Postoperative opioids, endocrine changes, and immunosuppression
Emerging therapies for neuropathic pain: new molecules or new indications for old treatments?
Tired of pain? Toward a better understanding of fatigue in chronic pain
Is burning mouth syndrome a neuropathic pain condition?
Current status of pain education and implementation challenges
Editorial

Is there a reason that pain management in South Africa and indeed the rest of the world is so badly performed? This question has been universally posed and it appears that three words can explain this situation. These three words are education, education, education!!!

A quick examination of the situation in South Africa reveals that the subject of pain and pain management is not included in the curricula of most medical schools, and when it is there are just a few hours dedicated to this purpose. The situation is similar at the post-graduate level in that only some of the medical schools dedicate time to pain management and even then, this is limited to some departments of anaesthesiology with very little teaching in the other specialties. A perusal of the syllabi of the various Colleges of Medicine of South Africa shows that pain management is not included in the required subject matter! It should therefore not surprise us that the level of pain management in our country is so poor.

As stated, this is a universal problem. This fact or educational deficiency has been recognised by many authorities and organisations and it has been noted that the basic problem is that of education.

It is not surprising that our parent body, the IASP, has acted and declared 2018 as the “Global year for excellence in pain education.” While this differs from the usual clinical situation, the need for education in pain management is acknowledged and we are seeing global initiatives in this regard. As usual, I shall feature the “fact sheets” as part of this Journal. This will enable the members of PAINSA to see where we as an organisation can act to not only educate our members but also to institute educational initiatives at our respective departments and institutions to improve pain management in South Africa.

It is appropriate that this issue of the Journal also corresponds with the annual Congress which serves as the showpiece of PAINSA education. I trust that many of our readers will be attending the Congress and wish the Council of PAINSA and the Congress organisers much success with this initiative.

Dr. Milton Raff  
BSc MB ChB FFA(SA)

All correspondence to the editor should be addressed to: raffs@iafrica.com
PAIN CLINICAL UPDATES
Postoperative opioids, endocrine changes, and immunosuppression
Simon Haroutounian

NEUPSIG REVIEWS
Emerging therapies for neuropathic pain: new molecules or new indications for old treatments?
Didier Bouhassira, Nadine Attal

TOPICAL REVIEW
Tired of pain? Toward a better understanding of fatigue in chronic pain
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Is burning mouth syndrome a neuropathic pain condition?
Satu K. Jäaskeläinen

GLOBAL YEAR EXCELLENCE IN PAIN EDUCATION
Current status of pain education and implementation challenges
Judy Watt-Watson, Beth B. Hogans, Kate Seers, Robert N. Jamison
Improve mobility by relieving inflammatory pain
Shorten your patient's recovery time, from acute, painful musculoskeletal spasm\(^1\)

- Muscle relaxant that is effective in treating muscle spasm associated with acute, painful musculoskeletal conditions, tenderness and in increasing range of motion\(^1,2,3,4\).
- Relieves acute muscle spasm based on the patient’s rating of medication helpfulness at day 4 of treatment\(^1,2\).
- Diffucaps formulation maintains therapeutic levels over 24 hours\(^1,6\).
- Generally well-tolerated with a low rate of reported somnolence\(^1\).
- Convenient once-daily dosing\(^6\).

Sustained efficacy for painful muscle spasm\(^1,4,5\).


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For full prescribing information refer to the package insert approved by the medicines regulatory authority. 1.0352598/05/2017.

# Scientific Programme

**FRIDAY 18 MAY 2018**

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<td>08h00 – 17h00</td>
<td>Registration &amp; Arrival Tea/Coffee</td>
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<tr>
<td>09h00 – 12h30</td>
<td><strong>Pain physiology refresher course</strong></td>
<td>Tony Madden, Romy Parker, Janieke van Nugteren, Rowan Duys</td>
<td><strong>Ultrasound guided workshop</strong> Pauline du Plessis, Celeste Barrow</td>
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<td>The pain physiology workshop aims to be a dynamic interactive session with very little didactic lecturing. We will start with a conceptual overview of pain followed by a look into a framework which involves thinking about the mechanisms of pain. Case studies will be used in order to improve understanding. Join us for a morning of challenging your understanding about pain!</td>
<td>Workshop stations: Brachial plexus above clavicle (e.g. interscalene / supraclavicular / Access for CVP) Brachial plexus below clavicle (e.g. infraclavicular / axillary / peripheral) Lumbar plexus (e.g. femoral / lateral cutaneous / obturator / fascia ilia / saphenous) Sacral plexus (e.g. sciatic / popliteal / lower leg / adductor canal) Trunk (e.g. paravertebral / Intercostal / ESP / GL / TAP / Rectus sheath</td>
<td>Fabia 1&amp;2</td>
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<td><strong>REFRESHMENTS</strong></td>
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<td>11h00 – 12h30</td>
<td><strong>Pain physiology refresher course continues</strong></td>
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<td>12h30 – 13h30</td>
<td><strong>LUNCH</strong></td>
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<td>13h30 – 15h00</td>
<td><strong>Talking and Listening to Chronic Pain patients</strong></td>
<td>Bev Bolton, Louise Frenkel</td>
<td><strong>Ultrasound guided workshop</strong> Pauline du Plessis, Celeste Barrow</td>
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<td>The clinical management of chronic pain remains extremely challenging despite major advances in the understanding of the mechanisms and pathological processes involved in pain. Much of the challenge stems from difficulties in the therapeutic alliance between clinicians and chronic pain patients. This short interactive workshop will look at some of the most common difficulties in engaging and forming therapeutic alliances with people with chronic pain. The focus of the workshop will be on how to establish a sense of trust and support and will explore some of the communication skills that have been found to be effective in empowering and motivating patients to develop realistic action plans to return them to lives that have value and meaning to them.</td>
<td>Workshop Continues</td>
<td>Julia</td>
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<td>15h00 – 15h30</td>
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<td>Chair: Romy Parker</td>
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<td>Opening Welcome</td>
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<td>15h35 – 16h30</td>
<td>What makes up the pain experience?</td>
<td>Tony Dickenson</td>
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<td>16h30 – 17h15</td>
<td>Cannabinoids – where are we in South Africa</td>
<td>Ernest Buitendag</td>
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<td>VENUE: Julia</td>
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<tr>
<td>17h30 – 18h30</td>
<td><strong>Evening Symposium - sponsored by Adcock Ingram</strong></td>
<td>Sean Chetty</td>
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<td></td>
<td>There’s no excuse for Neuropathic pain</td>
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DON’T LET THEM BE HELD BACK BY PAIN

THERE IS MORE TO SYNALEVE THAN PAIN RELIEF

SYNALEVE COMBINES THE ANALGESIC ACTION OF PARACETAMOL AND CODEINE WITH THE TRANQUILISING AND SKELETAL MUSCLE RELAXING PROPERTIES OF MEPROBAMATE

- Effective analgesia for patients experiencing pain and pain associated with tension
- The tranquilising action may assist in induction of sleep after patient has been woken up by pain
- Improved tolerability due to reduction in dose of each component being used
- Muscle-relaxing benefit for pain associated with tension

References:
2. Synaleve Capsules. Each capsule contains meprobamate 260 mg, paracetamol 400 mg, and codeine phosphate 8 mg. Recommended adult dosage is 1 capsule, 4 times daily.
3. For full prescribing information, please refer to the package insert approved by the medicines regulatory authority. 01/1998.

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## SATURDAY 19 MAY 2018

**07h00 – 08h30**  | Registration & Arrival Tea/Coffee
---|---
**08h30 – 09h00**  | Plenary Session 2  
Chair: Janieke van Nugteren
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08h30 – 09h00  | Mechanisms of pain – evidence for emotional and contextual influences  
Tony Maddren
09h00 – 09h30  | Pain in musculoskeletal conditions  
Tony Dickenson
09h30 – 10h00  | Gut biome and chronic pain: what do we know?  
Janieke van Nugteren
**10h00 – 10h30**  | REFRESHMENTS
---|---
**10h30 – 11h00**  | Current conversations in pain  
Chair: Antonia Wadley
---|---
10h30 – 11h00  | Changing gears for end-of-life pain relief  
Liz Gwyther
11h00 – 11h30  | Do we need a new approach to communicating with patients suffering chronic pain from stigmatizing to validating responses  
Bev Bolton
11h30 – 12h00  | Cognitive behaviour therapy in chronic pain management: who benefits?  
Hayley Meduric
12h00 – 12h30  | Physical Medicine and Rehabilitation  
Amriah Salman
12h30 – 13h00  | What the research in South Africa tells us about our population – or doesn’t?!  
Prinshla Pilay
**13h00 – 14h00**  | LUNCH
---|---
**13h00 – 13h30**  | PaedsPainSIG AGM  
Venue: Tiberius
---|---
**14h00 – 15h30**  | Parallel Session 2  
Chair: Michelle Casey
---|---
14h00 – 15h30  | Pharmacological and invasive management of pain  
Chair: Pauline du Plessis
14h00 – 14h30  | Procedural sedation and analgesia in paediatrics  
Anisa Bhettay
14h30 – 15h00  | General principles of paediatric palliation  
Mehraaz Aly
15h00 – 15h30  | The impact of alternate focus and play on pain and anxiety  
Karen van Zijl
**15h30 – 16h00**  | REFRESHMENTS
---|---
**16h00 – 17h00**  | Plenary Session 3  
Case studies  
Chair: Rowan Doys
---|---
16h00 – 17h00  | Case study – When the mood is worse than the disc bulge  
Romy Parker, Sudha Bechan, Kenny Louw, Louise Frenkel
16h00 – 17h00  | Case study – I am suffering because somebody else
17h00 – 18h00  | Ethics of Pain Management in Palliative Care (E)  
Mpho Ratshikana – Moloko
**18h00 – 19h00**  | PainSA AGM  
Venue: Fabia 1 & 2
**19h30**  | Networking dinner  
Venue: Fabia 1 & 2
**Veltex CR capsules**

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- Ankylosing spondylitis
- Osteoarthritis and Spondyloarthritis

**Acute Gout**2

**Primary Dysmenorrhoea**2

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### Scientific Programme Continued...

**SUNDAY 20 MAY 2018**

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<td>Jacqui Koep</td>
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<td>Tori Madden</td>
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<td><strong>Parallel Session 2</strong> Specific topics for general practice</td>
<td>2. The problems with imaging in lower back pain</td>
<td>Eric Hodgson</td>
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<td><strong>Debate:</strong> the first goal of treatment should be pain relief vs. return to function</td>
<td>3. Controversies in opioid therapy for non-cancer pain</td>
<td>Sudha Bechan</td>
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<td><strong>Return to meaningful life roles</strong></td>
<td>4. Addiction and pain</td>
<td>Michael West</td>
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<td><strong>Looking after yourself as a health care practitioner</strong></td>
<td>5. Managing acute and chronic herpetic neuralgia</td>
<td>Johan Smuts</td>
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<td>11h30</td>
<td><strong>Panier Session 4</strong></td>
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<td>Romy Parker</td>
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<td>11h30</td>
<td>The Future of Pain Control</td>
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<td>Tony Dickenson</td>
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<tr>
<td>12h00</td>
<td>Pain, Resilience and HIV</td>
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<td>Antonia Wadley</td>
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<tr>
<td>12h30</td>
<td>Ethics: What are the ethics of using the placebo effect in pain management? [E]</td>
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<td>Christina Lundgren</td>
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<td>13h30</td>
<td><strong>CLOSING</strong></td>
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</table>
WHEN ACUTE AND CHRONIC PAIN PRESENT

An affordable pain portfolio, quality assured

References:
1. Ibuprofen Forte Approved Package Insert, 10 March 2005.
2. Tramadol Co Approved Package Insert, 29 June 2013.
4. fendermal Approved Package Insert, 19 April 2013.

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a Novartis company

Step Up
Fendermal
TramaHexal Co
TramaHexal
Ibupain Forte

1,3,4,5,6
Postoperative opioids, endocrine changes, and immunosuppression

Simon Haroutounian

1. Introduction

“The pathetically grim and perspiring patient, fearful of moving or breathing, has become a constant fixture on postsurgical wards. His suffering was anticipated by his physician and is accepted in the knowledge that it will disappear in time.”

Acute postoperative pain is considered an unavoidable consequence of a surgery, and is somewhat anticipated, given the (typically) massive tissue injury, inflammation, and stress response as a result of a surgical procedure. However, it is well documented that the “perspiring patient, who is fearful of moving or breathing,” i.e., the patient who suffers from severe postoperative pain, is more prone to adverse outcomes. Patients, in whom severe pain impairs breathing, coughing, physical therapy, and early mobilization, are more likely to develop complications such as respiratory infections and thromboembolic events. The pain is also a significant stressor both from the psychological and physiological points of view.

The responses of the central nervous system and the hypothalamus-pituitary-adrenal (HPA) axis to a perceived stress involve a complex network of signaling molecules, including endorphins, catecholamines, and cortisol. The stress response to surgery is characterized by activation of HPA axis, as reflected by increased secretion of hypothalamic corticotropin-releasing hormone (CRH), and subsequently increased levels of adrenocorticotropic hormone (ACTH) and cortisol. In addition, surgical stress enhances the secretion of other catabolically active hormones, mainly catecholamines and glucagon, but also prolactin, growth hormone, and β-endorphin.

The enhanced postsurgical stress response, which leads to high cortisol levels, can result in immunosuppression, supporting the notion that the relief of pain should be beneficial in preventing, e.g., postoperative infections. In the setting of cancer surgery, the immune function may have even further implications, as animal studies have shown that surgery-induced stress is associated with impaired natural killer (NK) lymphocyte activity, impairing the body’s ability to clear tumor cells.

Although the description of a grim, perspiring, and suffering patient as a constant fixture may not have been surprising in the 1950s, one would expect that the development of novel drugs and multimodal analgesia approaches in the past few decades would dramatically improve the quality of postoperative pain management, and reduce the undesired hormonal and inflammatory consequences associated with the surgical stress. However, current data from inpatient and outpatient surgical settings indicate that between 30% and 50% of postoperative patients consistently experience moderate to severe pain.

Key Points

1. Surgery is associated with a massive inflammatory and stress response. Untreated postoperative pain results in immunosuppression, increases the risk of thromboembolic events, and delays recovery.
2. Chronic opioid therapy results in major endocrine changes such as opioid-induced androgen deficiency and bone demineralization. The clinical relevance of these phenomena with short-term opioid use for postoperative pain is unclear.
3. In the surgical setting, high-dose opioids may contribute to inhibition of immune responses and curbing of stress response (e.g., cortisol rise), but the clinical consequences of these observations are still unclear.
4. Multimodal postoperative approaches, especially those combining regional anesthesia with local anesthetics, help improve pain scores and reduce postoperative opioid requirements; however, contradictory data exist on their effect in reducing immune-mediated complications such as infections or tumor dissemination.

2. The role of opioids in the management of acute postoperative pain

Opioids are the most commonly used drugs for the management of acute postoperative pain. Depending on the setting and type of surgery, opioids are delivered systemically either through scheduled or pro re nata (as needed) dosing, or through a patient-controlled analgesia device. Alternatively, the postoperative opioid regimen may include neuraxial delivery through an epidural catheter, as a part of patient-controlled epidural
analgesia (PCEA) technique. Mostly, opioids that are used for acute postoperative pain relief, include the short-acting morphine, hydromorphone, oxycodone (in countries where parenteral formulation is available), and occasionally fentanyl or tramadol (which is a weak opioid agonist and a serotonin-norepinephrine reuptake inhibitor).

Opioids are very effective in treating acute postoperative pain; however, not without important side effects. Among their most commonly observed and reported adverse effects in this setting are nausea, vomiting, sedation, pruritus, and constipation. The more severe undesired outcome is respiratory depression, which is potentially life-threatening, and is the most feared side effect of opioid medications. The brainstem control of respiratory rate and tidal volume is driven by afferent input of partial pressure of arterial $O_2$ (through chemosensors in carotid and aortic bodies) and $CO_2$ (through chemosensors in the brainstem). Opioids, through $\mu$-opioid receptor-mediated depression of excitability of brainstem chemosensory neurons, depress the ventilatory response to increased $CO_2$, thus depressing respiration.31

3. Literature search methodology and focus
This update will focus on a different subset of effects associated with the use of opioid analgesics in the acute postoperative setting; these are endocrine changes and immunosuppression. This clinical update will discuss the evidence behind the role of opioids in contributing to each of these phenomena in the postoperative setting, discuss their clinical relevance, and summarize the recent data on approaches that could be considered when treating pain in patients after surgery.

To provide systematicity to literature retrieval, PubMed search was performed in September 2017 with the following keywords: “opioids” [All Fields] AND “surgery” [All Fields] AND “pain” [All Fields] AND (“immune suppression” [All Fields] OR “endocrine” [All Fields]). The search resulted in 125 articles, which were screened for relevant information, including articles identified from their reference lists.

To obtain a comprehensive evaluation of opioid effects in the perioperative setting, information on both postoperative opioids for pain relief and data on intraoperative opioids for analgesia/anesthesia purposes were considered. As rapid recovery from anesthesia is becoming an increasingly important outcome, opioids with faster offset such as remifentanil and sufentanil are used more commonly, but (especially remifentanil) may be associated with certain adverse effects.

4. Major endocrine changes associated with opioids
The current evidence suggests that opioids cause endocrine changes by 2 major mechanisms:

(1) Opioids affect the hypothalamic-pituitary-gonadal (HPG) axis.
(2) Opioids affect the HPA axis.

The impact on the HPG axis is a well-described dose-dependent effect of opioids, particularly related to treatment with daily doses above 100 to 200 mg of oral morphine equivalents for more than a few weeks. The HPG cascade is initiated by the release of gonadotropin-releasing hormone (GnRH) from the hypothalamus, which stimulates the anterior pituitary to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which stimulate the gonads to produce testosterone and estrogen. Opioids bind to $\mu$-opioid receptors in the hypothalamus, inhibiting the release of GnRH, thus decreasing LH and FSH secretion from the pituitary. Subsequently, this leads to decrease in testosterone levels and hypogonadism, a condition typically referred to as opioid-induced androgen deficiency (OPIAD).29

Opioid-induced androgen deficiency is a significant observation in the setting of chronic opioid therapy, affecting 53% to 90% of male patients on chronic opioid therapy.29 The long-term symptoms of OPIAD in this setting include decreased attention, decreased libido, fatigue, erectile dysfunction, and osteoporosis. In women receiving chronic opioids, LH and FSH levels are markedly reduced and are associated with amenorrhea and impaired adrenal androgen production.13

Some studies have questioned the suggestion that OPIAD is associated only with chronic opioid therapy. Several animal studies have shown that even acute opioid administration (eg, morphine, fentanyl, and buprenorphine), especially at high doses, results in reduced levels of testosterone,10 but the duration of this effect is reported to last between 24 hours to up to 8 weeks after treatment.11

A significant drop in total testosterone level in humans is also observed with a single 30 mg dose of methadone, or within 24 hours of perioperative morphine administration.30,41

Unfortunately, well-designed studies aimed at understanding the mechanisms of testosterone suppression, and the clinical relevance of short-term hypogonadism in the setting of acute opioid administration are lacking. Moreover, surgical stress may also contribute to these phenomena, and patients receiving ketamine (and not morphine) analgesia still display reduced testosterone plasma levels.30 Therefore, more careful studies are warranted to dissect the magnitude and the importance of OPIAD in the perioperative setting.

The impact of the opioids on the HPA axis is less well described. The HPA cascade is initiated by CRH release from the hypothalamus, which stimulates the pituitary to release ACTH to the systemic circulation, stimulating, in turn, the adrenal glands to produce 2 hormones—dehydroepiandrosterone (DHEA) and cortisol. Opioids seem to inhibit the functioning of the entire HPA axis. On one hand, they reduce the production/release of CRH, and on the other, they decrease the responsiveness of the anterior pituitary to CRH. Both processes lead to reduced ACTH secretion. Independently, opioids may also directly interfere with the adrenal gland production of cortisol and DHEA. Cortisol is important for mounting stress responses, and DHEA is an important precursor for testosterone (in men) and estradiol (in women).

The mechanistic data on opioid-associated changes in HPA axis come primarily from rodent and healthy volunteer experiments. For example, in healthy volunteers, single-dose morphine suppresses ACTH and cortisol levels both at baseline and after CRH stimulation.5 However, the extrapolation of healthy volunteer data to the surgical setting is not straightforward, as the surgical stress, and the postoperative pain per se, can have a substantial effect on the functionality of the HPA axis. The surgery typically results in an increased stress response, which subsides after about 24 hours. Certain opioids (remifentanil, particularly) are reported to acutely suppress plasma cortisol in a dose-dependent manner.1 In the setting of elective C-section, remifentanil administered as a bolus followed by continuous intraoperative infusion (compared with fentanyl administration after delivery) partially obtunded the neuroendocrine response to surgery with a decrease in ACTH rise (but not in norepinephrine, epinephrine, and growth hormone).14

The association between opioids and blunting ACTH or cortisol rise seems to be modest at best, and highly dependent on the timeframe of the assessment. In addition, some studies failed to find changes in cortisol levels after intraoperative remifentanil infusion.2 As in the case of reduced testosterone concentrations, the clinical relevance of altered cortisol levels in the setting of perioperative opioid therapy is not clear.
5. Opioids and immune response—inflammation and infections

Opioids do not possess strong anti-inflammatory properties such as nonsteroidal anti-inflammatory drugs or corticosteroid drugs, and their potential effects on inflammatory responses seem to be highly dependent on the setting. For example, in patients undergoing coronary artery bypass graft procedure, administration of continuous remifentanil infusions (vs intermittent fentanyl dosing) resulted in lower levels of proinflammatory cytokines (such as TNF-α and IL-6) at some time points after cardiopulmonary bypass. Eight hours after surgery, however, no differences were observed between the groups.40 On the contrary, some studies have reported lower inflammatory response (lower C-reactive protein level) with opioid-minimizing analgesia in the setting of colorectal surgery,38 or enhanced proinflammatory cytokine release in the spinal cord as a response to opioid challenge. The clinical relevance of these short-term effects of opioids on inflammatory markers remains to be investigated.

The 2 main areas of research focused on opioid-associated immune effects deal with (1) the effects of opioids on immune response to infections; and (2) opioid effects on tumor-specific immune responses, affecting tumor growth and dissemination. Major histocompatibility complex, class II (MHC-II) molecules, expressed on antigen-presenting cells, are important regulators of immune cell development and function. Morphine has been shown to alter gene expression of the MHC-II in circulating immunocytes (Beagles 2004), and thus suspected in causing immunosuppression. It is a matter of debate whether these effects are mediated by opioid-induced alteration in cortisol levels (as in adrenalectomized rats, morphine exposure does not affect MHC-II), or there is a direct immunosuppressive effect attributable to opioids. Interestingly, morphine withdrawal results in renewed increase in circulating corticosterone levels and a renewed suppression of MHC-II in previously opioid-tolerant animals.28,30

The risk of surgical site infection was higher after abdominal surgery with remifentanil anesthesia vs fentanyl anesthesia.21 The findings could be attributable to more substantial immunosuppression with remifentanil (although direct data are lacking), or to opioid withdrawal, which is more likely with the short-acting remifentanil. Additional data support this notion of immunosuppression associated with opioid withdrawal; for example, remifentanil discontinuation increased the risk of intensive care unit–acquired infection,27 and morphine withdrawal in mice (after 96-hour exposure) increased the risk of infection in an experimental model of septic shock. Interestingly, the most commonly detected organisms in tissue of morphine-withdrawn mice were bacteria that are part of the normal gastrointestinal flora.18 There are additional rodent studies suggesting that morphine, by altering gut microbiome, may increase the risk of sepsis by bacterial dissemination.24

A review examining whether opioids increase the risk of infections in the perioperative or intensive care setting, suggested that patients receiving higher doses of systemic opioids had an increased risk of developing pneumonia perioperatively.32 However, these results are not universal and were observed only if laparoscopic vs open surgery (or epidural vs systemic opioid therapy) was compared.

Overall, the data are both inconsistent and insufficient to determine the extent of opioid-associated immune suppression on infectious complications after surgery. Untreated pain itself can increase the risk of infections, eg, because of impaired mobility; pain also enhances the body’s stress response, which by enhancing circulating cortisol, can contribute to immunosuppression. It needs to be taken into account that low-dose opioid control groups in some studies (eg, epidural analgesia and laparoscopic surgeries) could have better quality of analgesia and improved ability to clear secretions. It is also possible that increased risk of infection is among the immunological sequelae of opioid withdrawal, rather that opioid therapy, per se. The microbiome-related effects of opioids (and the potential dissemination of gut microorganisms) are another area that requires additional research. Although some studies suggest that buprenorphine (partial μ-opioid agonist and a κ-opioid antagonist) may be devoid of immunosuppressive effects,33 whether different opioids have differential effects on immune function still requires detailed investigation.

6. Opioids and immune response—cancer

Opioids can suppress NK cell cytotoxicity. Both high-dose and low-dose fentanyl suppressed NK cytotoxicity for 24 hours.5 However, rate of recovery of NK cell suppression was longer in the high-dose fentanyl group. Rats, which were treated with 20 mg/kg morphine (vs saline), developed a decrease in B-lymphocyte blood expression of MHC class II molecules within 2 hours.4 The same group has previously reported that in rats, fentanyl suppresses NK cell cytotoxicity and increases the risk of tumor metastases.34 Although there might be a dose-dependent effect, it is not clear whether different opioids affect the NK function differentially. In this regard, data suggest that endogenous opioids (β-endorphin) inhibit T-cell proliferation to a lesser extent than exogenous morphine.15

Despite these experimental findings, it is unclear whether there is any long-term immunosuppression associated with similar changes in antigen-presenting cells in humans.

A large retrospective analysis of a national registry data from Denmark (n = 34,188) showed no difference of breast cancer recurrence as a function of opioid use.12 The researchers categorized “strong immunosuppressive opioids (codeine, morphine, and fentanyl) vs weakly immunosuppressive opioids (oxycodone, tramadol, buprenorphine, and hydromorphone),” based on previous literature, but found no difference between the groups.

Considering the immunosuppressive effects attributable to pain and the enhanced stress response (and cortisol increase), which opioids may blunt, it is currently unclear whether the clinically relevant “net effect” of postoperative pain management with opioids tips the immune balance towards immune suppression. There is also insufficient evidence to determine that some opioids produce strong immunosuppressive effects, whereas others produce only weak or no such effects.

7. Mitigation approaches

7.1. Stress response and inflammation

Inflammatory reaction after surgery is a physiological response that helps the healing process. An excessive inflammatory response can lead to complications, but immune suppression could negatively affect the healing process. With potential effects of opioids on inflammation, and potential immunosuppressant activity, the attempt in the recent years has been to use multimodal analgesia approaches that provide adequate analgesia, but avoid excessive opioid use, especially high-dose intraoperative remifentanil.
Patient-controlled epidural analgesia (with bupivacaine and fentanyl) after lower abdominal surgery have resulted in blunted postoperative elevation of cortisol and prolactin, and lower pain scores, compared with other opioid-only systemic analgesia regimens.\(^2\)\(^2\)

In a setting of retropubic prostatectomy, PCEA (with ropivacaine and sufentanil) resulted in lower pain intensity, and reduced the postoperative stress response (plasma cortisol and glucose), but not the acute inflammatory response (TNF-\(\alpha\) and IL-6 levels).\(^3\)\(^9\)

Another study in 24 women undergoing laparoscopic cholecystectomy assessed the effect of a single-dose intrathecal (bupivacaine with fentanyl) vs epidural (ropivacaine with fentanyl) anesthesia, before general anesthesia in both groups.\(^7\) Intraoperative cortisol, noradrenaline, and total catecholamine levels were significantly lower in the intrathecal (spinal) anesthesia group (and patients required less systemic fentanyl); ie, spinal anaesthesia produced a more favourable endocrine response than epidural anaesthesia.

In pediatric cardiac surgery, on the other hand, high-dose intraoperative fentanyl has demonstrated better (lower) profile of stress markers such as ACTH, glucose, cortisol, and lactate, compared with low-dose fentanyl. High-dose intraoperative fentanyl also resulted in lower postoperative opioid requirements.\(^2\)\(^6\)

The available results demonstrate that neuraxial anesthesia and analgesia (intrathecal route perhaps more advantageous than epidural), result in either lower pain scores or less systemic opioid requirements, and can blunt the stress response, with minimal effect on acute inflammatory response. This suggests that multimodal anesthesia with neuraxial opioid and local anesthetic delivery, where possible, may provide advantage to systemic (especially high-dose) opioid administration. The advantages in the pediatric surgery setting have not been explored sufficiently and merit more thorough investigation.

### 7.2. Cancer

The literature is divided on the topic of regional anesthesia approaches and their potential effect on cancer-related outcomes. Initial retrospective studies reported that peroperative use of regional (neuraxial or peripheral) anesthesia is associated with improved outcomes in terms of cancer recurrence and survival after breast and prostate surgery.\(^5\)\(^,\)\(^16\)

However, a later retrospective study in colorectal cancer surgery,\(^2\)\(^5\) an ad hoc analysis of a prostatectomy study,\(^3\)\(^5\) and a retrospective study in lung cancer did not show any benefit of regional anesthesia on cancer-related outcomes.\(^9\) A prospective randomized controlled trial\(^2\)\(^9\) did not demonstrate prolonged survival in major abdominal surgery, and a recent retrospective study in patients undergoing radical cystectomy for bladder cancer demonstrated more than 50% reduction in perioperative opioid consumption with spinal analgesia, but this difference was not associated with changes in outcomes such as all-cause mortality, bladder cancer mortality, or cancer recurrence.\(^3\)\(^9\)

A prospective study\(^8\) found that innate immunity (NK cells, CD4\(^+\), and CD8\(^+\) cells) was depressed in lung cancer patients undergoing resection, but postoperative epidural analgesia did not help preserve the immunity.

In addition, a recent systematic review of the literature (15 studies) found inconclusive evidence to support or refute the suggestion that paravertebral blocks in breast cancer can reduce cancer recurrence or improve survival.

Currently, there is no conclusive evidence that regional anesthesia, by either reducing opioid doses or by other mechanisms such as sympathetic blockade, can improve long-term cancer-related outcomes in cancer patients undergoing surgery. With that said, there is no major disadvantage in using regional techniques, and the opioid-sparing and stress response–blunting acute effects justify the widespread use of such approaches for postoperative pain relief.

### 8. Critical questions to be addressed by future research

The undesired effects attributable to opioids, which were discussed in this article, are often challenging to address, as some of these effects may be related to surgical stress or postoperative pain, per se. For example, endogenous opioids such as beta-endorphins play an important role in the regulation of gonadotropins through modulation of GnRH pulse amplitude and frequency. Therefore, with the question of OPIAD in mind, it is critical to control for this variable, as some data suggest that testosterone levels are lower in subjects with pain compared with controls, irrespective of opioid use.\(^2\)\(^3\) Are then patients, who are in more pain (and therefore are likely to require higher opioid dose) more likely to develop endocrine adverse effects? What is then the contribution of pain vs opioid (type and dose)? Is it more important to control the pain well, or avoid high-dose opioids, even at the expense of higher pain? These research questions are yet to be answered and need to be address accurately to move the field forward, toward safer and more rational perioperative opioid use.

In a similar scenario, severe pain is associated with enhanced stress response, accompanied by catecholamine and cortisol release. Numerous preclinical and clinical studies have focused on the effect of opioid analgesics on the postoperative stress response. As enhanced stress response may cause immune suppression and lead to postsurgical complications, blunting the stress response has been historically considered as a desirable perioperative outcome. However, the advantages of blunting the stress response with opioids should be weighed against potential immunosuppression, and more research is needed to achieve an optimal balance that would positively affect patient outcomes.

### Disclosures

The author has no conflict of interest to declare.

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### References


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Emerging therapies for neuropathic pain: new molecules or new indications for old treatments?

Didier Bouhassira*, Nadine Attal

Abstract
Neuropathic pain represents a highly unmet medical need because most of the available treatments have a modest efficacy or dose-limiting side effects. Hence, novel therapeutic perspectives are warranted. Many compounds acting on new pain targets are in preclinical or early clinical development. Only few clinical trials have suggested their clinical relevance in neuropathic pain. This concerns in particular Na\textsubscript{v}1.7 antagonists and angiotensin type II inhibitors. Another type of emerging drug therapy in neuropathic pain is represented by drugs largely used for other indications, such as botulinum toxin A and the antiepileptic oxcarbazepine, which have recently found to be effective in peripheral neuropathic pain. Emerging nondrug medical therapy with promising results in neuropathic pain also encompasses noninvasive brain neurostimulation techniques, such as repetitive transcranial magnetic stimulation and transcranial direct electrical stimulation. In this article, we review emerging medical treatments for neuropathic pain that are clinically available or with promising results from clinical trials.

Keywords: Neuropathic pain, Treatment, Review, Pharmacological treatments, Nonpharmacological treatments

1. Introduction
Neuropathic pain is still considered as a highly unmet medical need despite an increasing number of available therapies. Most of the treatments usually available have a modest efficacy or safety. Therefore, new therapeutic prospects are welcome.

Over 100 molecules acting on specific targets of potential interest for neuropathic pain are currently in development. These include sodium channel isoform-specific antagonists, vanilloid receptor antagonists, potassium channel agonists, NMDA/metabotropic glutamate receptor antagonists or novel modulators of NMDA receptors, novel opioid receptor agonists, histamine H3 receptor antagonists, serotonin modulators, nicotinic agonists, adrenoreceptor agonists, nitric oxide synthase inhibitors, orexin receptor antagonists, angiotensin type II receptor (ATR2) antagonists, imidazoline I2 receptor agonist, apoptosis inhibitors, cannabinoid CB2 receptor agonists, fatty acid amide hydrolase inhibitors, anti-nerve growth factor molecules, and gene therapy, etc. Most of these molecules, which are in early preclinical development, are beyond the scope of this review. We will only highlight some recent results concerning the few drugs for which clinical data are already available.

Interestingly, however, several older drugs largely used in nonpain indications such as botulinum toxin and oxcarbazepine have recently been found effective in neuropathic pain and therefore may also be considered as emerging drug therapy.

Beyond drug therapy, nonpharmacological treatments with generally encouraging results based on well conducted clinical trials mostly include noninvasive brain neurostimulation techniques. Although they are not new, these approaches may also be regarded as emerging treatment for neuropathic pain. Psychological therapies, for which there are insufficient data in neuropathic pain or other nonpharmacological therapies such as visual illusion or mirror therapy, which concern only small groups of patients with neuropathic pain (eg, complete spinal cord injury or phantom limb pain) and with limited evidence for efficacy have been reviewed elsewhere and will not be discussed here.

In this review, after a brief summary of available drugs currently recommended for neuropathic pain, we will deliberately focus on potential new treatments, pharmacological or nonpharmacological treatments for neuropathic pain, including new or older drug treatments with recently discovered antineuropathic activity. Only treatments with potential clinical relevance in neuropathic pain based on placebo-controlled trials in peripheral or central neuropathic pain will be discussed here.

2. Drugs currently recommended for neuropathic pain
Pharmacological agents found effective in neuropathic pain on the basis of randomized controlled trials (RCTs) include tricyclic antidepressants (particularly amitriptyline), serotonin and norepinephrine reuptake inhibitor antidepressants (particularly duloxetine), pregabalin, gabapentin, which are recommended first line, and tramadol, lidocaine patches, and capsaicin high-concentration patches, which are recommended second line (for peripheral neuropathic pain only as regards topical agents).
Given the evolving opioid crisis particularly in North America, and despite evidence for clinical efficacy in neuropathic pain, strong opioids are now recommended as the last choice in case of insufficient response and/or side effects to first-line or second-line medications with careful monitoring. Unfortunately, meta-analyses indicate that only a minority of patients with neuropathic pain have adequate response to drug therapy and that many of these drugs have dose-limiting side effects. Other drugs expected to be effective such as oromucosal cannabinoids, the opioid agonist, and norepinephrine reuptake inhibitor tapentadol and several antiepileptics (lamotrigine, oxcarbazepine, and topiramate) have yielded discrepant results, although some of them may be effective in subgroups of patients (see below).

3. Drugs acting on new targets with potential clinical relevance in neuropathic pain

3.1. Subtype-selective sodium channel blockers

Neuropathy causes alterations in ion channels within the affected nerve that affects spinal and brain sensory signalling. Increased expression and function of sodium channels in the sensory nerves lead to increased excitability, signal transduction, and neurotransmitter reuptake. The role of subtype-selective sodium channels, particularly NaV1.7 channels, has been recently linked to neuropathic pain in particular painful sensory neuropathies or trigeminal neuralgia through genetic studies. It has been found that gain-of-function mutations in NaV1.7 in particular may induce pain. Interestingly, selective NaV1.7 antagonists have been recently investigated in neuropathic pain and trigeminal neuralgia (Table 1). One phase II multicenter randomized placebo-controlled trial using a withdrawal enrichment design in 67 patients with classical trigeminal neuralgia (of whom 29 were randomly assigned to double-blind treatment) found no efficacy of the oral NaV1.7 antagonist BLB074 (Biogen Idec) on the primary outcome (a composite measure of treatment failure) but efficacy on multiple secondary outcomes including the proportion of responders. Safety was excellent with no more side effects in the active group compared with the placebo. Another proof of concept placebo-controlled RCT using a cross-over design conducted in 70 patients with postherpetic neuralgia (54 completers) used the topical NaV1.7 antagonist TV-45070 (Teva and Xenon pharmaceuticals) applied twice daily for 3 weeks. This study was negative on the primary endpoint (pain intensity) but found significant effect on the proportion of responders. Furthermore, in this study, 63% of the patients carrying the NaV1.7 R1150W gain-of-function polymorphism responded to the drug vs 35% of wild-type carriers. No significant side effects were reported.

Overall, these 2 clinical trials, although negative on the primary outcome, strongly suggest the potential clinical relevance of NaV1.7 antagonists in neuropathic pain and justify to continue their clinical development.

3.2. Angiotensin II type 2 receptor antagonists

The role of ATR2, which are expressed in human nociceptive sensory neurons, has also been recently discovered in neuropathic pain in preclinical studies. The analgesic properties of selective ATR2 antagonists have been reported in animals. Mechanisms of action are probably peripheral. More specifically, it has been found in human cultured sensory neurons that angiotensin II induces peripheral sensitization through a number of signaling pathways including protein kinase activation. EMA 401, a highly selective oral angiotensin type II antagonist (Novartis Pharmaceuticals Corporation), has been found to be effective in a phase 2 multicenter clinical trial of 28 days in 183 patients with postherpetic neuralgia, with a very good safety profile (Table 1). Selective angiotensin type II antagonists may represent a new class of analgesics for neuropathic pain and are currently in phase III clinical development.

3.3. Nerve growth factor antagonists

A number of antibodies targeting the biological activity of human nerve growth factors are currently in clinical development for the treatment of chronic pain mainly of nociceptive origin. Fulranumab (Johnson & Johnson Pharmaceutical Research and Development), an anti-NGF antibody administered subcutaneously, is the only drug of this class that was investigated specifically in a phase II clinical trial in neuropathic pain (Table 1). However, the study had to be stopped prematurely because of Food and Drug Administration hold (due to reports of rapidly progressive osteoarthritis with NGF antagonists in patients with osteoarthritis) and only one-third of patients (88 patients instead of 200) were enrolled. Results were negative on the primary and secondary outcomes in this group of patients with peripheral neuropathic pain. However, this does not exclude the potential clinical relevance of this drug class in neuropathic pain.

4. Drugs with recently discovered antineuropathic efficacy

4.1. Oxcarbazepine

Although antiepileptics acting on sodium channels seem to have limited efficacy based on large scale clinical trials, this may be because they do not target the relevant phenotypic profiles. One recent proof of concept clinical multicenter study using the sodium channel blocker oxcarbazepine (Novartis Pharma) in 97 patients (39 completers) with peripheral neuropathic pain in patients stratified into 2 groups based on clinical phenotypes, suggesting potential underlying mechanisms (irritable nociceptors with potential preserved nociceptive function vs deafferentation) reported that only patients with preserved nociceptive function were significantly responsive to oxcarbazepine, suggesting that this drug targets preferentially remaining hyperexcitable nociceptive fibers (Table 1). This suggests that older drugs acting on sodium channels may have significant efficacy at least in subgroups of patients with neuropathic pain and should be investigated in the future specifically using a phenotypic-based approach and not in aetiologically categorized patients.

4.2. Botulinum toxin A

Botulinum toxin type A (BTX-A) is widely used to treat muscle hyperactivity, based on its ability to inhibit synaptic exocytosis, and therefore to disable neural transmission. A number of experimental studies in animals or clinical models of pain in healthy subjects have indicated that BTX-A may have analgesic activity independent of its effect on muscle tone, possibly through a decrease in neurogenic inflammation. Four-pilot single-center RCTs including 20 to 60 patients have reported the long-term efficacy of BTX-A (one single set of subcutaneous or intradermal injections into the painful area at fixed doses or at doses adapted to the painful area, from 50 to
In line with this hypothesis, a recent single-center double-blind randomized placebo-controlled study conducted in 40 patients with spinal cord injury reported a beneficial effect of BTX-A on below level pain, which was more marked in patients with preserved sensory or motor function. 

These data have led to recommend BTX-A as a third choice in the therapeutic arsenal of peripheral neuropathic pain for refractory patients. 

200 units) in peripheral neuropathic pain (postherpetic neuralgia, traumatic nerve injury, or diabetic neuropathic pain) and were characterized by high response rate. In these studies, the onset of efficacy (about 1 week) and duration of effects (3 months) was remarkably similar. However, 1 unpublished proof of concept multicenter clinical study (sponsored by Allergan) was negative in 117 patients with postherpetic neuralgia. Three other small single-center placebo-controlled RCTs have also reported the efficacy of BTX-A administered, intradermally in the face, mucosa, or trigger points in classical trigeminal neuralgia. 

A recent 3-center double-blind randomized placebo-controlled trial assessed the sustained efficacy and safety of 2 subcutaneous administrations of BTX-A (Allergan) (up to 300 units depending on the painful area), 12 weeks apart in 66 patients with peripheral neuropathic pain (postherpetic neuralgia, posttraumatic nerve lesion, and painful polyneuropathy) with or without allodynia (Table 1). Results showed that BTX-A improved average pain intensity over 24 weeks, as compared with placebo (primary outcome), and that the second injection was of higher therapeutic benefit. Botulinum toxin type A was particularly effective on some neuropathic symptoms (allodynia and paroxysmal pain) and reduced mechanical allodynia and hyperalgesia evaluated using quantitative sensory testing. Safety was excellent with mainly pain during the injections. The response

### Table 1

**Summary of randomised multicentre double-blind placebo-controlled clinical trials (parallel design) with drugs acting on new pain targets and drugs with recently discovered antineuropathic activity.**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Treatment</th>
<th>Patients</th>
<th>Main results on efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zaleweska et al. (2017)</td>
<td>BIB074, an oral Na(_{V})1.7 antagonist, 150 mg tid for 21 d (open label) then 28 d double blind</td>
<td>Classical trigeminal neuralgia, n = 67 open label, n = 29 double-blind phase</td>
<td>No effect on the primary outcome (composite measure of treatment failure) but effects on the proportion of responders</td>
</tr>
<tr>
<td>Price et al. (2017)</td>
<td>TV-45070, ointment, a topical Na(_{V})1.7 antagonist twice daily for 3 wk</td>
<td>Postherpetic neuralgia, n = 70</td>
<td>No effect on the primary outcome (mean pain intensity) but significant effect on the proportion of responders (50% pain relief); 63% of patients carrying the Na(_{V})1.7 R1150W gain-of-function polymorphism responded the drug vs 35% of wild-type allele carriers</td>
</tr>
<tr>
<td>Wang et al. (2017)</td>
<td>Fulranumab, a subcutaneous NGF antagonist, 1 injection every 4 wk for 12 wk</td>
<td>Peripheral neuropathic pain (postheraptic and posttraumatic), n = 88 instead of 200 (study stopped prematurely by FDA)</td>
<td>Negative results for primary and all secondary outcomes</td>
</tr>
<tr>
<td>Rice et al. (2016)</td>
<td>EMA401, an oral angiotensin type II antagonist 100 mg bid for 28 d</td>
<td>Postherpetic neuralgia, n = 183</td>
<td>Positive results for primary outcome (pain intensity) and multiple secondary outcomes, including the proportion of responders and quality-of-life items. The NNT for 50% pain relief was 6.7.</td>
</tr>
<tr>
<td>Demant et al.</td>
<td>Oral oxcarbazepine vs placebo</td>
<td>Peripheral neuropathic pain, n = 83</td>
<td>Moderate effect on the primary outcome (pain intensity). Effect enhanced in the “irritable nociceptive” group (milder sensory deficit); greater effect in patients with paroxysmal pain.</td>
</tr>
<tr>
<td>Attal et al.</td>
<td>Botulinum toxin A SC (2 sets of injections 3 months apart) vs placebo</td>
<td>Peripheral neuropathic pain, n = 66</td>
<td>Positive effect on the primary outcome (pain intensity for up to 24 wk) and several secondary outcomes, including several neuropathic symptoms and allodynia. Effect enhanced in patients with mechanical allodynia and preservation of nociceptive function</td>
</tr>
</tbody>
</table>

**Footnotes:**

1. FDA, Food and Drug Administration; NGF, nerve growth factor.
5. Emerging nonpharmacological treatments: noninvasive brain stimulation

Noninvasive transcranial brain stimulation techniques have recently expanded for the treatment of neuropathic pain. Their initial therapeutic application stems from the discovery of the benefit of epidural motor cortex stimulation of the motor cortex in neuropathic pain.11 These techniques encompass conventional repetitive magnetic transcranial stimulation (rTMS) and transcranial direct current stimulation (tDCS). Their mechanisms may share similarities through an action on central modulatory systems.5,38 However, although these techniques are now widely used in psychiatry particularly for the treatment of major depression,31 their routine clinical use in neuropathic pain remains limited because no large-scale multicenter randomized controlled study has confirmed their efficacy (Table 2). Furthermore, studies of rTMS or tDCS all suffer from methodological limitations related to the lack of real double blinding because the active and sham stimulations were conducted with distinct coils in most studies. However, these limitations should now be overcome by the use of double face coils in newer rTMS studies or by the use of techniques such as deep rTMS in which the active and sham stimulations are conducted using the same equipment (see below).

5.1. Repetitive magnetic transcranial stimulation

In recent years, rTMS has been developed for the treatment of neuropathic pain.11,29,42 Repetitive magnetic transcranial stimulation uses a transient magnetic field to produce electrical currents in the cortex.29 In most studies, the motor cortex (M1) was the stimulation target. Neuropathic pain is generally relieved by high-frequency stimulations (5-20 Hz), but not low-frequency (0.5-1 Hz) stimulation of the contralateral M1 area. Most initial studies were based on single sessions. The latter produced delayed analgesic effects (by 2-4 days) lasting 6 to 8 days, which is not compatible with therapeutic application.42 The repetition of daily rTMS sessions for 3 to 10 days with at least 10-Hz intensity (80%-110% of the motor threshold) has also been found to produce cumulative effects in neuropathic pain, lasting for more than 1 week beyond the time of stimulation.1,5,23,25,26,27,62 These effects were obtained whatever the anatomical origin of neuropathic pain, involving either the central or the peripheral nervous system and seem to be similar in various neuropathic pain conditions. However, no study except in fibromyalgia37,45 has investigated the long-term efficacy of rTMS in chronic pain for several months. Safety is generally excellent, the main side effect of rTMS being transient headache. Contraindications include mainly epilepsy, brain tumour, and cardiac pacemaker.

In contrast to M1 stimulation, there are very few data regarding rTMS of other cortical targets in neuropathic pain. Thus far, the dorsolateral prefrontal cortex (DLPFC) has been mainly investigated. Its stimulation may modulate affective emotional networks related to pain. However, only 1 small sham-controlled study has been published to date and showed lack of efficacy of 10 days of high-frequency (10 Hz) rTMS of the left DLPFC in patients with central poststroke pain.12

Table 2

Randomised sham-controlled clinical trials with repetitive transcranial magnetic stimulation (conventional, deep repetitive transcranial magnetic stimulation with the Hesed coil) (repeated sessions for at least 3 days, at least 10 patients per treatment group) of the motor cortex or DLPFC for neuropathic pain.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Treatment</th>
<th>Patients</th>
<th>Main results on efficacy vs sham stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>rTMS of the motor cortex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Khedr et al. (2005)29</td>
<td>20 Hz for 5 d</td>
<td>Central pain and trigeminal neuralgia, n = 48</td>
<td>Significant effect immediately after sessions and 2 wk after last session.</td>
</tr>
<tr>
<td>Ahmed et al. (2011)1</td>
<td>20 Hz for 5 d</td>
<td>Phantom limb pain, n = 27</td>
<td>Significant effect on pain intensity (VAS) 5 d, 1 mo, and 2 mo after end of sessions.</td>
</tr>
<tr>
<td>Hosomi et al. (2013)23</td>
<td>5 Hz for 10 d (multicentre)</td>
<td>Multialgoiology NP, n = 64</td>
<td>Significant short-term effects (60 min) but no cumulative effect over 17 d.</td>
</tr>
<tr>
<td>Khedr et al. (2015)27</td>
<td>20 Hz for 10 d</td>
<td>Malignant neuropathic pain, n = 34</td>
<td>Significant effect persisting for 15 d but not at 1 mo.</td>
</tr>
<tr>
<td>Ma et al. (2015)34</td>
<td>10 Hz for 10 d</td>
<td>Postherpetic neuralgia, n = 40</td>
<td>Significant effect on pain intensity (VAS) persisting for 1 and 3 mo.</td>
</tr>
<tr>
<td>Attal et al. (2016)5</td>
<td>10 Hz for 3 d (crossover, 2 centres)</td>
<td>Painful lumbosacral radiculopathy, n = 35</td>
<td>Significant effect on pain intensity immediately after sessions and at 5 d; effect on cold pain thresholds.</td>
</tr>
<tr>
<td>Malavera et al. (2016)35</td>
<td>10 Hz for 10 d</td>
<td>Phantom limb pain, n = 54</td>
<td>Significant effect on pain intensity (VAS) for up to 30 d after treatment.</td>
</tr>
<tr>
<td>rTMS of the left dorsolateral prefrontal cortex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DeOlivera et al.12</td>
<td>10 Hz for 10 d</td>
<td>Central poststroke pain, n = 21</td>
<td>No effect on pain intensity after 1, 2 and 4 wk (interim analysis) and the study was stopped.</td>
</tr>
<tr>
<td>Deep rTMS (Hesed coil)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onesti et al. (2013)13</td>
<td>20 Hz for 5 d</td>
<td>Diabetic neuropathic pain of the lower limbs, n = 34</td>
<td>Significant effect of deep rTMS for up to 3 wk but not at 5 wk.</td>
</tr>
<tr>
<td>Shimizu et al. (2017)49</td>
<td>5 Hz for 5 d (crossover, comparison with conventional rTMS)</td>
<td>Multialgoiology neuropathic pain of the lower limbs, n = 18</td>
<td>Significant short-term effect of deep rTMS (60 min) but not of conventional rTMS.</td>
</tr>
</tbody>
</table>

Studies used a parallel group design unless otherwise indicated.
NP, neuropathic pain; rTMS, repetitive magnetic transcranial stimulation; VAS, visual analogue scale.
5.2. Transcranial direct current stimulation

Transcranial direct current stimulation is a widely used non-invasive technique for modulating neuronal excitability. It applies weak electric current of 0.5 to 3 mA to the skin to depolarize or hyperpolarize neurons in the brain.31 Anodal stimulation at the target electrode excites neuronal function, whereas cathodal stimulation inhibits it. Safety is generally excellent, with the main side effect of tDCS being a transient skin reaction below the stimulating electrodes.

Randomized small placebo-controlled trials of tDCS of the motor cortex in neuropathic pain used mainly repeated sessions (usually for 5 consecutive days) and reported either modest positive results or negative results (Table 3). A sham-controlled randomized comparative study of rTMS and tDCS of the motor cortex in painful radiculopathy showed only significant efficacy of rTMS after 3 days of treatment but not of tDCS compared with sham.5 Interestingly, however, 1 study showed significant prolonged effects of tDCS when combined with visual illusion of movement in patients with spinal cord injury pain and found that tDCS alone improved at least some neuropathic symptoms (paroxysmal pain).52 In any case, further studies are needed to clarify the effects of tDCS on neuropathic pain.

5.3. Newer brain neurostimulation techniques with promising effects in neuropathic pain

Standard TMS coils permit to stimulate only superficial cortical regions of the human brain. A newer cooled coil, the Hesed coil (H-coil), allows for deep brain stimulation without significantly increasing fields induced in superficial cortical regions.54 In healthy subjects, it has been found that the H-coil induces an effective field at a depth of approximately 3 to 4 cm beneath the surface of the skull. The H-coil also stimulates larger areas, that is, approximately 17 cm³ of the brain tissue compared with approximately 3 cm³ with conventional coils. The H-coil is already currently largely used in psychiatry for the treatment of psychiatric conditions, particularly major depression.31 Two small single-center RCTs have been conducted in patients with neuropathic pain. In 1 crossover trial including 25 patients with diabetic neuropathic pain and pain in the lower limbs, rTMS applied with H-coil for 5 consecutive data effectively relieved neuropathic pain vs sham stimulation for up to 3 weeks after the end of rTMS sessions. The effects were reversible and disappeared 2 weeks later.43 The other trial50 used a crossover design to compare conventional rTMS and H-coil of the motor cortex administered during 5 consecutive days in 18 patients with neuropathic pain and reported significant short-term pain relief immediately and 1 hour after H-coil stimulation but not after conventional rTMS stimulation as compared to sham stimulation. However, this study did not assess potential longer term effects of H-coil. Newer clinical studies comparing H-coil with conventional rTMS are required to confirm these preliminary results and demonstrate the clinical relevance of H-coil stimulation after repeated sessions in neuropathic pain.

6. Conclusion

New medical treatments in neuropathic pain include compounds acting on new pain targets. Most of them are in preclinical or early clinical development for neuropathic pain, but a few clinical trials have suggested the potential clinical relevance of NaV1.7 antagonists and angiotensin type II inhibitors in neuropathic pain. Another type of new drug therapy for neuropathic pain is represented by drugs largely used for other indications and for which analgesic effect has recently been discovered in neuropathic pain. Finally, emerging medical therapy with promising results in neuropathic pain includes noninvasive brain

Table 3

<table>
<thead>
<tr>
<th>Authors</th>
<th>Treatment</th>
<th>Patients</th>
<th>Main results on efficacy vs sham stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fregni et al.17</td>
<td>2 mA for 5 d</td>
<td>Spinal cord injury, n = 17</td>
<td>Short-term efficacy for pain intensity after end of treatment.</td>
</tr>
<tr>
<td>Mori et al.40</td>
<td>2 mA for 5 d</td>
<td>Multiple sclerosis, n = 19</td>
<td>Significant efficacy for pain intensity for up to 3 wk.</td>
</tr>
<tr>
<td>Soler et al.52</td>
<td>2 mA for 10 d (comparison with visual illusion and combined treatments)</td>
<td>Spinal cord injury, n = 39</td>
<td>No effect of tDCS alone on overall pain intensity; effect on paroxysmal pain; combination with visual illusion effective for up to 12 wk.</td>
</tr>
<tr>
<td>Kim et al.28</td>
<td>2 mA for 5 d</td>
<td>Diabetic neuropathic pain, n = 40</td>
<td>Significant effect on pain intensity, persisting at 2 and 4 wk.</td>
</tr>
<tr>
<td>Wrigley et al. (2013)59</td>
<td>2 mA for 5 d (crossover)</td>
<td>Spinal cord injury pain, n = 10</td>
<td>No effect on mean pain intensity or unpleasantness.</td>
</tr>
<tr>
<td>Hagenacker et al.71</td>
<td>2 mA for 2 wk (crossover)</td>
<td>Trigeminal neuralgia, n = 10</td>
<td>Significant effect on pain intensity but not on the frequency of painful attacks after 2 wk of treatment.</td>
</tr>
<tr>
<td>Yoon et al. (2014)63</td>
<td>2 mA twice a day for 10 d</td>
<td>Spinal cord injury pain, n = 16</td>
<td>Effect of active tDCS only on pain intensity; metabolism on PET scan increased in the medulla and decreased in the left dorsolateral prefrontal cortex.</td>
</tr>
<tr>
<td>Scuto et al. (2014)73</td>
<td>2 mA for 5 d</td>
<td>Pain due to HTLV1, n = 20</td>
<td>No significant effect of tDCS vs sham on primary outcome; large placebo effect.</td>
</tr>
<tr>
<td>Attal et al.8</td>
<td>2 mA for 3 d (crossover, 2 centers)</td>
<td>Painful lumbosacral radiculopathy, n = 35</td>
<td>No effect on pain intensity immediately after the sessions or 5 d later.</td>
</tr>
</tbody>
</table>

Studies used a parallel group design unless otherwise indicated.

tDCS, transcranial direct current stimulation.
neurostimulation techniques, such as rTMS and tDCS. Newer stimulation techniques such as deep rTMS also seem promising. However, one remaining issue before bringing the above interventions into routine clinical practice for neuropathic pain is the fact that most of the available evidence relies on proof of concept or single-center clinical trials. Multicenter large-scale confirmatory clinical trials are now warranted. Such trials are now being supported by drug companies for drugs acting on new targets. This seems more challenging for older compounds because of loss of interest by pharmaceutical industry and, as regards neurostimulation, because of the cost of equipment together with the necessity of highly trained investigators. However, multicenter clinical trials aiming to confirm the long-term efficacy of rTMS in particular are currently underway in France (https://clinicaltrials.gov/ct2/show/NCT02010281).

Conflict of interest statement

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Tired of pain? Toward a better understanding of fatigue in chronic pain
Stefaan Van Dammea,*, Susanne Becketb, Dimitri Van der Lindenc

1. Why we need a better understanding of fatigue in chronic pain

Fatigue is a prevalent complaint in people with chronic pain.11,46 A study in the general population showed that 64% of the individuals with chronic widespread pain reported co-occurring persistent fatigue.15 In patients with chronic pain due to spinal cord injury, 70% reported persistent fatigue.12 Such comorbid fatigue is likely to be an additional source of disability and suffering when left untreated.1,25,42 Moreover, fatigue might reduce patients’ ability and/or willingness to fully engage in treatments aimed at increasing physical activity, such as graded activity or exposure,38 possibly lowering effectiveness. As such, a good understanding of fatigue in chronic pain patients is crucial. The aim of this review is to discuss the current knowledge on fatigue in chronic pain, to provide conceptual clarification of fatigue, and to develop a theoretical framework explaining fatigue in the context of chronic pain. Based on this framework we discuss a new research agenda and provide recommendations for clinical practice.

2. What do we currently know about the interplay between chronic pain and fatigue?

A systematic review21 investigating fatigue in various chronic pain populations showed that nearly all studies found significant associations between self-reported pain and fatigue and that fatigue was more likely to occur if pain was more intense and present for a longer time. Particularly interesting is that in 5 of the 6 prospective studies included, fatigue developed after pain onset, suggesting that chronic pain might cause fatigue. To date, the influence of (chronic) pain on fatigue has been mainly explained in terms of so-called ego-depletion accounts. For example, it has been hypothesized that the challenges associated with chronic pain lead to depletion of self-regulatory resources, also referred as self-regulatory fatigue.44 However, depletion accounts have been criticized,61 and the precise mechanisms and temporal dynamics of the association between chronic pain and fatigue remain poorly understood.54

3. The problem of defining fatigue

Fatigue is a complex multifaceted construct with a diverse phenomenology comprising physiological as well as psychological states, and referring to perception as well as performance. This complexity is reflected in the large diversity in available definitions and the lack of a consensus definition. For instance, fatigue has been called not only as an overwhelming sense of tiredness/exhaustion and lack of energy associated with impaired physical and/or cognitive functioning62 but also as an aversive perception of growing effort needed to sustain a certain task or action.50

In this review, we will not focus on physiological aspects, such as muscle tiredness resulting from physical exertion,52 or sleepiness, which is the mere consequence of an imbalance in sleep-wake mechanisms.53 We will rather focus on the motivational component of fatigue. Going back to the seminal work of Thorndike,49 fatigue is considered an adaptive signal urging disengagement from current behavior of decreasing utility. From this old but still valid perspective, fatigue does not necessarily reflect depleted capacity or resources, but rather a motivational state, or “stop-emotion”, protecting against inefficient energy expenditure.26,36,55 In line with this and similar motivational accounts,7,9,16,32 we propose defining fatigue as an aversive motivational state urging disengagement from effortful behavior of which the costs are currently estimated as exceeding the benefits.

4. A motivational framework on fatigue in the context of chronic pain

In designing our theoretical framework, we integrated motivational perspectives on fatigue,7,9,16,26,32,36,55 and chronic pain,14,18,44,51,52,59,64 Key in our framework (Fig. 1) is that the balance between (expected) costs and benefits of current goal pursuit signals whether one should maintain the behaviour or not. When the benefits exceed the costs, this results in motivational drive, promoting goal persistence. When the costs exceed the benefits, the signal is perceived as fatigue, urging goal adjustment. We propose that this costs–benefits trade-off is affected by chronic pain through 3 pathways, namely (1) increased effort to maintain goal-directed behaviour, (2) heightened pain (expectations) during goal pursuit, and (3) impaired reward processing associated with goal-directed behaviour.

The first pathway describes what happens if chronic pain hinders goal progress,17,39 but one nevertheless wants to uphold goal-directed behaviour at a satisfying level. In that case, the...
describe some examples. First, fundamental complex functions and inter-

models of pain-related attention.\textsuperscript{15,33,34,53} What might further

attentional control over pain, as argued in affective-motivational

fear-avoidance\textsuperscript{58} and catastrophic thinking\textsuperscript{45} argue that chronic

maintaining goal-directed behaviours. Established pain theories on

be crucial in the development of persistent fatigue complaints.\textsuperscript{29}

of pain on the costs–benefits balance and could be protective

factors against the development of fatigue in chronic pain.\textsuperscript{29}

5. Towards a new research agenda

Our framework generates several possible paths for future research. We describe some examples. First, fundamental studies could systematically examine how pain during task performance may elicit various manifestations of fatigue, including difficulty to initiate or uphold goal-directed behaviour. One hypothesis is that the experience of pain-related task interference initially results in increased effort to uphold task performance, enhanced executive control, and suppression of pain,\textsuperscript{4,22} but gradually induces fatigue because of the increased demand of effort. This may yield adaptive strategies, that is, lowering performance standards, resulting in faster decline in performance. This hypothesis is intriguing, as it brings in a temporal aspect, in which fatigue might moderate the effect of pain on performance. Note that simple self-report measures will be insufficient to measure fatigue as described in this review. We recommend a mixed-method approach, adding behavioural paradigms such as the Effort Expenditure for Rewards Task,\textsuperscript{50} and psychophysiological measures such as the amplitude of the contingent negative variation or the error-related negativity (Ne/ ERN), which are well established in the fatigue literature and have been shown to reflect motivational aspects of fatigue.\textsuperscript{5}

Second, the proposed framework might shed new light on commonly observed problems in chronic pain populations such as cognitive dysfunction and attentional bias.\textsuperscript{23,38,53} Studies typically look only at mean performance levels, neglecting underlying processes such as shifts in motivation.\textsuperscript{6,28} We recommend studying attention dynamics and fluctuations over task course.\textsuperscript{31,57} Reduced physical activity in chronic pain patients is often explained by fear-avoidance beliefs.\textsuperscript{58} Yet, it has become clear that not all patients have “kinesiophobia”,\textsuperscript{14} and that reductions in activity levels are only partially accounted for by fear-induced avoidance.\textsuperscript{52} We propose the alternative view that reduced activity might reflect goal disengagement, triggered by fatigue when goal pursuit becomes effortful and unrewarding. This makes an interesting avenue for future research.

Third, our framework suggests ideas for future research about the involvement of neurophysiological mechanisms. Regarding brain circuits, a large processing network is conceivable because the model comprises various aspects (executive functioning, costs–benefits trade-off) known to be processed in many brain regions. One specific region central for executive control is the dorsolateral prefrontal cortex, which exerts top–down influence over information processing and plays a role in downregulation of pain.\textsuperscript{56} A brain area highly relevant for rewards–costs trade-offs and decision-making is the anterior cingulate cortex, particularly the dorsal part of this area, or the anterior midcingulate cortex.\textsuperscript{50} However, the model comprises complex functions and interactions, rendering it likely that the processes are mediated through altered functional connectivity within an extended
network of brain regions. On a neurochemical level, the dopaminergic system is a likely candidate to be involved in the processes described in the model.\(^3\) Fatigue is associated with failed activation of dopaminergic pathways.\(^7\) Furthermore, dopamine has been shown to mediate the interaction of reward and pain and to bias behaviour either towards pain avoidance to consume a reward or towards pain avoidance at the cost of not receiving a reward.\(^4,5\) Other neurotransmitter systems are likely to be involved,\(^7\) but evidence is missing. Further studies are needed to characterize the neurophysiological processes involved. Particularly, the idea that (chronic) pain may change the utility of current goal pursuit, in terms of rewards–costs trade-off, requires further investigation. Specifically, it should be tested whether pain is an additional cost of action, possibly shifting functional connectivity in the related brain circuits. Based on the available literature, we hypothesize this to be mediated by dorsolateral prefrontal cortex and anterior midcingulate cortex.

6. Potential treatment implications

Given that the hypothesized interactions between chronic pain and fatigue await further empirical examination, specific recommendations for clinical practice may be premature. However, we speculate about possible pathways toward better care for people with chronic pain. For instance, it is likely that for fatigued chronic pain patients, cognitive-behavioral interventions, such as exposure or graded activity are very effortful, possibly predicting poor treatment response. Pain treatment protocols should consider such barriers,\(^19\) for example, by specifically targeting processes underlying fatigue such as the rewards–costs balance of selected (treatment) goals. To make behavior more rewarding despite the effort required to maintain it when in pain, it is important to help patients selecting valued but feasible goals, for example, using motivational interviewing.\(^3\) Furthermore, techniques aimed at improving self-regulation skills, such as the use of action plans or implementation intentions,\(^42\) may help patients to reduce the effort required to pursue goals. It is only recently that such motivational and self-regulation approaches are explicitly added in pain treatment protocols,\(^10\) and their effect on fatigue remains to be investigated.

Conflict of interest statement

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Is burning mouth syndrome a neuropathic pain condition?
Satu K. Jääskeläinen

Abstract
Primary burning mouth syndrome (BMS) is defined as an “intraoral burning or dysaesthetic sensation, recurring daily… more than 3 months, without clinically evident causative lesions”. Although lacking clinical signs of neuropathy, more accurate diagnostic methods have shown neuropathic involvement at various levels of the neuraxis in BMS: peripheral small fiber damage (thermal quantitative sensory testing, electrogustatometry, epithelial nerve fiber density), trigeminal system lesions in the periphery or the brainstem (brainstem reflex recordings, trigeminal neurography, evoked potentials), or signs of decreased inhibition within the central nervous system (deficient brainstem reflex habituation, positive signs in quantitative sensory testing, neurotransmitter–positron emission tomography findings indicative of deficient striatal dopamine function). Abnormalities in electrogustatometry indicate the involvement of the small Aδ taste afferents, in addition to somatosensory small fibers. According to these findings, the clinical entity of BMS can be divided into 2 main subtypes compatible with either peripheral or central neuropathic pain, which may overlap in individual patients. The central type does not respond to local treatments and associates often with psychiatric comorbidity (depression or anxiety), whereas the peripheral type responds to peripheral lidocaine blocks and topical clonazepam. Burning mouth syndrome is most prevalent in postmenopausal women, having led to a hypothesis that BMS is triggered as a consequence of nervous system damage caused by neurotoxic factors affecting especially vulnerable small fibers and basal ganglia in a setting of decrease in neuroprotective gonadal hormones and increase in stress hormone levels, typical for menopause.

Keywords: Burning mouth syndrome, Clinical neurophysiology, Quantitative sensory testing, Neuropathic pain, Small fiber neuropathy, Central pain

1. Introduction
In the most recent classification by International Headache Society,21 burning mouth syndrome (BMS) is classified under the header “Painful cranial neuropathies” and defined as an “intraoral burning or dysaesthetic sensation, recurring daily for more than 2 hours per day over more than 3 months, without clinically evident causative lesions.” The pain is moderate to severe, similar to tooth ache in intensity but has a distinct superficial, burning character and is often accompanied by taste alterations and xerostomia (in 50% to 70% of the patients).31 The tip of the tongue is most frequently affected, but any part of the intraoral mucosa may be involved. The estimates of population prevalence of BMS range considerably, from 0.01% to 40%, but in more recent well-controlled studies using current diagnostic criteria, it has been estimated to be less than 1% to 3.7%.31 Prevalence of BMS is highest in postmenopausal women (18%), and reported female-to-male ratios range from 3:1 to 20:1.31 Many patients with BMS report night benefit; the pain does not disturb sleep and is better in the morning, getting worse during the day.31 By definition,21 clinical investigations and clinical sensory examination, without quantitative psychophysical measures, are normal and thus, BMS does not seem to fit the current IASP definition of neuropathic pain, which arises as a direct consequence of a lesion or disease affecting the somatosensory system, with both symptoms and clinical signs within a neuroanatomically plausible distribution.12 Thus, there seems to be a discrepancy between the IHS classification of BMS as a painful cranial neuropathy and the IASP definition of neuropathic pain. Nevertheless, research done on BMS during the last 2 decades, using strict clinical diagnostic criteria for primary BMS and sophisticated diagnostics with clinical neurophysiologic, psychophysical, and neuropathological tools as well as functional brain imaging, has revealed neuropathic involvement at various levels of the neuraxis in the majority of the patients with BMS [reviewed in detail in Ref. 26,31].

In the following section, the existing evidence for neuropathic etiology of primary BMS will be summarized.

2. Evidence for neuropathic involvement in burning mouth syndrome
2.1. Peripheral nervous system in burning mouth syndrome
Brainstem reflex recordings, mediated via large myelinated Aβ afferents have shown signs of damage in the trigeminal nerve or its brainstem circuits in approximately 20% of clinically typical primary patients with BMS.13,26,27 This subgroup of patients with BMS represents subclinical trigeminal neuropathic pain without
clear clinical signs, which is compatible with the poor diagnostic sensitivity of clinical sensory examination, especially at chronic stage after nerve injury.25,30,44,45

Thermal quantitative sensory testing (QST) and tongue mucosal biopsies have further elucidated the peripheral nervous system involvement in BMS pain. The majority (76%13) of patients with BMS show hypoesthesia in thermal QST, especially to innocuous cooling and warming and, to a lesser extent, hypalgesia.13,15,22,36,42 Quantitative sensory testing profiles in patients with BMS thus very much resemble those reported in a large cohort of different neuropathic pain conditions.35 These loss-of-function signs in thermal QST of patients with BMS have later been shown to be due to focal damage of the small nerve fibers of the tongue epithelium.4,33,38,47 In individual patients with BMS, overlap between large and small fiber pathology may occur.13,31,33 Furthermore, abnormalities in electrogustometry suggest that pathophysiological process in primary BMS involves the small Aδ taste afferents as well,11,16,24,37 giving explanation to frequent taste alterations in these patients. Of interest is that in BMS, the Aδ cool afferents seem to be more often impaired than C fibers,13,38 indicating an imbalance within small fiber input to the central nervous system. As the cool Aδ fibers exert a tonic inhibition of the polymodal C nociceptor signaling in normal conditions,9 this kind of more severe damage to the Aδ fiber system with relative preservation of C fiber function could lead to ongoing burning pain sensation because of unmasking or disinhibition of the system, in BMS26 similarly as in central pain.9

In addition to loss-of-function in thermal modalities, QST has shown gain-of-function in a small proportion of patients with BMS either in the form of decreased heat pain tolerance15,17 or heat pain hyperalgesia and allodynia.13,16 Likewise, brainstem reflex recordings have objectively shown disinhibition of the trigeminal brainstem complex in the form of deficient habituation of the blink reflex R2 component in approximately 1/3 of the patients.13,27,36 As blink reflex habituation is under descending nigrostriatal dopaminergic control,9 neurotransmitter–postsynon emission tomography (PET) studies have been conducted to elucidate possible central dopaminergic system pathophysiology in BMS. These were intended to test the hypothesis of deficient striatal dopaminergic top–down inhibition as a major trigger of neuropathic orofacial pain.18,19,26,28,29 The results, together with other converging evidence for central nervous system (CNS) involvement in primary BMS will be dealt with in the next part.

2.2. Central nervous system in burning mouth syndrome

Changes typical for neuropathic or central pain have been shown in BMS with functional brain imaging methods (for detailed review, c.f.31). Patients with BMS show less volumetric brain activation in fMRI to painful hot stimuli than control subjects, especially in bilateral thalamus,1 which is similar to functional brain imaging findings in other neuropathic pain conditions because of deafferentation of the somatosensory pathways.2

Neurotransmitter PET studies on the striatal dopaminergic system with fluor-DOPA and 11C-raclopride scans indicate a decrease in synaptic dopamine levels in patients with BMS compared to controls.18,28 The PET findings in BMS are similar to those in early Parkinson disease,20 in which central type neuropathic pain is rather common, and the incidence of BMS has been suggested to be increased compared to general population.7,8,36,39 Our neurophysiologic and neurotransmitter PET findings in BMS gave the first direct evidence in humans for the important role of basal ganglia, and especially the brain dopaminergic network in processing and modulation of clinical pain,18,19,28 which has later been further corroborated in several reviews.5,23,26,31 Experimental evidence supports the connection between the striatal DA system and trigeminal pain, as lesioning of the nigrostriatal DA pathway has been shown to induce allodynia within the trigeminal distribution.10

Furthermore, the genetically determined function of the dopamine D2 receptors (DRD2) via the DRD2 957C > T single-nucleotide polymorphism has been shown to be related to the risk for and symptom severity in neuropathic orofacial pain, including BMS.29 The prevalence of the homozygous 957 TT genotype, associated with low synaptic dopamine levels in the striatum, is increased (50%) in patients with neuropathic orofacial pain compared to general population (27%), and patients with this genotype report the highest pain intensities in NRS scores.29

In addition to psychophysical and neurophysiological methods, peripheral lidocaine block of the lingual nerve can be used to cluster patients with BMS into 2 distinct subgroups. The peripheral subgroup demonstrates good analgesic response to local anaesthesia, whereas the central subgroup shows no response or even hyperalgesia after peripheral nerve block.16 This easy procedure also seems to be able to predict the response to topical clonazepam treatment that was beneficial only in the peripheral subgroup of patients with BMS.16 Furthermore, the central subgroup showed higher scores in hospital anxiety and depression scores.

Psychiatric comorbidity in patients with BMS is recognized and currently often considered a secondary, nonspecific phenomenon frequently encountered in patients with chronic pain.14 However, most studies on psychological factors in BMS have applied questionnaires that cannot be used for proper psychiatric diagnostics. A novel explanation for psychiatric morbidity in BMS has been presented in a thorough study on patients with BMS utilizing structured psychiatric interviews, giving current (state) and lifetime (trait) diagnoses for both psychiatric (axis I) and personality (axis II) disorders.43 According to this study, patients with BMS seem to suffer only of psychiatric conditions attributed to low-brain dopamine tone: major depression and social phobia were found in 55% of the patients with BMS, and type C (fearful/neurotic) personality in 16% of the patients with BMS.43 Similar psychiatric profile has also been found in a BMS study using questionnaires.16 Thus, inherent or induced weakness of brain dopamine system may offer a common pathway to both chronic neuropathic pain and comorbid psychiatric disorders.26,31,43

Further support to the dopamine hypothesis of BMS pain comes from noninvasive brain stimulation studies showing that repetitive transcranial magnetic stimulation, by initially releasing dopamine in the striatum40,41 thereby activating the endogenous opioid system,32 also effectively relieves BMS pain.34,46

3. Discussion

Current converging evidence from several lines of investigations, covering neural pathways from the epithelial nerve fibers to the brain, indicates that clinically typical BMS, in the majority of cases, is a chronic neuropathic pain condition, consisting of 2 main subgroups, peripheral and central. These conditions are subclinical, as they do not show evident clinical signs of neuropathy and thus, they can be correctly identified and classified only by means of neurophysiologic, psychophysical, and neuropathologic investigations. Peripheral lingual nerve lidocaine blocks may also help in classifying the patients with BMS into peripheral and central subgroups, but this method should still be validated against thorough neurophysiologic, psychophysical, and neuropathological diagnostics. The first BMS subgroup
involves subclinical peripheral neuropathic pain, caused either by more extensive yet subclinical trigeminal neuropathies and trigeminal brainstem lesions, or by pure small fiber neuropathy of the intraoral mucosa with loss-of-function signs in confirmatory tests. The local small fiber type of BMS might also fit in the entity of non-length-dependent small fiber neuropathy that is more prevalent in women than men and shows a patchy distribution that may cover, for example, face or trunk. The other subgroup consists of central BMS with neurophysiologic and neurotransmitter PET signs, indicating low-brain dopamine tone and increased prevalence of psychiatric comorbidity and, sometimes, additional gain-of-function signs in QST. In individual patients, these subtypes, peripheral and central, may overlap with different combinations of loss- or gain-of-function signs.

Profile of comorbid psychiatric disorders in patients with BMS is interesting, especially regarding the PET findings of low striatal dopamine tone in these patients. Weak top–down inhibitory control via endogenous dopamine–opioid axis and basal ganglia circuits could represent shared vulnerability both to depression, anxiety as well as type C personality disorders, and to chronic neuropathic pain. Accordingly, for example, neuropathic pain and depression would not be causal to each other but, instead, result from common predisposition because of low-brain dopamine tone, genetic or acquired, in the presence of neuropathic involvement of the peripheral and/or CNS.

Recently, a novel hypothesis has been proposed to encompass various pathophysiological processes leading to BMS and to explain open questions regarding, for example, gender differences and age distribution of patients with BMS. Four key features of BMS have to be taken into account: (1) preponderance of postmenopausal women, (2) type of psychiatric comorbidity, (3) oral location of the symptoms, and (4) peripheral and CNS abnormalities found in confirmatory tests. In short, chronic anxiety/depression would not be causal to each other but, instead, result from common predisposition because of low-brain dopamine tone, genetic or acquired, in the presence of neuropathic involvement of the peripheral and/or CNS.

In addition, it is noteworthy that in neurophysiologic investigations, approximately 20% of clinically typical patients with BMS show subclinical trigeminal system pathology; for example, subclinical lingual of mandibular nerve injuries or brainstem level lesions. From the existing literature, it is obvious that clinical sensory examination does not provide tools sensitive and accurate enough for the diagnostics and classification of neuropathic orofacial pain. It may thus be argued that the current definition of neuropathic pain, requiring neuroanatomically plausible symptoms and clinical signs in addition to confirmatory tests for definite diagnosis of neuropathic pain, is not appropriate, as it does not recognize subclinical neuropathic pain conditions. Furthermore, it currently does not accept results of confirmatory tests alone as evidence for neuropathic nature of the pain. Nevertheless, for example, pure small fiber neuropathies and neuropathies within the orofacial region, where clinical sensory examination may be especially difficult, are challenging to diagnose with traditional clinical tools only. In the definition of neuropathic pain, a shortcut from symptoms to neurophysiologic, psychophysical, neuropathologic, and/or functional brain imaging findings, bypassing the requirement of neuroanatomically plausible clinical signs, could thus provide a reasonable way to establish definite diagnosis of neuropathic pain in conditions such as BMS. In addition, the distribution of symptoms and signs in non-length-dependent small fiber neuropathies and central pain conditions due to basal ganglia disorders does not comply with classic peripheral or central neuroanatomical distributions, which should be taken into account when defining criteria for neuropathic pain. Accordingly, taking into account the existing evidence for neuropathic etiology of BMS, the current IHS classification of BMS under painful cranial neuropathies seems most appropriate.

Correct diagnostics and classification of the 2 neuropathic subgroups of BMS, peripheral and central, is important, as this may in the future guide the choice of the best treatment on individual patient level. Patients with signs of peripheral neuropathic BMS pain could benefit from topical treatments, for example, with clonazepam or capsaicin, while pain in central BMS may best be alleviated by boosting the endogenous top–down control via brain dopamine–opioid axis with non-invasive neuromodulation techniques such as repetitive transcranial magnetic stimulation or with dopaminergic medications. Furthermore, signs of pure small fiber neuropathy in patients with BMS imply systematic investigation of possible etiologies for small fiber neuropathy, some of which may be curable. These options warrant further studies, controlled with appropriate and sensitive diagnostic methods.

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FACT SHEET No. 2

Current Status of Pain Education and Implementation

Challenges

Education in pain management continues to be a low priority in health professional curricula despite decades of research documenting unmet global needs. The 2016 Global Burden of Disease Study shows that persistent pain is a major and increasing cause of morbidity and disability worldwide [9]. Pain is one of the most common reasons patients seek a health-care professional; therefore, our graduates must possess the requisite knowledge and skills to be competent [3,4,10].

Challenges

Preclinical health professions training in pain management falls far below recommended standards in high-resource countries based on well-validated survey studies (2,7,8,12). The status of pain education in low-resource countries is unknown, but glaring deficits in pain management underscore a dire situation that demands greater effort [6]. Despite extensively developed and freely available curriculum resources, adoption of pain content into entry-to-practice programs is agonizingly slow. Until now, most health professionals have learned pain management only through an “informal curriculum” in clinical settings that perpetuate a culture of stigma and inadequate pain care practices.

Many health professionals feel unprepared to manage complex pain issues, particularly where comprehensive treatment is required (11). Critically, summative assessment of competency in pain management is not currently required for licensure of most health professionals (13).
Safe, proficient, and compassionate pain management will not happen without pain education for all health professionals. Therefore, two questions need to be addressed: What barriers are limiting integration of pain content in health sciences curricula, particularly at the prelicensure (undergraduate) level, and what resources are available?

**Resources and Strategies**

Challenges hindering the adoption and implementation of pain curricula and competencies are not well understood, but one factor is the lack of competency standards for licensure [11]. Changes in professional certification, and in pain education, have lagged far behind improved regulatory standards [1]. Teaching challenges in classrooms and clinical training sites remain obstacles as well. These challenges include curriculum models and priorities that do not address pain, insufficient faculty qualifications and lack of confidence in teaching about pain, and inconsistent opportunities for interprofessional learning [11].

Fishman and Young propose focusing on organizations with the influence to require pain content in health science curricula [3]. The Global Year “Prospectus to Promote Professional Pain Education” [link] can initiate a discussion with stakeholders with the appropriate authority. This document includes strategies to help regulatory and licensing bodies and accreditors understand the importance of endorsing core pain content and competency evaluation in health science curricula. Hospital accreditation standards, such as the Joint Commission’s Pain Standards, contain a powerful message that providers must be educated about pain [1]. Influencing professional bodies to include and increase required pain competencies in entry-to-practice licensing and maintenance of certification may have the greatest impact on pain education and clinical practice [13].

- Curriculum resources, such as the examples below, are available to help change traditional models that focus on pain as a symptom. The nociceptive processing system has protean impacts on clinical care and human experience far outstripping any significance as a subsystem of the sensory nervous system.
- Core pain competencies and curricula have been developed and tested, and these may be used as a basis for application in various health professional curricula.
- Curriculum mapping involves the process of examining content to identify the actual pain content faculties are addressing in order to address gaps, redundancies, and coherence. These data can help underscore the issue. For example, comparisons with veterinary medicine curricula stimulated discussions about why pets receive care from practitioners more qualified in pain management [13].
• Although faculty have not felt competent in teaching pain content, they have been described as the “ultimate resources of all educational institutions” and as “agents of knowledge transmission and role models” [4]. Attendance at professional conferences, engagement, recruitment, and collaboration to integrate pain content as a component of other topics, such as metabolic disorders or cardiovascular conditions, is essential to advance pain education.

• Fostering mentoring relationships with colleagues in academic and clinical settings encourages a shared understanding of pain and supports best practice modelling for students. Finding and working with local pain champions who are motivated to improve pain care and education can ensure efforts have positive outcomes.

• Stakeholder models can help identify key individuals in order to develop strategies to gain their support. Stakeholders to consider are deans, curriculum coordinators, librarians, pain experts, education design experts, clinicians, and patients.

• Effective pain management requires collaborative approaches that exceed the expertise of any one profession, so it is important to create interprofessional group learning opportunities. Students need to understand one another’s expertise, both shared and unique, that is essential to interprofessional and multiprofessional pain management.

Resource Examples

A. Interprofessional Pain Curriculum and Core Pain Competencies


B. Strategies to encourage regulatory/licensing bodies and accreditors

- Prospectus to Promote Professional Pain Education [link]

C. Strategies to identify stakeholders and build capacity for change

- Example of a practice model for building capacity for community and system change

D. Advancing pain education and mentoring utilizing SMART goals approaches to foster change*
In the next 3 months

Meet for at least 10 minutes with one person responsible for education at your institution to learn about their priorities

Spend one hour with colleagues who teach in your institution discussing possibilities for pain content integration within your institutional culture

Contact a colleague to plan inter-institutional education collaboration or offer opportunities for shared teaching of similar pain topics.

In the next 6 months

Attend a health professions education conference to acquire the language of teaching innovations useful for pain education. In follow-up to attending this meeting, build one new teaching alliance on the premise that pain is an opportunity to teach transferable skills in professionalism; e.g., shared-decision making, patient-centered communication skills, chronic disease models, and safe prescribing

Offer to spend one hour teaching a topic that others might view as burdensome but which has important implications for pain care; e.g., chronic pelvic pain, non-cardiac chest pain

Identify and contact one colleague who teaches in a related field to brainstorm about creative opportunities to bring pain into the discussion and discuss related modules that others have taught successfully

In the next year

Identify two seminal resources about new approaches to teaching (e.g., simulation, teachable moments) and assessment (e.g., formative assessment, script concordance, pain competencies); share with three others

Read and respond to recommendations and standards for pain education: IASP, Joint Commission, WHO, others; write a short blurb for your institutional media, tweet, or give one media interview

Mentor two people in pain education and seek the guidance of a mentor with more pain and teaching experience

Use multidimensional evaluation methods to examine outcomes and determine success or need for change in one educational intervention


REFERENCES


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