across a growing number of jurisdictions, clinicians will increasingly be faced with questions from patients and their family members about the use of cannabis as a form of pain management. Clinicians and patients will also be confronted with clinical decisions concerning combined cannabis and opioid use for chronic pain and the challenge of assessing and safely balancing the potential risks and benefits of this strategy. Unfortunately, there is no empirical evidence to guide clinicians in the management of chronic noncancer pain using opioid therapy for patients concurrently prescribed cannabis for a medical or psychiatric condition.

This study has several limitations. First, the sample comprises VHA patients and results may not generalize to non-VHA patients who discontinue LTOT. Second, to ensure identification of a cohort with chronic noncancer pain, we excluded patients with cancer diagnoses and surgeries in the year before discontinuation of LTOT; however, it is possible that some of these excluded patients’ pain may not have been due to cancer nor was it acute in nature. Third, we identified SUD patients as having a clinical encounter in the year before LTOT discontinuation in which SUD was linked to the clinical encounter. This may not fully capture all patients with SUD. Fourth, patients without SUD in this study were selected to match the cohort of patients with SUD, rather than randomly sampled from the population. Because of this, results for patients without SUD may not be fully generalizable to all non-SUD patients in VHA undergoing LTOT discontinuation. Fifth, discontinuation of LTOT was defined as 12 continuous months without filling an opioid prescription. Patients who were discontinued and then subsequently restarted opioid therapy within a year were not captured and may represent a selection bias. Sixth, some previous studies have defined LTOT as at least 90 days of opioid therapy. We sought to identify patients for whom opioids had become a very long-term approach to pain management and therefore implemented a more conservative definition of 12 consecutive months of opioid therapy. Finally, the sample comprises patients on LTOT for all of 2011 who discontinued opioids in 2012 and were followed through 2013. We chose this period because clinical practice guidelines for opioid therapy for chronic pain had been released one to 2 years prior, allowing us to examine discontinuation reasons after guidelines would likely have been implemented by clinicians. The data may not, however, reflect reasons for discontinuation of LTOT in more contemporary patient cohorts.

5. Conclusions

Discontinuation of LTOT is a decision overwhelmingly initiated by clinicians. Patients with SUD are more likely than patients without SUD to discontinue LTOT for aberrant behaviors. However, many patients without SUD screen positive for illicit and other substances and engage in aberrant behaviors that lead to opioid discontinuation. Increasing rates of opioid discontinuation are likely to occur due to policies and programs that encourage close monitoring of patients on LTOT for opioid misuse behaviors. Ensuring patients have access after opioid discontinuation to nonopioid analgesic pharmacotherapies, nonpharmacologic pain management approaches, and SUD treatment is critically important as inadequately treated pain can exacerbate other comorbid conditions—such as psychiatric disorders and SUDs—resulting in poorer quality of life. Integrating nonopioid pain therapies and SUD treatment into multiple settings such as primary care and specialty SUD care is one possible approach. Additional research is needed to determine if such models will prove efficacious for patients who discontinue LTOT.

Conflicts of interest statement

T. I. Lovejoy, J. W. Frank, and S. K. Dobscha report grants from the U.S. Department of Veterans Affairs during the conduct of the study. The remaining authors have no conflicts of interest to declare.


This work was supported by Locally Initiated Project Award # QLP 59-048 (PI: Lovejoy) from the United States (U.S.) Department of Veterans Affairs Substance Use Disorder Quality Enhancement Research Initiative. T. I. Lovejoy received additional support from Career Development Award IK2HX001914 from the U.S. Department of Veterans Affairs Health Services Research and Development during preparation of this manuscript. J. W. Frank received support from Career Development Award IK2HX001914 from the U.S. Department of Veterans Affairs Health Services Research and Development.

The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the U.S. Department of Veterans Affairs or U.S. Government.
Acknowledgements
We thank the VA Portland Health Care System and the U.S. Department of Veterans Affairs Health Services Research and Development Center to Improve Veteran Involvement in Care (CIVIC; CIN 13-404, PI: Dobscha) at the VA Portland Health Care System for the provision of support and resources for this project.

Appendix A. Supplemental Digital Content
Supplemental Digital Content associated with this article can be found online at http://links.lww.com/PAIN/A370.

Supplemental media
Video content associated with this article can be found online at http://links.lww.com/PAIN/A371.

Article history:
Received 25 May 2016
Received in revised form 21 October 2016
Accepted 27 October 2016
Available online 9 December 2017

References
Risk factors for neuropathic pain in diabetes mellitus

Harry L. Hébert*, Abirami Veluchamy, Nicola Torrance, Blair H. Smith

1. Introduction

According to the International Diabetes Federation, diabetes mellitus (DM) is estimated to affect around 415 million adults worldwide, roughly 8.8% of the adult population, with the figure projected to rise to over 600 million by 2040. Regional prevalence varies from 3.2% in Africa to 12.9% in North America. Diabetes mellitus is associated with a number of chronic sequelae and around 50% of people with DM go on to develop polyneuropathy. This condition has a variety of clinical manifestations, which are grouped into positive symptoms including dysesthesia (abnormal sense of touch), tingling and itching, and negative symptoms including numbness, muscle weakness, and trouble with balance. Up to 25% of people with diabetic neuropathy (DN) also develop neuropathic pain (NP). Neuropathic pain is defined by the International Association for the Study of Pain as “pain directly caused by a lesion or disease affecting the somatosensory system.” Symptoms of painful diabetic neuropathy (PDN) include those described above for nonpainful DN with additional “burning,” “electric shocks,” “stabbing,” and “pins and needles” symptoms all being described. Painful diabetic neuropathy is associated with increased distress and poor quality of life compared with nonpainful DN, DM, and the general population including depression, anxiety, and sleep disturbance. In addition, an association has been described with reduced productivity and employability at work compared with nonpainful DN. The combination of these factors places a large economic burden on patients and health care services, a situation likely to grow steadily worse with the aforementioned projected rise in DM prevalence. This situation is further exacerbated by the fact that 13% of patients with PDN do not report their symptoms to primary care, and 39% of patients with PDN have never received treatment. Even for those patients who do attend primary and secondary care for their diabetes, pain is not a symptom that is always included in clinical assessments. Furthermore, not all patients with DN develop PDN, and the reasons for this are unclear.

Understanding the risk factors for PDN will go some way to resolving this and will also help to inform management and prevention of this painful condition by health care services. Any factor that increases the risk of DM or DN is likely to be a risk factor for PDN. However, it is the specific nature and magnitude of the risk that remains unclear and is the focus of this topical review.

2. Risk factors

There have been relatively few published studies examining risk factors specifically for PDN in DM. Clinical, environmental, and genetic factors have been shown to be predictive of developing DM and some of these have also been implicated in the development of DN, including age, body mass index, hypertension, smoking, and waist circumference. Given the likely overlap of risk factors between DM and DN, it seems reasonable to hypothesize that some of these factors will also influence the development of PDN.

We conducted a literature search using relevant key words and terms aiming to identify a wide range of studies that investigated risk factors for PDN and to include all the important studies (Table 1). A number of limitations can be identified with these studies as a whole. Most of these studies are cross sectional in nature and therefore unable to establish temporal relationship between patient characteristics/factors and PDN. Some studies report only univariate analysis and are therefore unable to assess intervariable relationships and to identify confounding between variables. In addition, it is not always clear in the methods and statistical analyses whether PDN or nonpainful DN is being analysed and what control group the PDN subjects are being compared with. In some studies, those in the control group are diabetic participants with nonpainful neuropathy and in others they are diabetic participants without neuropathy of any form. In other studies, it is not possible to determine the nature of the control group from the description of the methods. There was considerable heterogeneity in PDN case ascertainment, with only 6 studies using a validated NP screening questionnaire (the DN4 or the Leeds assessment of neuropathic symptoms and signs) with the remainder using nonvalidated questionnaires or clinical examinations. This makes it difficult to assess the sensitivity and specificity of each study to identify PDN cases and to make direct comparisons between studies as effect size estimations and associations are likely to be different. Despite these limitations, some potential risk factors have emerged, including environment, clinical, lifestyle, and genetic factors.
2.1. Demographic

Two nonmodifiable factors—age \(^{2,17,21,38,42}\) and sex \(^{1,11,17,21,41}\)—have been specifically associated with PDN, in addition to their known roles as risk factors for DM. Although these are of limited use to clinicians in terms of intervention, they could provide useful clues as to the underlying biological pathways involved and increased awareness of at-risk patients. In particular, the association of PDN with older age (>50 years) is likely to be related to the time it takes for nerve damage and painful symptoms to develop after the onset of DM and the decreased ability of the body to deal with this. Similarly, gender associations may indicate possible subtle differences in biology and psychosocial factors that affect the risk of PDN, something that requires further investigation. It is interesting to note that while 4 of the studies report greater risk in women, \(^{1,11,21,21}\) 1 study reports greater risk in men. \(^{41}\) This discrepancy in the latter study could be related to the limited statistical analysis, which did not adjust for potential confounding factors. Despite the prevalence of DM varying according to ethnicity, this has not been found as a risk factor so far for PDN. \(^{1,12,17,21,32,38}\) One study reported that South Asians were more likely to report painful symptoms than people in other ethnic groups in the absence of clinical neuropathy. \(^{1}\) Another found an association with pain among people with DM residing in a Gulf state and Lebanon compared with Egypt, but did not analyse ethnic origin. \(^{21}\)

2.2. Clinical

Clinical and physiological factors associated with PDN are important for clinicians and primary care as they may indicate possibilities for targeted treatment or primary prevention strategies. The clinical diagnosis of the type of DM and the duration since onset of the disease may be particularly relevant. Two studies found an association with DM type in multivariate analysis, with 1 identifying type 1 diabetes (T1D) \(^{21}\) and the other type 2 diabetes (T2D) \(^{1}\) as conferring greater risk of PDN. Differences in case definition and study populations could have contributed to the heterogeneity in these results. A clearer consensus is apparent for DM duration with risk increasing over time since diagnosis. \(^{2,6,17,21,32,38}\) Severity of preceding neuropathy has been found to be associated with PDN, but associations with neuropathy duration and comparison with type of (peripheral or sensory) neuropathy have not been found. \(^{9,11,33,36}\) Most studies included only 1 type of neuropathy in their analysis. A number of clinical factors and comorbidities have been found to be associated with PDN. These include poor glycaemic control and high HbA1c levels, \(^{2,18,36}\) hypertension, \(^{2,18}\) retinopathy, \(^{2,36}\) nephropathy, \(^{2,36}\) cardiovascular disease, \(^{2,42,43}\) and glycosuria. \(^{18}\) However, as these conditions are all known complications of DM, it is uncertain from cross-sectional analysis whether these factors are contributing to PDN risk and onset, or simply coexisting factors, perhaps confounded by other factors or with shared aetiology. Biomarkers for the development of PDN can be exploited by providing preventative or diagnostic tests. In this respect, tumour necrosis factor alpha and inducible nitric oxide synthase expression, \(^{30}\) triglycerides, and low high-density lipoprotein cholesterol \(^{38}\) all show promising associations but require replication to be confident in their role in disease pathogenesis.

2.3. Lifestyle

Behavioural and social circumstances are important lifestyle aspects that patients can theoretically influence and act on, with greater or less practical difficulty. In particular, some physical characteristics known to be associated with DM and DN are also implicated in PDN. Body mass index has been clearly linked to PDN, particularly in the form of obesity \((>=30 \text{ kg/m}^2)\) \(^{21,33,38}\) while in another study, weight was reported independently of height and found to be significantly associated with PDN, although this was attenuated in multivariate analyses. \(^{42}\) A related study also found a positive correlation with increased waist circumference and high levels of physical activity and risk of PDN. \(^{43}\) Despite being included in the analyses in most of the studies, \(^{1,2,4,8,17,18,21,32,33,38,42,43}\) smoking and alcohol consumption have not been specifically associated with PDN. Psychological factors have also been widely reported in the context of general chronic pain, but its relationship with PDN is less clear. Increased depression, anxiety, enjoyment of life, and social relationships are associated with PDN, but without prospective studies and longitudinal analysis, the temporal relationship cannot be established. \(^{7,11}\)

Figure 1. Schematic of the process from diabetes mellitus to diabetic neuropathy and finally painful diabetic neuropathy. Both diabetes mellitus and diabetic neuropathy have their own set of risk factors, both of which could provide important clues as to the risk factors that contribute to painful diabetic neuropathy.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type</th>
<th>Population</th>
<th>Criteria for NP</th>
<th>Sample size</th>
<th>Analysis</th>
<th>Variables analysed</th>
<th>Predictors</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott et al., 2011</td>
<td>Cross sectional</td>
<td>UK</td>
<td>NSS ≥ 5 and NDS ≥ 3</td>
<td>3242 DM with NP</td>
<td>Multivariate logistic regression</td>
<td>Age, alcohol, diabetes duration, diabetes treatment, diabetes type, ethnicity, foot ulcer, foot deformities, impaired vision, lower limb amputation, nephropathy, PAD, sex, and smoking</td>
<td>T2D</td>
<td>2.1 (1.7-2.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12,372 DM without PDN</td>
<td></td>
<td></td>
<td>Women</td>
<td>1.5 (1.4-1.6)</td>
</tr>
<tr>
<td>AlQuliti, 2015</td>
<td>Case control</td>
<td>Saudi Arabia</td>
<td>Foot examination and NSS ≥ 3</td>
<td>99 T2D with PDN</td>
<td>Univariate analysis</td>
<td>Age, CVD, diabetes duration, glycaemic control, HbA1c, hypertension, insulin use, nephropathy, oral antidiabetic drugs, PVD, retinopathy, sex, smoking, stroke, and working status</td>
<td>Age (&gt;50 y)</td>
<td>1.93 (1.09-3.41)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>99 T2D without PDN</td>
<td></td>
<td></td>
<td>CVD</td>
<td>3.37 (1.28-8.89)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>99 T2D without PDN</td>
<td></td>
<td></td>
<td>Diabetes duration (&gt;10 y)</td>
<td>3.38 (1.88-6.07)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>99 T2D without PDN</td>
<td></td>
<td></td>
<td>Glycaemic control</td>
<td>0.42 (0.12-0.96)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>99 T2D without PDN</td>
<td></td>
<td></td>
<td>Hypertension</td>
<td>2.85 (1.57-5.17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>99 T2D without PDN</td>
<td></td>
<td></td>
<td>Nephropathy</td>
<td>8.93 (2.58-30.95)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>99 T2D without PDN</td>
<td></td>
<td></td>
<td>Retinopathy</td>
<td>13.22 (4.49-38.95)</td>
</tr>
<tr>
<td>Benbow et al., 1997</td>
<td>Cross sectional</td>
<td>UK</td>
<td>Clinical history and examination; burning/shooting pain/ hyperesthesia ≥6 mo and at least 1 abnormal neurological sign from decrease in light touch, vibration, or pinprick sensation</td>
<td>49 DN with NP</td>
<td>Univariate analysis</td>
<td>Age, diabetes duration, diabetes type, HbA1c, sex, and smoking</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>23 DN without NP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cheng et al., 2010</td>
<td>Genetic case–control/ cross sectional</td>
<td>Taiwan</td>
<td>Pain VAS ≥ 4 and grade 3-5 of occurrence of pain in daily activities</td>
<td>15 DFU (and DN) with NP</td>
<td>Univariate analysis / Fisher exact</td>
<td>Age, albumin, amputation, BMI, diabetes duration, diabetes type, haemoglobin, HbA1c, hyperlipidemia, hypertension, rs1799971 of OPRM1, and sex</td>
<td>rs1799971</td>
<td>0.24 (0.07-0.8)</td>
</tr>
<tr>
<td>Cortez et al., 2014</td>
<td>Cross sectional</td>
<td>Brazil</td>
<td>DN4 ≥ 4</td>
<td>12 T2D with PDN</td>
<td>Multivariate analysis</td>
<td>Age, depressive symptoms, diabetes duration, drug adherence, sex, and glycaemic control</td>
<td>Diabetes duration</td>
<td>P = 0.031</td>
</tr>
<tr>
<td>D’Armato et al., 2016</td>
<td>Cross sectional</td>
<td>Italy</td>
<td>DN4 ≥ 4 (DN4 interview ≥ 3)</td>
<td>25 DN with NP 46 DN without NP 110 without DN</td>
<td>Multivariate analysis</td>
<td>Depression</td>
<td>Depression (BDI-II)</td>
<td>4.56 (1.09-19.1)</td>
</tr>
</tbody>
</table>

(continued on next page)
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type</th>
<th>Population</th>
<th>Criteria for NP</th>
<th>Sample size</th>
<th>Analysis</th>
<th>Variables analysed</th>
<th>Predictors</th>
<th>OR (95% CI)/P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daousi et al., 2004</td>
<td>Cross sectional</td>
<td>UK</td>
<td>Typical NP symptoms in legs ≥1 yr, PSS ≥ 3 and NDS ≥ 6 or NDS ≥ 3 and NSS ≥ 5</td>
<td>56 DM with PDN</td>
<td>Univariate analysis</td>
<td>Age, alcohol, angina, BMI, BP, CVA, depression, diabetes duration, diabetes type, foot ulceration, HbA1c, hypertension, MI, PVD, sex, and smoking</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>289 DM without PDN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Davies et al., 2006</td>
<td>Cross sectional</td>
<td>UK</td>
<td>Positive response to “Do you have a burning, aching or tenderness in your legs or feet?” from DNSS and TCSS score ≥ 5</td>
<td>71 T2D with PDN (51 with NP and 20 with mixed NP and non-NP)</td>
<td>Univariate analysis</td>
<td>Age, diabetes duration, HbA1c, neuropathy severity, and sex</td>
<td>Severity of neuropathy</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>99 T2D with non-NP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>99 T2D with no pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erbas et al., 2011</td>
<td>Cross sectional</td>
<td>Turkey</td>
<td>LANSS ≥ 12</td>
<td>156 DM with PDN</td>
<td>Univariate analysis</td>
<td>Age, blood urea, BUN, creatinine, diabetes duration, diabetes type, PPG, HbA1c, PPG, and sex</td>
<td>Duration of diabetes</td>
<td>P = 0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>975 DM without PDN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gore et al., 2003</td>
<td>Cross sectional</td>
<td>USA</td>
<td>Physician diagnosed</td>
<td>255 with PDN</td>
<td>Univariate analysis</td>
<td>Anxiety, depression, enjoyment of life, mental health, mood, and relationship with others</td>
<td>Anxiety (HADS)</td>
<td>All P &lt; 0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>361 DM without PDN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halawa et al., 2010</td>
<td>Cross sectional</td>
<td>Saudi Arabia</td>
<td>DN4 ≥ 4</td>
<td>678 DM with PDN</td>
<td>Univariate analysis</td>
<td>Age, BMI, diabetes duration, diabetes type, ethnicity, smoking, and sex</td>
<td>Diabetes duration</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>361 DM without PDN</td>
<td></td>
<td></td>
<td>Women</td>
<td>P = 0.024</td>
</tr>
<tr>
<td>Harris et al., 1993</td>
<td>Cross sectional</td>
<td>USA</td>
<td>Positive response to, “During the past 3 mo, have you had a painful sensation or tingling in your hands or feet?”</td>
<td>2392 with DM (26.8% of whom had pain/tingling in hands/feet?)</td>
<td>Multivariate logistic regression</td>
<td>Age, amputation, angina, diabetes age, diabetes duration, ethnicity, family income, foot sores, height, higher education, hypertension, insulin, nephropathy, obesity, periodontal disease, proteinuria, retinopathy, sex, smoking, and stroke</td>
<td>Glocosuria</td>
<td>2.31 (1.54-3.47)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20,037 without DM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(continued on next page)
| Reference          | Study type     | Population       | Criteria for NP                                      | Sample size | Analysis          | Variables analysed                                           | Predictors                              | OR (95% CI)/P |
|-------------------|----------------|------------------|-----------------------------------------------------|-------------|-------------------|-------------------------------------------------------------|------------------------------------------|----------------|----------------|
| Jambert et al., 2011<sup>11</sup> | Cross sectional | Middle East Region | DNA4 ≥ 4                                             | 2144 DM with PDN | Multivariate regression | Age, BMI, diabetes duration, diabetes type, ethnicity, sex, and smoking | Age (50-64 y)                          | 1.75 (1.48-2.08) |
|                   |                |                  |                                                     | 1845 DM without PDN |                  |                                                                             | Age ≥65 y                              | 2.13 (1.72-2.62) |
|                   |                |                  |                                                     |              |                   |                                                                             | BMI (≥30 kg/m²)                        | 1.35 (1.17-1.56) |
|                   |                |                  |                                                     |              |                   |                                                                             | Diabetes duration ≥10 y                 | 2.43 (2.10-2.81) |
|                   |                |                  |                                                     |              |                   |                                                                             | Living in a Gulf State (compared with Egypt) | 0.44 (0.35-0.56) |
|                   |                |                  |                                                     |              |                   |                                                                             | Living in Lebanon (compared with Egypt) | 0.66 (0.54-0.81) |
|                   |                |                  |                                                     |              |                   |                                                                             | T1D                                    | 1.59 (1.24-2.05) |
|                   |                |                  |                                                     |              |                   |                                                                             | Women                                  | 1.27 (1.11-1.49) |
| Li et al., 2015<sup>20</sup>   | Genetic case control | USA/Canada               | NCT00501202: lower extremity pain ≥3 mo NCT00870454: as above and NCT0093018: Symmetrical pain beginning in feet ≥6 mo and NCT00455520: clinical diagnosis with signs and symptoms ≥6 mo and at screening | 887 DM with PDN | Univariate analysis | SNPs across SCN9A gene region rs74449889 (SCN9A) | rs74449889 (SCN9A) | 2.6          |
|                   |                |                  |                                                     | 1029 without DM and PDN |                   |                                                                             | rs3750904 (SCN9A)                       | 2.2          |
|                   |                |                  |                                                     |              |                   |                                                                             | rs4369876 (SCN9A)                       | 2.1          |
|                   |                |                  |                                                     |              |                   |                                                                             | rs12478318 (SCN9A)                      | 2.1          |
| Meng et al., 2015<sup>27</sup>  | GWAS          | UK               | Prescription of at least one from duloxetine, gabapentin, pregabalin, capsaicin cream/patch, and lidocaine patch. And positive monofilament test in at least 1 foot | 572 DM with PDN | Fisher exact | SNPs across whole genome rs17428041 (Chr8p21.3) | rs17428041 (Chr8p21.3) | 0.67 (0.57-0.78) |
|                   |                |                  |                                                     | 2491 DM without PDN |                   |                                                                             |                                        |              |
| Meng et al., 2015<sup>28</sup>  | GWAS          | UK               | Multiple usage of at least 1 from duloxetine, gabapentin, pregabalin, capsaicin cream/patch, lidocaine patch | 961 DM with PDN | Logistic regression | SNPs across whole genome rs71647933 (Chr1p35.1) | rs71647933 (Chr1p35.1) | 2.31 (1.68-3.17) |
|                   |                |                  |                                                     | 3260 DM without PDN |                   |                                                                             | rs6986153 (Chr8p23.1)                  | 1.67 (1.34-2.08) |

(continued on next page)
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type</th>
<th>Population</th>
<th>Criteria for NP</th>
<th>Sample size</th>
<th>Analysis</th>
<th>Variables analysed</th>
<th>Predictors</th>
<th>OR (95% CI) / P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purwata, 2011</td>
<td>Case control</td>
<td>Indonesia</td>
<td>Pain intensity VAS &gt;0 (representing no pain)</td>
<td>59 DN with NP</td>
<td>Univariate analysis</td>
<td>Age, diabetes duration, FG, HbA1c, iNOS expression, plasma TNF-α, TNF-α expression, and 2h-G</td>
<td>iNOS expression</td>
<td>3.546 (1.613-7.795)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>51 DN without NP</td>
<td></td>
<td></td>
<td>Plasma TNF-α</td>
<td>5.053 (2.241-11.392)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TNF-α expression</td>
<td>4.125 (1.805-9.423)</td>
</tr>
<tr>
<td>Sorensen et al., 2002</td>
<td>Cross sectional</td>
<td>Australia</td>
<td>Bilateral and symmetrical foot pain—patient specifically asked about foot pain</td>
<td>2610 T2D (3.3% with PDN)</td>
<td>Multivariate logistic regression</td>
<td>Age, alcohol, diabetes duration, diabetes treatment, ethnicity, HbA1c, height, sex, and smoking</td>
<td>Diabetes Duration</td>
<td>1.09 (1.06-1.1)</td>
</tr>
<tr>
<td>Sperlino et al., 2011</td>
<td>Cross sectional</td>
<td>Italy</td>
<td>Clinical examination and history</td>
<td>78 DN with NP</td>
<td>Multivariate logistic regression</td>
<td>Age, alcohol, BMI, BP, creatinine, CVD, diabetes duration, diabetes type, HbA1c, HLD, hypertension, PAD, physical activity, retinopathy, sex, smoking, triglyceride, and waist circumference</td>
<td>BMI (kg/m²)</td>
<td>1.22 (1.08-1.37)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>57 DN without NP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>56 without DN or NP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Themistocleous et al., 2016</td>
<td>Cross sectional</td>
<td>UK</td>
<td>IASP/NeuPSIG grading system</td>
<td>70 DPN with moderate/severe NP</td>
<td>Univariate analysis</td>
<td>Age, BMI, diabetes duration, diabetes type, ethnicity, HbA1c, neuropathy severity, orthostatic hypotension, ratio, sex, standing and lying BP, and waist–hip circumference</td>
<td>HbA1c and neuropathy severity</td>
<td>$P &lt; 0.01$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>41 DPN with mild NP</td>
<td></td>
<td></td>
<td></td>
<td>$P &lt; 0.01$</td>
</tr>
<tr>
<td>Van Acker et al., 2009</td>
<td>Cross sectional</td>
<td>Belgium</td>
<td>DN4 ≥ 4 and positive Neupen test</td>
<td>157 DN with NP</td>
<td>Multivariate logistic regression</td>
<td>Age, BMI, BP, diabetes duration, foot lesions, HbA1c, HLD, insulin, LDL, nephropathy, retinopathy, sex, triglyceride, and waist circumference</td>
<td>Age (per 10 y)</td>
<td>1.47 (1.20-1.81)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>321 DN without NP</td>
<td></td>
<td></td>
<td>Diabetes duration (per 5 y)</td>
<td>1.14 (1.02-1.28)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HDL cholesterol ($≥1 mmol/L for men, $≥1.3 mmol/L for women)</td>
<td>2.17 (1.38-3.41)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nephropathy</td>
<td>1.69 (1.10-2.59)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Obesity ($≥30 kg/m²)</td>
<td>1.62 (1.05-2.48)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Triglycerides ($≥1.7 mmol/L)</td>
<td>1.76 (1.13-2.79)</td>
</tr>
<tr>
<td>Wu et al., 2007</td>
<td>Cross sectional</td>
<td>France</td>
<td>MNSI ≥ 7 and Q5 of BPI ≥ 1</td>
<td>72 DN with NP</td>
<td>No statistical analysis</td>
<td>Age, diabetes duration, diabetes type, education, employment, region, and sex</td>
<td>Age (over 65 y)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12 DN without NP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(continued on next page)
2h-G, 2 hours glucose; BDI-II, Beck Depression Inventory II; BMI, body mass index; BP, blood pressure; BPl, brief pain inventory; BUN, blood urea nitrogen; CI, confidence interval; COVA, cardiovascular accident; CVD, cardiovascular disease; DFU, diabetic foot ulcer; DM, diabetes mellitus; DN, diabetic neuropathy; DNA, Double Nucleotide; ENS, Diabetic Neuropathy; ENS Score; ENSP, diabetice peripheral neuropathy; FG, fasting glucose; PG, fasting plasma glucose; GWS, genome-wide association study; HADS, Hospital Anxiety and Depression Scale; HDL, high-density lipoprotein; IASP, International Association for the Study of Pain; iNOS, inducible nitric oxide synthase; LANSS, Leeds Assessment of Neuropathy Screening Instrument; NA, not applicable; NDS, Neuropathic Disability Score; NeuPSI, Neuropathic Pain Special Interest Group; NP, neuropathic pain; OR, odds ratio; PAD, peripheral arterial disease; PG, postprandial plasma glucose; PVD, peripheral vascular disease; SCIENCE, adiponectin/melanocortin-4 receptor-1 gene; T1D, type 1 diabetes; T2D, type 2 diabetes; TCF, type 2 diabetes; TCSS, Toronto Clinical Scoring System; TNF-alpha, tumour necrosis factor alpha; UK, United Kingdom; USA, United States of America; VAS, visual analogue scale.

Numerous published studies have found that both T1D and T2D have a heritable component, although genetic studies have yet to be conducted. Available candidate gene and association studies have been conducted in one population for T2D, but not for T1D. This work has been conducted in one population for T2D, but not for T1D.
running Mendelian randomization studies, something that has been used in DM. Mendelian randomization studies establish causal relationship by comparing 2 groups of individuals with and without a genetic marker known to influence the variable being studied. As genotype assignment is random and not subject to confounding typically found in epidemiological studies, a higher prevalence of disease in the group with the marker implies causality. However, we would first need clearer evidence to identify genetic factors associated with PDN. Finally, greater clarity is needed in specifying whether painful or nonpainful DN is being analysed. This can be enhanced by forming a consensus on PDN phenotype definition, to enable studies to be more comparable.

B. H. Smith is a member of the DOLORisk consortium which is running Mendelian randomization studies, something that has been addressed for his institution, occasional lecture and consultancy fees from Pfizer Ltd, Napp Pharmaceuticals, Grunenthal and Eli Lilly. Received 12 September 2016

Conflict of interest statement

B. H. Smith is a member of the DOLORisk consortium which is running Mendelian randomization studies, something that has been addressed for his institution, occasional lecture and consultancy fees from Pfizer Ltd, Napp Pharmaceuticals, Grunenthal and Eli Lilly.

Article history:

Received 12 September 2016
Received in revised form 16 November 2016
Accepted 30 November 2016
Available online 7 December 2016

References


Intraoperative ketamine reduces immediate postoperative opioid consumption after spinal fusion surgery in chronic pain patients with opioid dependency: a randomized, blinded trial

Rikke Vibeke Nielsen*, Jonna Storm Fomsgaard, Hanna Siegel, Robertas Martusevicius, Lone Nikolajsen, Jørgen Berg Dahl, Ole Mathiesen

Abstract
Perioperative handling of surgical patients with opioid dependency represents an important clinical problem. Animal studies suggest that ketamine attenuates central sensitization and hyperalgesia and thereby reduces postoperative opioid tolerance. We hypothesized that intraoperative ketamine would reduce immediate postoperative opioid consumption compared with placebo in chronic pain patients with opioid dependency undergoing lumbar spinal fusion surgery. Primary outcome was morphine consumption 0 to 24 hours postoperatively. Secondary outcomes were acute pain at rest and during mobilization 2 to 24 hours postoperatively (visual analogue scale), adverse events, and persistent pain 6 months postoperatively. One hundred fifty patients were randomly assigned to intraoperative S-ketamine bolus 0.5 mg/kg and infusion 0.25 mg·kg⁻¹·h⁻¹ or placebo. Postoperatively, patients received their usual opioids, paracetamol and IV patient-controlled analgesia with morphine. In the final analyses, 147 patients were included. Patient-controlled analgesia IV morphine consumption 0 to 24 hours postoperatively was significantly reduced in the ketamine group compared with the placebo group: 79 (47) vs 121 (53) mg IV, mean difference 42 mg (95% confidence interval −59 to −25), P < 0.001. Sedation was significantly reduced in the ketamine group 6 and 24 hours postoperatively. There were no significant differences regarding acute pain, nausea, vomiting, hallucinations, or nightmares. Back pain at 6 months postoperatively compared with preoperative pain was significantly more improved in the ketamine group compared with the placebo group, P = 0.005. In conclusion, intraoperative ketamine significantly reduced morphine consumption 0 to 24 hours after lumbar fusion surgery in opioid-dependent patients. The trend regarding less persistent pain 6 months postoperatively needs further investigation.

Keywords: Pain, Postoperative, Analgesia, Postoperative, Ketamine, Spine

1. Introduction
The increasing number of surgical patients with chronic pain and opioid dependence represents a complex challenge in the perioperative period. This patient population has a high risk of opioid-induced hyperalgesia or tolerance, and may have an excessive need for opioids for up to 3 times that of opioid-naive patients, and an increased risk of postoperative pain. Furthermore, these patients are often discharged from hospital with a higher opioid prescription than before surgery.

Ketamine is a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist blocking NMDA receptors in the central and peripheral nervous systems. Clinical trials in opioid-naive patients have demonstrated reduced opioid consumption and pain with subanesthetic IV doses of ketamine intraoperatively. Recently, intraoperative ketamine was suggested as an ideal candidate for managing perioperative pain in opioid-dependent patients with chronic pain. The evidence for this indication is still sparse, and only one clinical trial has addressed this issue. Loftus et al. demonstrated that ketamine reduced postoperative opioid consumption 0 to 48 hours postoperatively, and reduced pain 6 weeks after surgery in opioid-dependent patients. The trial, however, suffered from lack of standardization of the analgesic regimens.

Thus, clinical trials are needed to clarify the role of ketamine for managing acute postoperative pain in opioid-dependent patients with chronic pain. Furthermore, data are needed on the role of perioperative ketamine for persistent postoperative pain.

The primary aim of this trial was to examine if intraoperative low-dose ketamine would reduce postoperative opioid consumption and acute pain compared with placebo in opioid-dependent patients. The primary outcome was 24-hour postoperative morphine consumption. Secondary outcomes were acute pain at
rest and during mobilization 2 to 24 hours postoperatively, adverse effects, and persistent pain 6 months postoperatively.

2. Methods

This single-centre, prospective, randomized, blinded trial was approved by the Regional Research Ethics Committee and the Danish Data Protection Agency and registered at clinicaltrials.gov (NCT02085577) on March 11, 2014. The trial was performed at Rigshospitalet—Glostrup, Copenhagen University Hospital, Denmark during the period from May 19, 2014 to October 2, 2015, and was monitored by the Copenhagen University Hospital Good Clinical Practice Unit. The study fulfilled the guidelines for Good Clinical Practice and the Helsinki Declarations. The protocol, design, and reporting of the study complied with the Standard Protocol Items, Recommendations for Interventional Trials (SPIRIT) statement8 and the Consolidated Standards of Reporting Clinical Trials statement (CONSORT).9 All patients gave written informed consent before participating in the trial.

2.1. Inclusion and exclusion criteria

Patients undergoing lumbar fusion surgery during general anesthesia were approached for inclusion in the trial. Additional inclusion criteria were chronic back pain >3 months preoperatively, daily use of strong opioids for back pain >6 weeks preoperatively (morphine, oxycodone, tramadol, buprenorphine, fentanyl, or ketobemidone), age 18 to 85 years, American Society of Anesthesiologists (ASA) physical status classification of I to III, and body mass index between 18 to 40 kg/m². Exclusion criteria were inability to cooperate, inability to speak or understand Danish, participation in other drug trials, daily use of methadone, previous or current psychotic episodes, uncontrolled hypertension, increased intraocular pressure, pregnancy, allergy to drugs applied in the trial, and alcohol or drug abuse.

2.2. Randomization and blinding

Patients were randomly assigned to 1 of 2 groups: S-ketamine bolus 0.5 mg/kg immediately after induction of anesthesia followed by infusion of S-ketamine 0.25 mg·kg⁻¹·h⁻¹, or placebo (bolus and infusion). Randomization was performed by the Capital Region Pharmacy according to a computer-generated block randomization list (each block containing 10 numbers) in a 1:1 ratio. Study medication and placebo were produced in identical ampules and pre-packed by the pharmacy in consecutively numbered boxes according to the computer-generated randomization list, containing identical 2 mL ampules of either S-ketamine (25 mg/mL) (Pfizer Aps, Denmark), or isotonic sodium chloride (NaCl) 9 mg/mL. After inclusion, patients were given the treatment corresponding to their randomization number. Information about treatment was concealed in consecutively numbered, sealed, opaque envelopes to enable unblinding in case of acute complications. The intervention was blinded to all patients, investigators, surgeons, and clinical personnel.

Before breaking the randomization code, enrolment of all patients and the 6-month follow-up period had ended; the data had been computed twice and afterwards double-checked in Microsoft Excel; exclusion of patients was decided, and statistical handling of the data was completed.

2.3. Interventions

One hour before surgery, all patients received their usual dose of opioids and oral paracetamol 1000 mg. General anesthesia was induced and maintained with propofol (variable rate) and remifentanil (fixed rate 40 μg·kg⁻¹·h⁻¹). Rocuronium (0.6-1.0 mg/kg) was used to facilitate orotracheal intubation with a cuffed tube. Immediately after induction of anesthesia, patients received study medication according to randomization, that is either S-ketamine (25 mg/mL) bolus 0.5 mg/kg, followed by infusion S-ketamine 0.25 mg·kg⁻¹·h⁻¹ or placebo bolus followed by placebo infusion (isotonic NaCl bolus 0.02 mL/kg and infusion isotonic NaCl 0.01 mL·kg⁻¹·h⁻¹). The infusion was discontinued at last suture of the skin.

Hypotension was treated at the discretion of the anesthetic staff with isotonic NaCl, ephedrine (5-10 mg), and/or metaxedrin (0.1-0.2 mg) intravenously.

The permanent spine surgeons at Centre for Rheumatology and Spine Diseases performed the lumbar fusion surgery. Forty-five minutes before expected completion of surgery, morphine 0.4 mg/kg was administered intravenously. If the patient was in unacceptably low pain or awakening in the operating room, IV sufentanil bolus 5 μg was administered at the discretion of anesthetic staff.

For all patients, postoperative pain treatment during the first 24 hours consisted of 1000 mg oral paracetamol every 6 hours, starting 2 hours postoperatively, and the patients’ usual opioid treatment. In addition, all patients received IV patient-controlled analgesia (PCA) with morphine (bolus 2.5 mg, lock-out time 5 minutes, and no background infusion). Rescue medication (IV morphine 2.5 mg p.n.) was administered by a nurse, in the postanesthesia care unit for the first postoperative hour in case the PCA was insufficient.

Moderate to severe nausea or vomiting assed by the patient was treated with IV ondansetron 4 mg, supplemented with 1 mg doses if needed. If ondansetron was ineffective, supplemental droperidol was available. No other analgesics, antiemetics, or sedative drugs were administered during the first 24 postoperative hours. After 24 hours, the PCA was discontinued and all patients were treated according to the department’s standard regime.

2.4. Assessments and outcomes 0 to 24 hours postoperatively

Preoperatively, patients were guided by one of the investigators in the use of the visual analogue score (VAS)-scale and the PCA pump. The introduction to the VAS-scale and the PCA pump was standardized. All postoperative assessments were performed by the trial investigators or trained nurses.

Cumulated PCA IV morphine consumption was registered from 0 to 24 hours postoperatively. Pain and adverse effects were evaluated at 2, 6, 12, 18, and 24 hours postoperatively. Pain was assessed on a VAS-scale (0-100 mm; 0, no pain; 100, worst imaginable pain), at rest, and during mobilization defined as moving from recumbent position to sitting bedside. Nausea and sedation were evaluated by the patients on a verbal rating scale: none, light, moderate, and severe nausea or sedation (0-3). The number of vomiting episodes with a volume greater than 10 mL was assessed by the nurse, and registered by the investigator. The need for antiemetics in the first 24 hours postoperatively was recorded. Episodes of hallucinations or nightmares were recorded by asking the patient 24 hours postoperatively. Other potential adverse effects were recorded.

The primary outcome was total PCA morphine consumption 0 to 24 hours postoperatively.

Secondary outcomes included pain during mobilization 2 to 24 hours postoperatively calculated as a “weighted average level”
area under the curve (AUC) (in mm) pain at rest (wAUC, 2-24 hours), morphine-related adverse events (nausea, vomiting, sedation, and postoperative use of antiemetics), episodes of hallucinations or night mares 0 to 24 hours postoperatively, and persistent pain 6 months postoperatively.

2.5. Questionnaires

Preoperatively, all patients filled out 3 written questionnaires screening for chronic pain (Brief Pain Inventory), pain catastrophizing (Pain Catastrophizing Scale), and anxiety and depression (Hospital Anxiety and Depression Score).

The Brief Pain Inventory36 is summarized as a pain score, an interference score, and a total score. Data are calculated as mean values of scores on a range from 0 to 10, with 10 indicating the worst possible situation. The Pain Catastrophizing Scale32 is summarized as one total score (range 0-52) calculated as the sum of all scores. A higher score indicates a higher degree of catastrophizing. The Hospital Anxiety and Depression Scale5 results are summarized as an anxiety score, a depression score, and a total score. An anxiety or depression score ≥8 indicates that anxiety or depression is likely. A total score ≥16 indicates a significant level of distress.

Six months postoperatively, patients filled out 5 written questionnaires. The DaneSpine Questionnaire35 included questions about demographic data, back and leg pain (VAS 0-100 mm), back and leg pain compared with preoperative pain levels (0 = no pain before, 1 = gone, 2 = much better, 3 = somewhat better, 4 = unchanged, 5 = worse), use of analgesics, duration of sick leave, working capability, and contentment with the results of the operation.

The Oswestry Low Back Pain Disability Questionnaire17 is summarized as an Oswestry Index Score with a range 0 to 100: 0 to 20, minimal disability; 21 to 40, moderate disability; 41 to 60, severe disability; 61 to 80, crippling back pain; 81 to 100, bedbound.

The Short Form 36 survey (SF-36) is summarized as 2 summary scores, one for the physical component summary score and one for the mental component summary score as described by McDowell.27 Using norm-based scoring for the summary scores, each scale is scored to have the same mean (50) and SD (10) as in the general Swedish population, provided by the SF-36 organization. Anytime a scale score is below 50, health status is below average relative to the general Swedish population.

The EuroQol 5D Questionnaire (EQ-5D)17 contains 5 questions with a score from 1 to 3; a higher score corresponds to severe problems. An index score is calculated from the median of all questions. Furthermore, the questionnaire includes a self-rated health status: VAS 0 to 100, higher score corresponds to better health.

The Douleur Neuropathique 4 Questionnaire (DN4)6 is summarized as one total score. Answering positively to one question adds 1 point. The minimum score is 0; the maximum score is 10. A total score ≥4 indicates that pain is likely to be neuropathic.

Figure 1. CONSORT flowchart of trial.
If patients had not returned the questionnaires after 3 weeks, they received one written reminder.

2.6. Statistical methods

Prestudy data from our own department showed that patients with spinal fusion have a mean morphine consumption 0 to 24 hours postoperatively of 36 mg IV, SD 24. With a type 1 error (α) of 5% and a power (1 − β) of 80%, sample size calculations showed that 64 patients in each group were required to detect a 30% reduction in morphine consumption (primary outcome). Taking dropouts and uncertainty about our calculated SD into account, we decided to include 150 subjects.

We analysed data using SPSS version 22.0 for Windows (SPSS, Chicago, IL). We performed complete case analysis for the AUC calculations because very few data were missing. For the rest of the outcome measures, we analysed the available data.

Variables were tested for normal distribution by visual inspection and with the Kolmogorov–Smirnov test. Data are presented as mean and SD or 95% confidence interval (CI), medians and lower and upper quartiles or frequencies, as appropriate. Data that followed normal distribution (morphine consumption, VAS-pain) were compared using the independent samples t test. Pain is presented as weighted average AUC 2 to 24 hours (wAUC) (in mm) for the period calculated according to the method described by Altman.1 The Mann–Whitney U test was used for data that were not normally distributed (6-month follow-up, nausea, vomiting, sedation; use of antiemetics, hallucinations, and nightmares). Categorical data were analysed using the χ² test or Fisher exact test if any cells had expected counts less than 5. For comparisons of nausea and sedation scores, we calculated the arithmetic mean scores by attributing numerical values to the scores from each patient; none = 0, slight = 1, moderate = 2, and severe = 3. The nature of the hypothesis testing was 2-tailed.

P values of less than 0.05 were considered statistically significant. Secondary outcomes were Bonferroni corrected where relevant and by the number of times the outcomes were measured. The primary investigator performed all statistical analyses.

3. Results

Two hundred eighty-three consecutive patients were considered for inclusion and eventually, 150 patients were included and randomly assigned to the treatment or the placebo group. Three patients were excluded and consequently, 147 patients were included in the final analysis, 74 and 73 patients in the ketamine and placebo groups, respectively (Fig. 1).

There were no significant differences in patient characteristics, or preoperative and perioperative characteristics between the 2 groups (Table 1). The preoperative daily use of opioids (oral morphine equivalents) was median 60 (33-80) mg and 58 (30-78) mg in the ketamine and placebo groups, respectively. The ketamine group received ketamine bolus 38 (33-43) mg and infusion 25 (20-34) mg intraoperatively. The placebo group received equivalent volumes of isotonic NaCl. In both groups, patients were operated on median 1 (1-2) lumbar spine segments.

### 3.1. Morphine consumption

The total 24-hour PCA morphine consumption was significantly reduced in the ketamine group compared with the placebo group: 79 (47) vs 121 (53) mg IV morphine with a mean difference of 42 mg (95% CI −59 to −25), P < 0.001. There was no significant difference in rescue IV morphine consumption during the first hour at the PACU postoperatively, median (quartiles): 13 (3-26) vs 15 (7-26) mg IV, P = 0.35.

### 3.2. Acute pain

Pain during mobilization (wAUC 2-24 hours) was comparable in the ketamine and placebo groups: 63 (21) vs 64 (18) mm respectively, with a mean difference of 1 mm (95% CI −8 to 5),
P = 0.63 (Fig. 2). Likewise, for pain at rest (wAUC 2-24 hours), there was no significant difference between groups: 46 (19) vs 48 (20) mm in the ketamine and placebo groups, respectively, with a mean difference of 2 mm (95% CI –8 to 5), P = 0.62 (Fig. 3).

### 3.3. Adverse events

There were no significant differences in nausea scores or ondansetron consumption between groups 0 to 24 hours postoperatively, both regarding number of patients with nausea, and severity of nausea (Table 2). Three patients received droperidol because of insufficient effect of ondansetron. The total number of vomiting episodes 0 to 24 hours was lower in the ketamine group, but the difference was not significant. Sedation was generally low in both groups, but significantly reduced at 6 hours and 24 hours postoperatively in the ketamine group (Table 2). There was no significant difference between groups in episodes of hallucinations or nightmares assessed 24 hours postoperatively (Table 2). One patient in the ketamine group experienced 10 hallucinations 0 to 24 hours postoperatively. No other adverse events were reported.

### 3.4. Persistent pain

The DaneSpine Questionnaire: at 6 months postoperatively, back pain levels (VAS) seemed lower in the ketamine group compared with the placebo group; however, the difference was nonsignificant after Bonferroni correction (Table 3). For leg pain levels (VAS), there were no significant differences between groups (Table 3).

When asked how patients evaluated their actual back pain compared with preoperatively, the ketamine group reported significantly more improvement of their pain compared with the placebo group: median 3 (2-3) vs 4 (3-4) respectively, P < 0.006 (Table 3).

Walking distance was significantly longer in the ketamine group, P = 0.012 (Table 3).

No significant differences between groups were observed regarding daily use of analgesics. In the ketamine group, 44%
(95% CI 30-58) and in the placebo group 62% (95% CI 48-75) of patients, respectively, had a daily use of opioids.

Results from the Oswestry Low Back Pain Disability Questionnaire, Short form 36 survey, EuroQol 5D Questionnaire, and The Douleur Neuropathique 4 Questionnaire are summarized in Table 4. The Oswestry index score demonstrated significantly less disability in the ketamine group, $P = 0.006$ (Table 4). No differences were demonstrated regarding Short form 36 survey, EuroQol 5D, or The Douleur Neuropathique 4 results.

Post hoc, we conducted an analysis of the effect of ketamine stratified by preoperative opioid consumption. Patients consuming $\geq 36$ mg oral morphine equivalents daily, preoperatively achieved a reduction in 24-hour PCA IV morphine consumption of 37% when receiving intraoperative ketamine, $P < 0.001$ (74 [37] mg vs 118 [50] mg in the ketamine and placebo groups, respectively). Patients consuming <36 mg/24 h of morphine equivalents preoperatively had no significant effect of ketamine (Table 5).

4. Discussion

We have demonstrated that intraoperative low-dose IV ketamine significantly reduced supplemental IV PCA morphine consumption during the first 24 hours after lumbar fusion surgery in opioid-dependent patients. Sedation was significantly reduced in the ketamine group.

Six months postoperatively, patients in the ketamine group reported significantly more improvement of their back pain compared with the placebo group; further, walking distance was improved compared with the placebo group. The Oswestry index score demonstrated significantly less disability in the ketamine group.

To our knowledge, only one previous trial has explored the effect of intraoperative ketamine infusion on chronic pain patients with opioid dependency.27 Loftus et al.23 reported a 30% reduction in total opioid consumption at 24 hours, and a 37% reduction at 48 hours. This finding is comparable with our results. However, the analgesics they used for PCA (primary outcome) were not standardized and included morphine, fentanyl, and hydromorphone, among others. Furthermore, the transition from PCA to oral analgesics at approximately 24 hours postoperatively was not standardized. Also, the ketamine group received intraoperative nonsteroidal anti-inflammatory analgesics (NSAIDs) more frequently than the placebo group (ketamine group: 26%; placebo group: 6.0%, $P = 0.006$), and the groups may not have been comparable because a significantly higher number of spine levels were operated on in the ketamine group.23

Table 3

Follow-up 6 months postoperatively. The DaneSpine Questionnaire.

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Ketamine</th>
<th>Placebo</th>
<th>$P$</th>
<th>$P$, corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate, n (%)</td>
<td>43 (58)</td>
<td>52 (71)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time from operation to follow-up, d</td>
<td>183 (175-192)</td>
<td>183 (173-200)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height, cm</td>
<td>173 (8)</td>
<td>170 (8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>79 (13)</td>
<td>75 (14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex, female/male</td>
<td>26/17</td>
<td>34/18</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Outcome

<table>
<thead>
<tr>
<th></th>
<th>Ketamine</th>
<th>Placebo</th>
<th>$P$</th>
<th>$P$, corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS back pain, 0-100 mm</td>
<td>30 (11-58)</td>
<td>54 (22-70)</td>
<td>0.04</td>
<td>0.24</td>
</tr>
<tr>
<td>VAS leg pain, 0-100 mm</td>
<td>30 (7-50)</td>
<td>34 (13-68)</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>VAS back pain &gt;0 mm, n (%)</td>
<td>38 (88)</td>
<td>49 (94)</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>VAS leg pain &gt;0 mm, n (%)</td>
<td>36 (84)</td>
<td>46 (89)</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>Back pain now compared with preoperative pain*</td>
<td>3 (2-3)</td>
<td>4 (3-4)</td>
<td>&lt;0.001</td>
<td>&lt;0.006</td>
</tr>
<tr>
<td>Leg pain now compared with preoperative pain*</td>
<td>2 (2-3)</td>
<td>2 (2-4)</td>
<td>0.37</td>
<td></td>
</tr>
</tbody>
</table>

Use of daily analgesics, mg

<table>
<thead>
<tr>
<th></th>
<th>Ketamine</th>
<th>Placebo</th>
<th>$P$</th>
<th>$P$, corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids†</td>
<td>0 (0-40)</td>
<td>0 (0-60)</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Paracetamol</td>
<td>1000 (0-3000)</td>
<td>3000 (0-4000)</td>
<td>0.02</td>
<td>0.08</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>0 (0-0)</td>
<td>0 (0-400)</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>0 (0-0)</td>
<td>0 (0-600)</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Work status, %</td>
<td></td>
<td></td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>Still on sick leave</td>
<td>42 (27-58)</td>
<td>59 (41-76)</td>
<td>0.05</td>
<td>0.012</td>
</tr>
<tr>
<td>Retired</td>
<td>26 (18-40)</td>
<td>22 (17-38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working</td>
<td>32 (20-46)</td>
<td>19 (10-31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sports active, %</td>
<td>54 (39-69)</td>
<td>33 (20-47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking distance, %</td>
<td>&lt;100 m</td>
<td>5 (0-12)</td>
<td>0.05</td>
<td>0.012</td>
</tr>
<tr>
<td>100-1000 m</td>
<td>44 (15-66)</td>
<td>49 (18-70)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1000 m</td>
<td>51 (37-66)</td>
<td>28 (16-41)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Satisfaction with surgical result, % (yes/no/unsure)</td>
<td>62 (45-75)</td>
<td>61 (47-75)</td>
<td>0.10</td>
<td></td>
</tr>
</tbody>
</table>

Data are mean (SD), median (lower and upper quartiles), or frequencies (95% confidence interval).

* Back and leg pain compared with preoperative pain levels (0 = no pain before, 1 = gone, 2 = much better, 3 = somewhat better, 4 = unchanged, and 5 = worse).
† Morphine, oxycodone, tramadol, buprenorphine, fentanyl, or ketobemidone. Significant $P$ values regarding pain are Bonferroni corrected 6 times, and 4 times regarding analgesic use.

VAS, visual analogue scale.
In our trial, the effect of low-dose perioperative ketamine was assessed with supplemental IV PCA morphine only. Apart from paracetamol to all patients, no further analgesics were used in the trial.

Our post hoc analysis showed that the ketamine-related reduction in morphine consumption was primarily due to reductions for opioid-dependent patients with a habitual consumption of oral morphine equivalents of $\geq 36$ mg/24 hours preoperatively. This result is similar to results from Loftus et al.23

Loftus et al.23 reported a significant effect of ketamine on immediate, but not late postoperative pain after surgery. In this trial, we did not observe any effect of ketamine on acute pain levels, neither at rest nor during mobilization. A possible explanation could be that all patients may have titrated PCA morphine to equally acceptable pain levels in the 2 groups. This would support the reduced PCA morphine consumption as the true analgesic effect of perioperative low-dose ketamine.28 Interestingly, we found postoperative pain levels comparable with those preoperatively in both groups, which may be due to the chronic nature of this pain.

Similar to previous trials of intraoperative ketamine, we demonstrated limited side effects.12,23 We found no differences between groups regarding nausea and vomiting. Significantly lower sedation scores were demonstrated in the ketamine group 6 and 24 hours postoperatively, possibly due to the higher opioid consumption in the placebo group. Generally, sedation was mild, and the clinical relevance of this result is probably negligible. Overall, opioid-related side effects were low in this specific patient population, which could be due to opioid habituation.14

Regarding specific side effects related to ketamine (hallucinations and nightmares), we found no significant differences between groups. One patient in the ketamine group experienced 10 hallucinations 0 to 24 hours postoperatively. However, these hallucinations were not reported as unpleasant, and did not need intervention. Our findings are comparable with previous results when using subanesthetic doses of ketamine, despite our choice not to administer prophylactic benzodiazepine.12

Six months postoperatively, patients in the ketamine group reported significantly more improvement of their back pain compared with the placebo group. Furthermore, patients in the ketamine group reported a longer walking distance, and had less disability on the Oswestry index score.13 Persistent pain after surgery often has neuropathic characteristics.15,20,24 thus an increased DN4 score in the placebo group could have been expected, but this was not found. Our data do not clarify whether pain measured 6 months postoperatively was new onset pain from the operation or remaining chronic pain also present preoperatively. However, the reduced persistent pain levels can possibly be due to ketamine’s blockage of the NMDA receptors and reduced wind-up and central sensitization.4,10 Recent evidence also indicate that ketamine has potent antidepressant qualities.31 Patients with chronic pain often have depression or depression-like symptoms as it was evident in our preoperative screening. We could, however, not demonstrate an effect of ketamine on mental health postoperatively. Whether this effect of ketamine in patients with chronic pain is short lived or has long-lasting impact needs further investigation.31

Loftus et al.23 found reduced pain levels 6 weeks postoperatively in the ketamine group. Pain levels 6 weeks postoperatively, however, may not be descriptive for the true risk of developing persistent pain which is usually defined as pain persisting beyond 3 months.29 Only 2 previous studies, none of which included patients with chronic pain and opioid dependency, have demonstrated effects of ketamine 6 months postoperatively.11,34 A review and meta-analysis investigated ketamine’s role in preventing persistent postoperative pain.21 In this analysis, only one of the 9 pooled estimates of postoperative pain demonstrated marginally significant pain reduction.21 Current evidence is still too sparse to draw conclusions.

Our results regarding persistent pain are limited by the low response rate of 65% at the 6-month follow-up, rendering data with low strength to draw conclusions on ketamine’s role in preventing persistent postoperative pain. We do not know the status of patients who did not respond. Our data must be considered exploratory secondary outcomes, and the sample size calculation was not based on these outcomes. The follow-up suffers from other well-known weaknesses of written questionnaires: a level of subjectivity, recall bias, interpretation of questions, and researcher imposition. Furthermore, it would have been ideal if the pain level method testing preoperatively and postoperatively was similar for an optimal comparison.

The strength of the overall trial is that few investigators were involved in the trial, leading to few protocol violations, and very few original data missing. Patient-groups were well matched for preoperative pain, opioid consumption, and a number of psychological factors. Surgery on the spine can induce severe postoperative pain and is associated with a high risk of persistent postsurgical pain, with a frequency of 5% to 75%.9,18 Lumbar fusion surgery is one of the top 6 surgeries with highest pain scores on the first postoperative day.16 We therefore considered
spinal fusion surgery to pose a rather well-defined surgical model to investigate the effect of intraoperative ketamine in opioid-dependent patients.

In conclusion, intraoperative low-dose S-ketamine significantly reduced PCA-morphine consumption during the first 24 hours after lumbar fusion surgery in chronic opioid-dependent patients, confirming our primary hypothesis. There was no effect on acute postoperative pain levels. Patients receiving ketamine reported significantly more improvement of their back pain, improved walking distance, and less disability in the Oswestry index score 6 months postoperatively. These latter findings are exploratory, and needs further confirmation.

Conflicts of interest statement

J. B. Dahl discloses to have served as a member of the Editorial Boards of Acta Anaesthesiologica Scandinavia, Pain, BMC Anesthesiology, and Scandinavian Journal of Pain within the last 5 years. The remaining authors have no conflicts of interest to declare.

The study was supported by the Department of Neuroanesthesiology Rigshospitalet, Glostrup, Copenhagen University Hospital.

Acknowledgements

We acknowledge and thank the nurses at the Department of Neuroanesthesiology and the nurses and surgeons at the Centre for Rheumatology and Spine Diseases, Rigshospitalet, Glostrup for their invaluable help and cooperation.

Article history:
Received 27 July 2016
Received in revised form 7 October 2016
Accepted 28 November 2016
Available online 6 January 2017

References

The patients we describe in this review are those who use illicit opioids, such as heroin, those who use diverted prescription opioids for nonmedical use, or those who take other illicit drugs. These drugs include stimulants (amphetamines, cocaine), depressants (alcohol, barbiturates, benzodiazepines), and others including cannabis, mescaline, and LSD.

Definitions

The nomenclature around the illicit use of drugs remains confusing, but the recent International Statistical Classification of Diseases and Related Health Problems (ICD-10, released by the World Health Organization [WHO] in 2016) uses “dependence syndrome” as the preferred term [32]. Other terms such as “addiction,” “substance use disorder,” and “substance misuse” relate to the same condition, but for the purpose of clarity and simplicity we use “dependence syndrome” in this review. Dependence syndrome is defined as:

A cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and that typically include a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal state [32].

Patients may have active dependence, where they are currently using the drug, or controlled dependence, where they are on a clinically supervised maintenance or replacement regimen, or they may be currently abstinent. Those who are currently abstinent are no longer physically dependent on the drug but are particularly vulnerable to relapse, owing to the chronic changes induced by drug use. The American Society of Addiction Medicine defines “addiction” (or “dependence syndrome” in the newer nomenclature) as a chronic disease of brain reward, motivation, memory, and related circuitry [2].

In the context of pain management, we also need to be aware of pseudoaddiction, a syndrome associated with the undertreatment of pain, characterized by problem behaviors around seeking more opioid analgesia. Pseudoaddiction can be distinguished from true addiction in that the behaviors cease when pain is effectively treated.

Background

Globally, the United Nations estimate that around 250 million people (5% of the world’s adult population) used an illicit drug at least once in 2014, while the number of people classified as having a drug use disorder is estimated to be 29 million [29]. Of the drugs abused,
opioids are used less often than cannabis, cocaine, or amphetamine but contribute to 82% of fatal overdoses. Alcohol is one of the one of the most frequently used drugs, with Germany citing one in five perioperative patients having an alcohol use disorder [14].

Recent figures suggest there are 1.3 million high-risk opioid users in the European Union. Approximately 435,000 people in the United States use heroin, while almost 5 times that number—1.9 million—meet criteria for prescription opioid use disorder [26]. Australia has seen a similar increase in prescription opioid misuse, with 3.3% of Australians having used prescribed opioid analgesics for nonmedical purposes in the past year, compared to 0.1% using heroin [1]. Those misusing prescription opioids may tamper with tablets to adapt them for inhalation, intravenous use, or smoking, leading manufacturers to investigate abuse-deterrent formulations.

Assessment and Screening of Patients

The stigma associated with addiction, often fueled by misinformation or prejudice on the part of healthcare professionals, is often a barrier to good medical care for those with a current or past history of dependence. Competence in managing patients with dependence requires knowledge of pharmacology; an understanding of the diagnosis of dependence and recognition of withdrawal; skills in communication and collaborative working; and a nonjudgmental, empathic attitude. It is essential to establish good patient-clinician rapport to promote an atmosphere of trust and understanding. This will allow an open discussion to accurately ascertain which drugs the patient is currently taking, address the patient’s anxieties, manage expectations, and plan care collaboratively, thus reducing discord between the patient and the healthcare team.

On or before admission, clinicians should reconcile the patient’s medicines with the patient’s primary care physician and/or drug and alcohol worker. In preparation for discharge, the team should arrange community support to provide follow-up and manage the process of analgesia reduction during the recovery phase.

There is a high prevalence of psychiatric comorbidities in those with drug dependence, with more than 50% of patients showing evidence of significant psychopathology, particularly anxiety disorders and affective disorders, including depression [5]. Such comorbidities may further complicate patients’ behavior and their interaction with staff while in the hospital.

In some cases, urine screening could be considered to detect drugs and assist in formulating a treatment plan while in hospital. Table 1 lists the duration of time that drugs may be detected in urine.

Concerns in Treating Acute Pain in Patients with Drug Dependence Syndrome

On admission to hospital, patient concerns center on:
- The fear of withdrawal, such as when the usual opioids used in substitution therapy are not given promptly. These anxieties are most obvious after long waits in the emergency department or immediately after admission to the hospital, when the drug has not yet been prescribed or released by the pharmacy. If doses are omitted or delayed, there will be a re-emergence of withdrawal symptoms and drug cravings.
- The fear of pain not being taken seriously, with restricted access to analgesia and pain left unrelieved.
- The fear of discrimination, often based on previous poor hospital experiences, leading to clinician distrust.
- In those currently abstinent, the fear of relapse if re-exposed to opioids or untreated pain.

Clinician concerns center on:
- Mistrust of those with addiction.
- Overtreatment of pain, leading to opioid-induced ventilatory impairment.
- The possibility that reports of pain may be fabricated to acquire opioids for euphoria.
- The diversion of prescribed opioids.
- Fear that patients may leave the hospital against medical advice (elopement) and not completing essential medical care (e.g., infection control).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Urine detection of drugs (approximate duration in hours/days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine and metabolites:</td>
<td>8 days</td>
</tr>
<tr>
<td>Cocaine metabolite:</td>
<td>48–72 hours</td>
</tr>
<tr>
<td>Methadone maintenance dosing:</td>
<td>7–8 days</td>
</tr>
<tr>
<td>Heroin (diamorphine), detected as morphine, codeine, dihydrocodeine, and propoxyphene:</td>
<td>48 hours</td>
</tr>
<tr>
<td>Cannabinoids, single use:</td>
<td>3–4 days</td>
</tr>
<tr>
<td>Cannabinoids, heavy or chronic use:</td>
<td>up to 45 days</td>
</tr>
<tr>
<td>Amphetamines:</td>
<td>48 hours</td>
</tr>
<tr>
<td>Benzodiazepine (short-acting, such as midazolam):</td>
<td>12 hours</td>
</tr>
<tr>
<td>Benzodiazepine (long-acting, such as diazepam):</td>
<td>over 7 days</td>
</tr>
<tr>
<td>Source: Adapted from Vadivelu et al. [30].</td>
<td></td>
</tr>
</tbody>
</table>
Key Issues to Assess on Hospital Admission for Dependence Syndrome [12]

- The appropriate use and dosage of opioid substitution therapies (OST) (methadone, buprenorphine); doses will need to be verified by the opioid prescriber and the dispensing pharmacist
- Other prescribed medications, over-the-counter drugs or illicit substances including heroin, alcohol, nicotine, benzodiazepines, cannabis, and cocaine (polyabuse is common)
- Routes of administration—some patients may be injecting prescription drugs intended for oral, transdermal, or sublingual use
- Medical comorbidities, e.g., HIV/AIDS, hepatitis, cirrhosis, tuberculosis, endocarditis, cellulitis, abscesses, chronic pain
- Psychiatric comorbidities, e.g., anxiety, depression, personality disorder, post-traumatic stress disorder
- Social factors, e.g., abuse, interpersonal violence, homelessness
- Support systems after discharge

Principles of Acute Pain Management in Opioid-Dependent Patients

The goals of treating acute pain in patients using opioids are to provide adequate analgesia, to prevent withdrawal, and to avoid triggering a relapse or worsening of the addiction disorder. The principles of treating acute pain in a patient with opioid addiction are summarized in Table 2.

Patients with an opioid dependency have three interlinked obstacles to effective pain management: (1) opioid-induced hyperalgesia (OIH), resulting in increased pain sensitivity; (2) opioid tolerance, leading to reduced effectiveness of opioids used to treat pain; and (3) opioid withdrawal, producing sympathetic stimulation and heightened stress responses if the usual opioids, such as those for OST, are not given.

1. Opioid-Induced Hyperalgesia

Quantitative sensory testing (QST) has shown that, similar to pain patients taking long-term opioids, those abusing heroin and those on methadone and buprenorphine substitution therapy may develop hyperalgesia [23]. Once opioids are stopped, it is unclear when this pain sensitivity reverses, but it would appear that heat and pain perception remain abnormal for months after cessation. It is wise, then, to consider patients who are currently abstinent to also be at risk of OIH.

Management of OIH

Multimodal analgesia should be optimized by adding opioid-sparing analgesics such as paracetamol (acetaminophen), nonsteroidal anti-inflammatory drugs (NSAIDs), or cyclooxygenase-2 (COX-2) inhibitors, using local anesthetic regional techniques where appropriate, and considering opioid rotation.

In addition, adjuvants have an important role in pain management. Ketamine attenuates OIH in patients on long-term opioids. Gabapentin and pregabalin reduce OIH in animal models, human volunteers, and patients. There is some evidence that alpha-2 agonists—clonidine and dexametomidine—may decrease hyperalgesia, while experimental results indicate that COX-2 inhibitors may also have a role [23].

2. Opioid Tolerance

Opioid tolerance is the decreased effectiveness of opioids over time, such that higher doses are needed to achieve the same effect. Given that opioids are the mainstay of treating severe acute pain, it is unfortunate that opioid tolerance and OIH combine so that opioids are least effective for those patients with, arguably, the most pain.

Opioid-tolerant patients report higher pain scores, have slower pain resolution, and experience a longer hospital stay with increased chance of readmission, compared to opioid-naive patients [7, 10]. They have higher opioid requirements, but interpatient variability is high, so doses need to be titrated to effect for each patient, with careful observation for signs of opioid toxicity.

Management of Opioid Tolerance

Where opioids are required, higher doses are needed in opioid-tolerant compared to opioid-naive patients.

---

### Table 2: Principles of treating acute pain in a patient with opioid dependence

<table>
<thead>
<tr>
<th>Principles of treating acute pain in a patient with opioid dependence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Create a supportive, nonjudgmental environment</td>
</tr>
<tr>
<td>Establish whether other drugs are misused</td>
</tr>
<tr>
<td>Analgesic plan:</td>
</tr>
<tr>
<td>- Optimize nonopioid analgesia</td>
</tr>
<tr>
<td>- Use increased doses of opioids compared to opioid-naive patients but with careful monitoring for side effects</td>
</tr>
<tr>
<td>- Change from parenteral to oral formulations of opioids as soon as possible</td>
</tr>
<tr>
<td>Withdrawal management plan:</td>
</tr>
<tr>
<td>- Continue opioid substitution therapy or replace with an appropriate opioid</td>
</tr>
<tr>
<td>- Consider withdrawal syndromes of other drugs taken</td>
</tr>
<tr>
<td>Minimize stress</td>
</tr>
<tr>
<td>Allow for multidisciplinary discharge planning</td>
</tr>
</tbody>
</table>
The adjuvants employed to reduce OIH also reduce opioid tolerance. Ketamine particularly has been found to improve postoperative pain in opioid-tolerant patients. In various experimental and clinical models, gabapentin and pregabalin, paracetamol, NSAIDs, COX-2 inhibitors, and alpha-2 agonists all moderated tolerance [23].

3. Opioid Withdrawal
Opioid withdrawal symptoms are caused by sympathetic overactivity and include tachycardia, anxiety, restlessness, insomnia, sweating, diarrhea, rhinorrhea, muscle aches, yawning, and “gooseflesh.” Scoring systems such as the Subjective Opiate Withdrawal Scale (SOWS) or the more objective Clinical Opiate Withdrawal Scale (COWS) [31] offer ways to assess the severity of withdrawal. These symptoms contribute to stress and anxiety, which in itself will increase pain sensitivity, reduce coping ability, and drive drug craving.

Some patients may be established on opioid substitution therapy (OST), also known as opioid maintenance treatment. This treatment involves providing controlled doses of long-acting opioids to maintain blood levels within a narrow range, such that patients experience minimal intoxication and minimal withdrawal, thus reducing the sensations driving opioid drug seeking and drug misuse [9]. Sublingual buprenorphine and oral methadone are most commonly used for OST and have recognized benefit in reducing levels of drug use, offending, overdose risk, and the spread of blood-borne viruses, as well as providing stability for drug users and their families. Some people may subsequently achieve long-term sustained abstinence.

The central tenet of withdrawal management is to prevent its development, providing more stability for patients and reducing psychological and physiological stress. This is important both in the short term during hospital admission, and in the longer term to ensure that patients maintain their commitment to the OST program. An acute pain episode can precipitate disengagement from OST and a return to haphazard drug-taking, with poorly treated acute pain increasing that risk further [4].

Methadone
When patients are taking methadone for OST, clinicians should continue this drug after confirming the dose with the usual prescriber or the dispensing pharmacy. Withdrawal suppression lasts around 24 hours, so the dose can be continued once a day as in the community, or given in two or three divided doses during hospital admission. It is important to understand that the patient will not gain any meaningful analgesia from this dose, and that withdrawal prevention and analgesia provision should be treated as separate entities.

Methadone can cause prolongation of the corrected electrocardiographic QT (QTc) interval, which may predispose patients to the ventricular arrhythmia torsades de pointes. Acute illness and co-prescription of acute medicines may increase the risk of cardiac arrhythmia in the hospital in patients who may have previously been stable. Circumstances include electrolyte abnormalities such as hypokalemia or hypomagnesemia; impaired liver function; and the use of drugs with QTc-prolonging properties, for example antibiotics and benzodiazepines [8].

Buprenorphine
Buprenorphine is a partial agonist at the mu-opioid receptor with a high binding affinity. At high doses of 16–32 mg, such as those used in OST, there is little free receptor availability, such that additional pure opioid agonists including heroin would impart no benefit. For this reason it had been thought that buprenorphine should be stopped during hospital admission to allow receptor accessibility for opioids used for analgesia. Studies are beginning to emerge to question that approach. It would now appear that, when given in divided doses, some patients on buprenorphine OST may do better if the buprenorphine is continued [16]. The total dose should be split into two or three divided doses during hospital admission and then converted back to a daily dose on discharge into the community [23].

Withdrawal Prevention for Patients Not on OST
If a patient with opioid dependence is not on an OST program, withdrawal remains a problem and can be assessed using the COWS measure alongside routine patient observations. Small doses of methadone (10–20 mg depending on the severity of withdrawal) can then be used on the basis of the COWS score.

Methadone is preferred over morphine for withdrawal prevention as it provides longer-lasting withdrawal prevention and reduces craving (the psychological need for more opioid).

Withdrawal Prevention for Patients on Nil by Mouth
For patients with unreliable enteral absorption, intravenous patient-controlled analgesia (PCA) should be established with the bolus providing analgesia. A background infusion can then be added to the PCA for opioid withdrawal prevention. Careful monitoring of withdrawal symptoms, sedation, and respiratory rate are essential to guide dose requirements. Although those with opioid dependence demonstrate tolerance to the analgesic effects of
opioids, tolerance to the side effects will vary, so sedation and opioid-induced ventilatory insufficiency remain a risk. A tamper-proof housing should be used to reduce access to the programmable device and the analgesic medicine.

**Risk of Relapse in Abstinent Patients**

The rate of absorption of an opioid and the peak concentration attained determine its abuse potential [22]. Intravenous opioids given for analgesia will therefore have a stronger reinforcing effect and present more of a threat to relapse in an abstinent patient than oral opioids, with sustained-release preparations lowering the abuse potential further. Conversely, the severity of acute pain will fluctuate according to activity, so such pain is best treated with short-acting formulations. A balance should be found between the two with a plan to switch to oral opioids as soon as is practicable.

Some patients who are currently abstinent will be very reluctant to have intravenous opioid boluses, and this preference should be respected, with other drugs given instead where possible. There is some evidence to suggest that the risk of relapse is small with the use of perioperative opioids, although unrelieved pain could be a trigger [23]. If an abstinent patient relapses, he or she should be supported to engage with addiction services to aid recovery.

**Nonopioid Substance Dependence in Acute Pain**

An appreciation of the patterns of nonopioid substance misuse is necessary to reduce the risk of drug interactions and to identify and treat withdrawal. Commonly misused drugs are outlined below with information about the signs and symptoms of withdrawal and toxicity. Withdrawal from central nervous system (CNS) stimulants is predominantly affective rather than physical, while withdrawal from CNS-depressant drugs leads to CNS and autonomic hyperexcitability.

Substance misusers are one of the groups of patients at high risk of self-discharge against medical advice [11]. They, like opioid-dependent patients, are at risk of pseudoaddiction if their acute pain is undertreated.

The U.S. Preventive Services Task Force recommends the screening of all patients for alcohol misuse, but it does not recommend screening for other substance use disorders as there is limited evidence [18].

**Illicit Drugs**

A full medical history related to prescription and illicit drug use may identify a number of agents that could potentially require adjustment of inpatient analgesia for pain. These illicit drugs may include stimulants (amphetamine, cocaine); depressants (alcohol, barbiturates, benzodiazepines); and others including cannabis, mescaline, and LSD. An overview of the origin and mode of action appears below for each subgroup of drugs together with the signs and symptoms of withdrawal or abstinence, along with considerations for a treatment plan.

**Stimulants**

**Amphetamines (Eye-openers, Dexies, Poppers, Speed, or Uppers)**

Amphetamines are CNS stimulants commonly prescribed for narcolepsy and hyperactivity disorders, e.g., attention deficit hyperactivity disorder. One common stimulant, methylphenidate (sold under the trade name “Ritalin” in some countries and often called the “Smart Drug” or “Study Drug”), is commonly abused by students as they perceive that it helps them concentrate.

The release of sympathetically active substances by the use of amphetamines, most commonly 3,4-methylenedioxyamphetamine (MDMA), can lead to euphoria, aggression, and personality changes. Toxic MDMA levels lead to tachycardia, sweating, rhabdomyolysis, malignant hyperpyrexia, and hepatorenal failure. Long-term use is associated with psychosis, cardiac problems, malnutrition, and convulsions.

Abstinence or withdrawal from this class of drug within the first week produces a “crash” phase that lasts for a few days, characterized by severe dysphoria, irritability and melancholia, anxiety, hypersomnia (but with poor quality sleep) and marked fatigue, intense craving for the drug, and paranoia [24]. Three components of amphetamine withdrawal have been described: (1) a hyperarousal factor involving drug craving, agitation, and vivid or unpleasant dreams; (2) a reversed vegetative factor involving decreased energy, increased appetite, and increased craving for sleep; and (3) an anxiety factor involving loss of interest or pleasure, anxiety, and slowing of movement [25].

Aspects of the withdrawal syndrome might be mediated by different neurotransmitter systems including dopamine, norepinephrine, and serotonin [24]. Trauma patients presenting to the emergency department with the use of cocaine and/or amphetamines prior to their acute injury had analgesic and sedation requirements (where ventilated) similar to those of a control cohort [15].

**Khat (Kat, Qat, Chat)**

Khat contains an alkaloid stimulant (cathinone) and is derived from the shrub Catha edulis. The leaves are chewed like tobacco or, less frequently,
are used to make tea. Khat is a euphoric stimulant less potent than amphetamines. Khat is widely used in the Arabian Peninsula (especially Yemen) and the Horn of Africa. WHO has identified that khat has the ability to cause mild to moderate psychological dependence. In the developing world khat is often used to relieve fatigue [13]. Since physiological withdrawal is unknown with khat, no substitution is required.

**Cocaine**

The easy availability of cocaine coupled with a relative reduction in consumer cost has led to widespread use. It is available in two forms: hydrochloride (white powder), and free base (crack cocaine), which is made by combing the hydrochloride with an alkali. With a bioavailability of up to 90% by the inhalation or intranasal route, cocaine inhibits the presynaptic uptake of dopamine, serotonin, epinephrine, and norepinephrine, thus leading to an increased availability to act on the adrenergic receptors stimulating the cardiovascular, renal, and central nervous systems [23]. Excessive stimulation by cocaine can lead to seizures, myocardial infarction, stroke, respiratory depression, cardiac arrhythmias, and sudden death. The features of cocaine withdrawal include agitation, restlessness, depressed mood, fatigue, increased appetite, vivid dreams, extreme suspicion, and paranoia. Cocaine use is associated with particular types of acute pain, for example chest pain, including acute coronary syndrome [23].

**Depressants**

**Alcohol**

A full discussion of inpatient management of patients with alcohol dependence is beyond the scope of this review, but it is important to identify patients with problem alcohol use.

SBIRT (Screening, Brief Intervention, and Referral to Treatment) is a strategy used to determine those with risky drug use and to guide early intervention. It has become one of the major tools recommended for use in primary care by governments and expert panels, including the Joint Commission on Accreditation for Health Care Organizations (JCAHO), the major accrediting body for hospitals in the United States, which uses SBIRT as a quality indicator for general hospital care. The American Society of Addiction Medicine provides detailed guidance on managing acute alcohol withdrawal [19] and has been updated by Makdissi et al. in 2013 [17]. The summary of alcohol and acute pain in Acute Pain Management: Scientific Evidence reports no cross-tolerance between alcohol and opioids in animal studies and states that effective remifentanil concentrations do not differ between alcoholic and nonalcoholic patients [23]. Thus, there is no need to use higher than standard doses of opioids in alcohol-dependent patients. Abstinence or withdrawal from alcohol may produce withdrawal seizures and delirium tremens.

The National Institute for Health and Care Excellence suggests following a symptom-triggered regimen for drug treatment [21] and recommends using a tool such as the Clinical Institute Withdrawal Assessment—Alcohol, revised [CIWA–Ar] scale to supplement clinical judgment [27]. The treatment for alcohol withdrawal seizures includes offering a benzodiazepine, carbamazepine, or chlorpromazine. Delirium tremens may be treated using oral lorazepam, escalating to parenteral lorazepam, haloperidol, or olanzapine. A short-acting benzodiazepine such as lorazepam may be used if the patient experiences seizures. Phenytoin should be avoided [21].

© Copyright 2017 International Association for the Study of Pain. All rights reserved.

For permission to reprint or translate this article, contact: International Association for the Study of Pain 1510 H Street NW, Suite 600, Washington, D.C. 20005-1020, USA Tel: +1-202-856-7400 Fax: +1-202-856-7401 Email: iaspdesk@iasp-pain.org www.iasp-pain.org
Barbiturates

Derivatives of synthetic barbituric acid, barbiturates are sedative hypnotics; they include phenobarbital and sodium thiopental. Although usually consumed in tablet form, barbiturates may be injected intravenously or intramuscularly. Most commonly, barbiturates are taken by misusers to counteract the effects of amphetamines and cocaine or to produce a state of euphoria (a “high”). Abstinence or withdrawal from this class of drug produces hallucinations, high temperatures, restlessness, and seizures. There is little high-quality evidence for the safe management of barbiturate withdrawal.

Benzodiazepines

The most commonly used anxiolytics and hypnotics, benzodiazepines act at gamma-aminobutyric acid (GABA) receptors. Abrupt withdrawal of a benzodiazepine may produce confusion, toxic psychosis, convulsions, or a condition resembling delirium tremens.

Withdrawal syndrome may develop at any time up to 3 weeks after stopping a long-acting benzodiazepine (such as diazepam) but may occur within a day in the case of a short-acting one (such as lorazepam). Withdrawal is characterized by insomnia, anxiety, loss of appetite, loss of body-weight, tremor, perspiration, tinnitus, and perceptual disturbances. Some symptoms may continue for weeks or months after stopping benzodiazepines. The dangers of co-prescribing of benzodiazepines and opioids have been outlined in a previous issue of Pain: Clinical Updates [3]. There is no need to use higher than standard opioid doses in benzodiazepine-dependent patients [23].

Hallucinogens

Cannabis (Marijuana, Weed, Dope)

Derived from the Cannabis sativa plant, the extract from dried leaves is known as marijuana, whereas hashish is produced from a concentrated resin, resulting in a stronger drug effect. Delta-9-tetrahydrocannabinol is the psychoactive agent that inhibits the muscarinic receptor of the parasympathetic system, increasing the turnover of acetylcholine [30]. Users report feelings of euphoria, enhanced mood, and reduction in nausea. Marijuana is usually smoked, but may be eaten or taken in tea. Withdrawal presents in chronic users as insomnia, craving, aggression, headaches, fatigue, hot/cold flushes, and aching muscles. There is limited evidence for the need for higher opioid doses for acute pain in recreational cannabis users [23].

Synthetic Cannabinoids (Spice, K2, Clockwork Orange, Black Mamba)

These drugs bear little relation to cannabis, but the synthetic cannabinoids are usually sprayed onto plant materials to make them look like marijuana. The varieties of chemicals used are far stronger [8] than in naturally occurring cannabis, with a high potential for addiction and abuse and a risk of psychosis or central nervous system depression. Withdrawal states may mimic those for opioids. As these synthetic cannabinoids cause tachycardia, agitation and nausea, supportive care will be needed for 8 hours after use [28].

Mescaline (Buttons, Cactus, Mesc)

Mescaline (peyote) is a small, spineless cactus with button-like protrusions on its roots that contain mescaline, an hallucinogen. These cacti grow in the United States, Mexico, and Peru. The bitter protrusions are cut and allowed to dry, then ground into a powder and soaked with tobacco or cannabis. Alternatively, they may be soaked in water, with the user drinking the liquid. The drug can also be chemically synthesized in the laboratory [6]. Users report being in a pleasant dreamlike state that lasts 12–18 hours, although mescaline can cause vomiting, headaches, and a feeling of anxiety.

LSD (Acid, Battery Acid, Blotter, Elvis, Loony Tunes, Lucy in the Sky with Diamonds)

LSD (lysergic acid diethylamide) is a synthetic drug that has been abused for its hallucinogenic properties since the 1960s. If consumed in a sufficiently large dose, LSD produces delusions and visual hallucinations that distort the user’s sense of time and identity. Lysergic acid derives from the ergot fungus, found on grains such as rye. LSD is manufactured by mixing the ergot fungus with other substances. It is hardened and crystalized, then liquefied, and finally sold on the streets, usually as gelatin squares or tablets. LSD is not considered an addictive drug by the National Drug Intelligence Center [31], but LSD users may develop tolerance to the drug, meaning that they consume progressively larger doses of the drug in order to continue to experience the hallucinogenic effects that they seek. Unpleasant flashbacks can occur weeks after taking the drug [20].

Discharge

Discharge planning begins at admission [12] to ensure that the patient is discharged into a safe and supportive environment. Referral to a hospital social worker should be undertaken upon awareness of a patient with a drug dependence syndrome to allow sufficient time to explore any community housing needs and to inform the discharge plan.

Good communication with primary care clinicians, dispensing pharmacists, and drug treatment services is essential to ensure that patients re-engage with support services and maintain their pre-hospital management.
Where opioids for analgesia are needed on discharge, decisions on how to provide that safely will be based on the services available in individual hospitals. Immediate-release formulations would be most appropriate for the ongoing treatment of acute pain, but they carry a higher risk of diversion or overdose. Some hospitals may be able to offer frequent outpatient appointments in the time immediately following discharge so that limited doses of short-acting opioids can be given and weaned under close supervision.

Where this intense control is not available, supervised consumption of long-acting preparations may be the safest and most appropriate way of providing short-term pain relief and preventing diversion, with a clear and specific plan to guide dose reduction.

References
• **FACT SHEET No. 9**

**Management of Postsurgical Pain in Patients Treated Preoperatively with Opioids**

Increasing numbers of patients present for surgery after having received opioids preoperatively because of:

- Cancer-related pain
- Chronic non-cancer pain (e.g., due to osteoarthritis)
- Recurrent acute pain (e.g., sickle cell disease or pancreatitis)
- Substance use disorder treated with daily opioid maintenance
- Illicit, untreated substance (i.e., opioid) use disorder
- Exposure to high doses and/or high potency opioids for prolonged intervals after surgery or trauma

Many of these patients are tolerant to the analgesic effects of opioids. “Tolerance” refers to the physiologically-based decrease in the effect of a drug administered repeatedly over time—or equivalently, the need for increasing doses over time to evoke the same physiological response as the initial dose.

Opioid-tolerant patients are at increased risk of acute and chronic postsurgical pain and of undertreatment of pain. Their management presents challenges that are best met with a systematic, evidence-guided strategy. Overarching principles of postoperative pain management in opioid-tolerant patients are:

- Careful assessment (including psychosocial factors)
- Provision of effective analgesia despite reduced efficacy of opioids
- Attenuation of tolerance and opioid-induced hyperalgesia (OIH)
- Prevention of opioid abstinence syndrome
- Close communication with other health-care professionals
- Appropriate discharge planning

IASP brings together scientists, clinicians, health-care providers, and policymakers to stimulate and support the study of pain and translate that knowledge into improved pain relief worldwide.
Provision of Effective Analgesia

Even in opioid-tolerant patients, opioids can be used to provide analgesia in the postsurgical setting. However, opioid dosing must be titrated to effect (ideally initially by use of patient-controlled analgesia), and their analgesic effect may be limited. Multimodal analgesia is particularly useful in this setting:

- Regional analgesia techniques as feasible given the nature and site of the operation, and absence of contraindications such as coagulopathy
- Use of non-opioid analgesics
- Use of adjuvant medications as outlined immediately below

Attenuation of Tolerance and Opioid-Induced Hyperalgesia (OIH)

Long-term use of opioids may, in addition to producing analgesic tolerance, also induce increased sensitivity to nociceptive stimuli—the latter termed “opioid-induced hyperalgesia” (OIH). A number of strategies have been described to attenuate these effects:

- “Rotation”—switching to a different opioid
- Use of NMDA receptor antagonists (e.g., ketamine)
- In some cases, modulators of the alpha-2-delta calcium channel (gabapentin, pregabalin)

Prevention of Opioid Withdrawal in Inpatients After Surgery

Long-term use of opioids induces physical dependence, which creates a risk of withdrawal reactions when opioids are abruptly reduced or stopped or if the opioid antagonist naloxone is administered. Strategies to prevent postoperative opioid withdrawal include:

- Maintenance of preoperative opioid baseline doses perioperatively
- Substitution with a different opioid if pretreatment was with an oral agent and the oral route is not available postoperatively
- Caution when using opioid antagonists (e.g., to treat presumptive opioid-induced hypoventilation); when doing so, divide the intended naloxone dose into small aliquots and titrate to the minimal desired effect
- Alpha-2 adrenergic agonists (clonidine, lofexidine, dexmedetomidine) can attenuate withdrawal reactions, as may possibly alpha-2-delta modulators (gabapentin, pregabalin)

Discharge Planning

Discharge of opioid-tolerant patients requires careful planning and coordination with the health-care professionals who will look after patients in the outpatient setting (including staff of opioid maintenance programs for substance use disorder). Emphasis should be placed upon the appropriate use of the lowest likely dose of postoperative opioids (allowing
for the frequent presence of analgesic tolerance to opioids) for the shortest necessary duration after discharge. Vigilance must be maintained for chronicification of acute pain so as to permit early treatment.

Patient-Centered Information

There is an increasing use of opioids, morphine-like painkillers, worldwide, as well for pain treatment as in drug addiction and its treatment. Patients on opioids require specific care in the postoperative period, as they have an increased risk of postsurgical pain. Management requires careful use of appropriate painkillers and specific measures to reduce withdrawal reactions.

RESOURCES AND REFERENCES


AUTHOR

Stephan A. Schug, MD, FANZCA, FFPMANZCA
Chair of Anaesthesiology
Pharmacology, Pharmacy, and Anesthesiology Unit
School of Medicine and Pharmacology
University of Western Australia
Director of Pain Medicine, Royal Perth Hospital
Perth, Australia

REVIEWERS

Hazem A. Ashmawi, MD, PhD
Head of the Pain Clinic, Department of Anesthesia
Hospital das Clínicas of the University of São Paulo School of Medicine
Collaborative Professor, Department of Surgery
University of São Paulo School of Medicine
São Paulo, Brazil

Maria Dolma Gudez-Santos, M.D., M.H.A.
Director, Pain Management Clinic
Consultant, Department of Anesthesiology
The Medical City General Hospital
Manila, Philippines
MUNDIPHARMA, DEDICATED TO PAIN

At Mundipharma we are thinking differently about pain. We know pain is a reality, but when it becomes prolonged and not well managed we recognise that there is a role for us to play in providing effective solutions. We know we can’t cure this pain but we can address the pain-life balance – shifting people’s experiences away from pain and back towards the enjoyment of life.

Mundipharma is committed to pain, and has a proven track record of bringing pain innovations to market since the 1980s - successfully launching MST Continus®, Sovenor®, OxyNorm®, OxyContin® and TarginAct®. We want to build on this heritage - using our medical expertise, and experience of the market to identify unmet needs in the management of pain and in the development of new innovative treatments for patients.

We are continuing our endeavour to be the HCPs partner in pain, by not only providing medication, but also by improving education around pain and its appropriate management. We are proud to have launched a Pain Podcast App (available from 1st August 2016), which was developed in partnership with local HCPs with expertise in pain. This platform provides monthly educational talks, with a new pain podcast uploaded every 1st Monday of the month for you to LEARN and EARN 3 CPD Points.

2017 Programme:

Monday 2 January: Pain: definitions, classifications and syndromes – Dr Bechan (Anaesthetist, Durban)
Monday 6 February: Treating arthritis pain 4-6 hourly dosing prn – Dr van Duuren (Rheumatologist, Pretoria)
Monday 6 March: The management of cancer pain: Discussing the ESMO clinical practice guidelines – Dr Langenhoven (Oncologist, Cape Town)
Monday 3 April: The importance of the correct pain management in renally impaired patients - Dr Bihl (Nephrologist, Somerset West)
Monday 1 May: Approach to Low Back Pain: Common Sense to Approach a Common Problem – Dr Jansen van Rensburg (Rheumatologist, Bloemfontein)

And many more to follow…
## 2017 PAINSA ACADEMY MEETINGS

<table>
<thead>
<tr>
<th>Name</th>
<th>Date</th>
<th>Venue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durban Pain Academy</td>
<td>Saturday 10 June</td>
<td>Coastlands Umhlanga &amp; Convention Centre, Durban</td>
</tr>
<tr>
<td>Pretoria Pain Academy</td>
<td>Saturday 9 September</td>
<td>Protea Hotel Fire &amp; Ice Menlyn, Pretoria</td>
</tr>
<tr>
<td>Cape Town Pain Academy</td>
<td>Saturday 28 October</td>
<td>Crystal Towers Hotel, Century City, Cape Town</td>
</tr>
<tr>
<td>Port Elizabeth Pain Academy</td>
<td>Saturday 18 November</td>
<td>The Boardwalk Convention Centre, Summerstrand, Port Elizabeth</td>
</tr>
</tbody>
</table>

**SAVE THE DATE**

PainSA Congress  
18 - 20 May 2018  
Birchwood Conference Centre  
Boksburg
What are the benefits of membership to you?
- Indirect affiliation to the International Association for the Study of Pain (IASP) without the expense of yearly international subscriptions
- Receive your quarterly Journal of Painsa
- Painsa Congresses (at reduced rates to Members)
- Regional Group symposia
- Contact through forums with other professionals in pain management
- Earn CPD points

<table>
<thead>
<tr>
<th>Is this your first application for membership?</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are you a registered Health Professional?</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

If yes, what is the nature of your practice?

| Professions Registration Number (if any) E.g. HPCSA. |

| Title e.g. Prof / Dr / Mr / Mrs / Miss |

<table>
<thead>
<tr>
<th>Surname</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Name</td>
</tr>
<tr>
<td>Address</td>
</tr>
<tr>
<td>City</td>
</tr>
<tr>
<td>Province</td>
</tr>
<tr>
<td>Country</td>
</tr>
<tr>
<td>Phone</td>
</tr>
<tr>
<td>Telefax</td>
</tr>
<tr>
<td>E-mail</td>
</tr>
</tbody>
</table>

Contact details:
Phone: 011 356 6086 / Telefax: 086 630 5093 / Email: painsa@global.co.za

Annual Membership Fee: R200.00

A direct deposit can be made into the account of:
Painsa, Standard Bank, Northcliff, Account No. 204 422 264, Branch Code 006305

Or send your cheque to:
Painsa, Postnet Suite 199, Private Bag X2600, Houghton, 2041

www.painsa.co.za