CONTENTS

REVIEW: Emerging factors in the progression of cancer-related pain
*Pain Manag.* Vol. 6 Issue 5

INTERVIEW: Four steps to eliminate or reduce pain in children caused by needles (part 1)
*Pain Manag.* Epub ahead of print

RESEARCH ARTICLE: Chronic postsurgical pain and persistent opioid use following surgery: the need for a transitional pain service
*Pain Manag.* Vol. 6 Issue 5

RESEARCH ARTICLE: The moderating and covarying effects of social support and pain intensity on depressive symptomology among racially and ethinically diverse older adults
*Pain Manag.* Vol. 7 Issue 1

REVIEW: Abuse-deterrent formulations of prescription opioid analgesics in the management of chronic noncancer pain
*Pain Manag.* Vol. 6 Issue 5

www.Neurology-Central.com
Emerging factors in the progression of cancer-related pain

David K Lam*

Most cancer patients experience severe pain during their disease course, and the management of cancer pain is a major challenge for patients and the healthcare team. Many diverse translational models of cancer pain in recent years have improved our understanding of cancer-related pain. Cancer and associated cells in the cancer microenvironment may release various peripheral mediators, including ATP, formaldehyde, protons, proteases, endothelin, bradykinin, TNF and NGF, that result in the activation and/or sensitization of peripheral and central neurons, that contribute to the clinical manifestations of cancer-related pain.

Identification of these mediators and the peripheral and central mechanisms by which they contribute to cancer-related pain may provide novel therapeutic targets to alleviate cancer patient suffering.

First draft submitted: 12 November 2015; Accepted for publication: 21 March 2016; Published online: 6 May 2016

Practice points

- Cancer patients may experience pain related to the primary cancer per se, pain related to the treatment for the cancer or pain unrelated to cancer or its treatments. The optimal management of cancer pain requires the identification of these likely causes of pain.
- This review will focus on the emerging factors in the progression of cancer-related pain. Clinical manifestations of cancer-related pain depend on the histologic type of the cancer, anatomic location of the primary cancer and the anatomic location of any metastatic lesions.
- Opioids, such as morphine, are the mainstay analgesic therapy in treating moderate–severe cancer-related pain. However, opioids and other existing analgesics have limited efficacy for cancer-related pain in many patients and there are unfortunate adverse side effects associated with many of these drugs.
- Cancer-related pain likely results from the release of peripheral mediators in the cancer microenvironment, resulting in activation and/or sensitization of peripheral and central neurons.
- Molecular changes within the CNS due to cancer-related pain are often distinct relative to the changes induced by neuropathic or inflammatory pain.
- Changes in peripheral and central processing may explain the allodynia, hyperalgesia, spontaneous pain, and pain spread or referral, that are characteristic of many of cancer-related pain conditions.
- Targeting identified peripheral and central pain mechanisms may not only provide novel therapeutics for cancer-related pain but may also improve the analgesic efficacy of existing drugs such as morphine.
Most cancer patients experience severe, uncontrollable pain during the course of their disease, and many patients are living longer with cancer and may endure protracted cancer pain. The management of cancer pain is a primary challenge for both the patient and the healthcare team. There are generally three major causes of pain in patients with cancer: cancer-related (93%), treatment-related (21%) and/or unrelated to cancer or its treatments (2%) [1]. Cancer-related pain may be a consequence of cellular, tissue and systemic changes that occur during proliferation, invasion and metastasis. Cancer progression may result in tissue damage and/or nerve injury through various mechanisms, such as infiltration, obstruction, compression and fracture; and consequent exacerbation of cancer-related pain. Cancer treatments such as surgery (e.g., post-mastectomy pain), radiation (e.g., mucositis) and medical therapy (e.g., chemotherapy-induced peripheral neuropathy) may contribute to treatment-related pain. Patients with cancer may also concomitantly suffer from various acute and/or chronic pain conditions unrelated to cancer or its treatments, such as sprains, toothaches, arthritis and fibromyalgia. The optimal management of cancer pain requires the identification of these likely causes of pain. This review will focus on the emerging factors in the progression of cancer-related pain.

The clinical manifestation of cancer-related pain depends on the: histologic type of the cancer; anatomic location of the primary cancer; and the anatomic location of metastases [2]. It is particularly noteworthy that there may be significant differences between spinal and trigeminal processing of cancer-related pain. For example, oral cancer patients experience pain at their primary site during oral function early in the carcinogenesis process, whereas breast cancer patients rarely present with breast pain but usually experience pain secondary to skeletal metastases [2]. Existing analgesic drugs show only limited efficacy for cancer-related pain in many patients and there are unfortunate adverse side effects associated with many of these drugs. As such, there is a clear need to better understand the underlying mechanisms contributing to cancer-related pain. The establishment of diverse translational animal models of cancer pain in recent years has provided some insights into the molecular mechanisms of cancer pain. These studies suggest cancer-related pain is due to mediators generated and released by cancer cells that recruit and affect other cells within the cancer microenvironment. These putative mediators subsequently directly or indirectly activate and/or sensitize both peripheral and central neurons. We will discuss these key mediators thought to contribute to cancer-related pain in the cancer microenvironment and review their effects on peripheral and central pain processing (see Figure 1).

Peripheral mechanisms
Peripheral mechanisms contributing to cancer-related pain likely result from a combination of nerve injury and release of peripheral mediators in the cancer microenvironment. In a model of neuropathic cancer-related pain, Shimoyama and colleagues [3] inoculated sarcoma cells around the sciatic nerve in mice and observed cancer-induced mechanical allodynia, thermal hyperalgesia and spontaneous pain behaviors. It is likely that nerve injury contributed to cancer-related pain in this sarcoma model since histologically, gradual compression by the cancer cells resulted in progressive damage to both myelinated and unmyelinated fibers. More recently, various cancer pain models have also implicated peripheral mediators, including ATP, formaldehyde, protons, proteases, endothelin, bradykinin, TNF and NGF in the cancer microenvironment in cancer-related pain. These mediators may increase the excitability of nociceptors in the cancer microenvironment by activation and/or sensitization of receptors which lead to alterations in ion channel permeability and/or second messenger systems. The resultant increased responsiveness to noxious stimuli, decreased activation threshold and/or spontaneous activity of nociceptive afferents is likely to contribute to the hyperalgesia, allodynia and spontaneous pain that are characteristic of cancer-related pain.

- **ATP**

One of the early studies suggesting a role for ATP in cancer-related pain was in a bone cancer pain model using fibrosarcoma cells showing increased expression of ATP (P2X3) receptors on calcitonin gene-related peptide-positive nerve fibers associated with tumor growth [4]. More recently, increased levels of ATP in oral cancer tissues have been demonstrated to positively correlate with self-reported pain in oral cancer patients [5]. In addition, ATP in the oral cancer microenvironment results in upregulation of
ATP (P2X2/3) receptors in trigeminal neurons, activation and sensitization of these neurons and pain behaviors in mouse oral cancer models [5]. Similar upregulation of P2X3 receptors in trigeminal neurons [6] and dorsal root ganglia (DRG) neurons as well as ATP-induced sensitization in these neurons was demonstrated in a bone cancer pain model using breast carcinoma cells [7]. The application of P2X3 or P2X2/3 receptor antagonists locally, systemically or intrathecally has been shown to significantly attenuate electrical, mechanical and thermal stimuli-evoked dorsal horn excitability and pain behavior induced by bone cancer [7,8].

Not only is ATP implicated in cancer-related pain but it may also contribute to decreased opioid responsiveness in cancer patients. Chizhmakov and colleagues [9] evaluated rat nodose neurons co-cultured with fibrosarcoma cells by using whole-cell patch clamp recordings and noted that cancer cells release diffusible factors altering the properties of desensitization kinetics of neuronal ATP receptors and, in particular, decreased neuronal sensitivity to opioid inhibitory control. Thus neurons in the cancer microenvironment may have increased neuronal excitability initiated by peripheral ATP release and thereby contribute to the decreased analgesic efficacy of opioids in cancer patients.

- **Formaldehyde**
  Endogenous formaldehyde can contribute to cancer-related pain and LSD1 is one of the major enzymes that catalyze the production of formaldehyde. Patients with breast, prostate or bladder cancer have increased levels of formaldehyde in their blood or urine [10,11]. Formaldehyde concentrations are also elevated in the cancer cells, bone marrow, sera and tumor tissues in a rat model of bone cancer pain [12]. The measured concentration of formaldehyde was in sufficient concentrations to induce pain behaviors in normal rats. Systemic injection of a LSD1 inhibitor in this cancer pain model reduced bone cancer pain behaviors.

- **Protons**
  An acidic pH is commonly associated with the cancer microenvironment, reflecting increased metabolic activity and anaerobic conditions that occur during carcinogenesis. In the case of bone cancer or metastasis, cancer colonization of bone leads to the activation of osteoclasts, thereby producing local tissue acidosis and osteolysis.
This acidic cancer microenvironment may contribute to cancer-related pain via activation of acid-sensing ion channels (ASICs) and TRPV1 receptor mechanisms. In a bone cancer pain model, the acidic microenvironment has been shown to result in cancer-related pain behavior via upregulation of ASICs in DRGs [13]. The role of TRPV1 in cancer-related pain has been widely demonstrated in numerous cancer pain models [14–19]. In various soft tissue cancer pain models, cancer-related pain behaviors occurred along with increased expression of TRPV1 in the trigeminal ganglia [6] and DRG [19], and pain behaviors were inhibited with TRPV1 antagonists. Similarly, TRPV1 antagonists attenuate cancer-related pain behaviors in a rodent bone cancer pain model [15]. Formaldehyde in the bone cancer microenvironment may also upregulate TRPV1 expression in DRGs [20]. Certain sarcoma cell lines also release lipophilic factors that activate trigeminal neurons via TRPV1 [21].

### Proteases
Cancer cells produce and release proteases that result in tissue destruction and cancer spread. The serine protease trypsin has been identified in various cancers such as ovarian carcinoma, pancreatic cancer, hepatocellular and cholangiocarcinomas, lung neoplasms, colorectal cancers, fibrosarcoma, erythroleukemia, gastric cancer and oral cancer [22–27]. While these cancer cells are likely the primary source of proteases in the cancer microenvironment, other sources of locally released serine proteases may also contribute to cancer-related pain. Epithelial cells surrounding the cancer may be an additional source of trypsin [28]. Blood vessels surrounding cancers such as gastric carcinoma [29] also express trypsin as do fibroblasts in the surrounding stroma of oral cancer [22].

Protease-activated receptors (PAR1 to PAR4) are G-protein-coupled receptors that are activated by proteolytic cleavage. PAR2 is activated following cleavage from a serine protease to expose a tethered ligand that binds to the PAR2 receptor [30]. PAR2 activation can sensitize TRPV1 and TRPV4 receptors on nociceptive afferents and result in thermal and mechanical hyperalgesia [31,32]. PAR2 and serine proteases have been implicated in oral cancer-induced pain behavior in various mouse models [26–27,33]. Acute pain behavior is abolished by serine protease inhibition and absent in PAR2 knockout mice [26,27]. Chronic pain behavior is associated with elevated serine proteases in the cancer microenvironment and PAR2 upregulation in trigeminal neurons [27]. Serine protease inhibition attenuates the severity of persistent cancer pain in wild-type mice, but most strikingly, the development of chronic cancer pain is prevented in PAR2 knockout mice [27]. These findings implicate a direct role for PAR2 in acute cancer pain and suggest that PAR2 upregulation may favor the development and maintenance of chronic cancer pain.

More recently, Lam and colleagues demonstrated a novel membrane-bound serine protease in cancer-related pain [33]. Patients with head and neck or prostate cancers have a higher prevalence of cancer pain than those with melanoma or breast cancers and there are higher levels of TMPRSS2 in these more painful cancer cell lines. TMPRSS2 levels correlated with pain severity in head and neck cancer patients, and TMPRSS2 induced proteolysis, neuronal activation and pain behaviors via a PAR2-dependent mechanism [33]. These recent findings suggest TMPRSS2, found on the surface of painful cancer cells, may have potential as a biomarker and possible target for anticancer and cancer-related pain therapy.

### Endothelin
Endothelin-1 (ET-1) is a potent vasoactive peptide that activates endothelin A (ET_A) and B (ET_B) receptors, and is secreted in high concentrations in various cancers. ET_A receptors are expressed on peripheral sensory neurons; whereas ET_B receptors are expressed on nonmyelinating Schwann cells of peripheral nerves, DRG satellite cells [34,35], and keratinocytes, which are known to secrete opioids [36–38]. The role of ET-1 in cancer-related pain was first described in bone cancer models [39,40] demonstrating ET-1 induced pain behaviors and peripheral sensitization, and is now well demonstrated in various cancer pain models [41–44]. Schmidt and colleagues [42] demonstrated a role for ET-1 in oral cancer-induced pain behavior. ET-1 mRNA and protein levels are upregulated in oral cancer tissues and pain behavior is attenuated with a selective ET_A receptor antagonist [43]. Recently, an interesting mechanism of ET-1 sensitization of ATP release of endothelial cells in response to mechanical stimulation has been shown [44]. This released ATP in turn activates P2X2/3 receptors on nociceptors to induce pain. Since the cancer microenvironment is highly vascular, both ET-1 and ATP...
may potentially work synergistically to produce cancer-related pain.

Harnessing the role of endogenous opioid analgesia in ET receptor-mediated analgesia may be a promising pharmacologic alternative to morphine therapy for the treatment of cancer-related pain. Peripheral application of an ET$_B$ receptor agonist attenuates cancer-induced pain behavior in mice by modulating β-endorphin release from oral cancer cells [45]. Oral cancer cells (squamous cell carcinoma) are malignant keratinocytes that bear ET$_B$ receptors and release opioids which may modulate the activity of nociceptors in the cancer microenvironment. ET-1 activation of ET$_A$ receptors on keratinocytes results in analgesia that is reversed with naloxone, implicating keratinocytes as a source of opioid released upon ET$_B$ receptor activation [2]. Also, increased production of β-endorphin and leu-enkephalin occurs in oral cancer cells treated with an ET$_A$ receptor antagonist [46]. Local application of naloxone or a selective mu-opioid receptor (MOR) antagonist in mice blocked the analgesic effect of the ET$_A$ receptor antagonist or ET$_B$ receptor agonist.

Most cancer-related pain conditions are at least initially responsive to opioid therapy such as morphine, but unfortunately tolerance often develops and escalating doses are required, resulting in untoward side effects. Modulation of ET receptors in the management of cancer-related pain may also be beneficial since ET$_A$ receptor antagonism may decrease morphine tolerance [2,47–50]. Thus the combination of ET$_A$ receptor antagonism, which produces analgesia and simultaneously prevents morphine tolerance, and ET$_B$ receptor agonism, which leads to local opioid release, may hold promise for the treatment of cancer-related pain.

**Bradykinin**

Bradykinin (BK), like ET-1, is a vasoactive peptide that contributes to cancer-related pain. In a melanoma cancer model, there are elevated bradykinin levels in the cancer microenvironment and upregulation of bradykinin B1 and B2 receptors in the DRG of mice with cancer-related pain behaviors [51]. Moreover, cancer-related spontaneous pain behavior was inhibited by B1 and B2 receptor antagonists, whereas allodynia was only attenuated with B2 receptor antagonists. Similarly, in a murine model of bone cancer pain, pharmacologic blockade of the B1 receptor was also effective in reducing bone cancer-related pain behaviors [52]. Interestingly, BK increased the secretion and expression of ET-1 through B2 receptors in melanoma cells [53]. Thus modulation of BK receptor mechanisms may also further modulate the contribution of ET receptor mechanisms in some cancer-related pain conditions.

**TNF**

Cytokines such as TNF are often produced at high levels in cancer [54,55]. Elevated TNF (TNF-α) levels in fibrosarcoma tumors of mice are associated with mechanical hypersensitivity that is reversed with a TNF antagonist [54]. Similarly, elevated TNF levels in lung carcinomas of mice are associated with heat hyperalgesia that is abolished with a TNF antagonist [55]. In this model, TNF results in cancer-related heat hyperalgesia by TRPV1 upregulation and sensitization via TNFR2.

**NGF**

NGF may activate a high-affinity tyrosine receptor kinase A (TrkA) receptor and a low-affinity p75 receptor on peripheral nerves [56]. NGF exposure leads to an increase in the neuronal expression of TRPV1, ASICs, sodium channels, BK and P2X3 receptors, which all contribute to cancer-related pain [57–62]. The source of NGF in the cancer microenvironment may be the cancer cell itself. Both NGF mRNA and protein levels are elevated in oral cancer tissues [63]. Constituent cells may also release NGF, as is the case with prostate cancer [64]. NGF blockade is effective in inhibiting cancer-related pain behavior and nerve sprouting in various cancer pain models [63,65–67]. NGF blockade in two separate mouse oral cancer models decreased tumor proliferation, nociception and weight loss through modulation of proinflammatory cytokines and leptin production. NGF blockade also decreased expression levels of TRPV1, TRPA1 and PAR2 [63]. As such anti-NGF therapy may be a promising treatment for both cancer-related pain and cachexia.

**Central mechanisms**

Peripheral afferent inputs activated by cancer-related nerve injury and/or mediators in the cancer microenvironment can enhance the transmission of nociceptive signals in the spinal dorsal horn, brainstem and/or other CNS regions. This activity can lead to long-lasting neuroplastic changes in transmission termed...
central sensitization. This central sensitization is reflected in enhanced excitability of nociceptive neurons in the spinal dorsal horn, brainstem, thalamic and cortical regions, and may result in increased spontaneous activity, expansion of their mechanoreceptive field, lowering of their activation threshold and/or increase in their response to peripheral stimuli. These changes are believed to be involved in mediating the spontaneous pain, pain spread and referral, and hyperalgesia and allodynia frequently associated with cancer-related pain.

Until recently, there has been limited relevant cancer-related pain research in the trigeminal region. Most of our understanding of cancer-related pain mechanisms was derived from rodent spinal models [2,68]. Studies in these rodent spinal models suggest a role for central sensitization of spinal neurons, as reflected in increased spontaneous activity, receptive field expansion and increased responses to stimulation in cancer-related pain [69–73]. Molecular changes within the spinal cord due to cancer-related pain are often distinct relative to the changes induced by neuropathic or inflammatory pain [69,74]. Glia, in addition to their well-known functions of maintaining homeostasis, and providing support and protection for neurons in the CNS, have recently been shown to have a vital role in central sensitization and associated nociceptive behavior. Spinal astrocyte activation, reactive astrogliosis and increased levels of substance P receptor internalization, c-Fos, dynorphin, TNF-α and Interleukin-1β have also been reported in various spinal cancer pain models [68,74–78]. These cancer-related spinal cord neurochemical changes and associated pain behavior may be attenuated pharmacologically or with focal radiotherapy. Bisphosphonates may reduce cancer-related pain behavior and neurochemical signs of central sensitization [79–82]. The analgesic effect of low dose radiation of bone cancer is associated with the alteration of nociceptive transmission in the CNS [72]. More recently, Hidaka and colleagues [83] demonstrated a role for central, but not peripheral, glial activation in their rat facial cancer pain model. Following administration of a glial hyperactivation inhibitor, central glial activation was attenuated, and cancer-induced pain behaviors were prevented. Sago and colleagues [84] also demonstrated that central glial hyperactivation, transient microglial hyperactivation and persistent astrocytic hyperactivation, contributed to the development of pain hypersensitivity but not to the maintenance of pain in orofacial cancer-related pain.

CXCL12 and its major receptor, CXCR4, are known to play a critical role in modulating various nervous system developmental processes and in regulating synaptic plasticity. CXCL12/CXCR4 signaling has recently been shown to contribute to the development and maintenance of bone cancer pain behaviors in rat spinal models by producing central sensitization in nociceptive neurons and activating astrocytes and microglia [85,86]. CXCL12/CXCR4 signaling has also been shown to mediate the induction of TNF-α release from glial cells [87], which could lead to further cancer-related central sensitization. The blockade of this chemokine signaling in the spinal cord may play a vital role in cancer-related pain management.

EphrinB-EphB receptor signaling is involved in cancer-related pain and morphine tolerance in a bone cancer pain model [88]. Cancer pain behavior is associated with upregulation of EphB1 receptor and its ligand ephrinB2 in the dorsal horn and primary sensory neurons. Spinal inhibition of the EphB1 receptor reverses bone cancer pain behaviors and associated spinal neurochemical changes. In addition, spinal blocking of EphB1 receptor reverses morphine tolerance in treating bone cancer pain in rats and defensive pain in mice. Similarly, cancer pain behavior and morphine tolerance is also associated with upregulation of metabotropic glutamate receptors (mGluR) in astrocytes and neurons in the dorsal horn [89]. Co-administration of mGluR antagonists are known to suppress morphine tolerance and enhance antinociception, and a novel bivalent ligand (MMG22) containing both MOR agonist and mGluR antagonist pharmacophores has recently been shown to produce potent antinociception in a bone cancer pain model [90]. The enhancement of antinociception during cancer progression may be due to inhibition of NMDA receptor-mediated hyperalgesia via antagonism of mGluR, and concomitant activation of MOR by the MMG22-occupied heteromer. Since MMG22 has a 250,000-times greater potency than that of a mixture of the MOR agonist and mGluR, antagonist monovalent ligands, targeting the putative MOR-mGluR heteromer may be superior to univalent interaction with receptors in reducing cancer-related pain. Astrocyte activation has also been shown to contribute to the development of morphine tolerance to
analgesia and cancer-related pain via spinal D-amino acid oxidase (DAAO) mechanisms in a bone cancer model [9]. DAAO, found in spinal astrocytes, catalyzes oxidation of D-amino acids to hydrogen peroxide. Hence, EphB1, DAAO and mGluR, inhibitors may be potential treatments for cancer-related pain administered alone or in combination with morphine to improve the analgesic effect of morphine clinically.

Conclusion
Our understanding of cancer-related pain has improved dramatically over the past decade. Cancer and associated cells in the cancer micro-environment may release various mediators that result in the activation of peripheral and central neurons, but may also produce a sustained sensitization of these neurons. The molecular and neurobiologic changes within the CNS due to cancer-related pain are often distinct relative to the changes induced by neuropathic or inflammatory pain conditions, and there is emerging evidence pointing to the crucial involvement of glial cells in these cancer-related pain conditions. Taken together, these changes in peripheral and central processing may explain the allodynia, hyperalgesia, spontaneous pain and pain spread or referral, that are characteristic of many of cancer-related pain conditions. Targeting one or more of these identified peripheral and central mechanisms may not only provide novel therapies but may also improve the analgesic efficacy of existing drugs such as morphine.

Future perspective
Although recent animal models of cancer pain appear to better reflect the complex pain states observed in cancer patients and have identified various potential therapeutic targets, it is unlikely that a single treatment will target all of the different cancer pain-related symptoms in patients and that combined treatment strategies should be investigated in animal models. There also remains a paucity of animal model research on the neuropathic contributions to cancer-related pain and this area is an important future research direction. The existence of multiple peripheral and central mechanisms in different cancers may not only provide a rational basis for the use of combination therapy in cases where a single agent is not sufficient, but may also serve to usher in the era of personalized cancer pain medicine. Using advancements in genomics and proteomics, the development of diagnostics targeting an individual cancer pain patient’s unique cancer cell mediators and genetic makeup, may not only provide targeted analgesic therapy but may potentially eliminate ineffective analgesics, reduce adverse drug reactions, lower costs and improve quality of life.

Acknowledgements
The author wishes to thank BJ Sessle for his expert review of this manuscript.

Financial & competing interests disclosure
This work was supported by a grant from the Bertha Rosenstadt Endowment. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References
Papers of special note have been highlighted as:
• of interest

5 Study demonstrates changes in epidermal nerve fibers during tumor development.
11 Spanel P, Smith D, Holland TA, Al SW, Elder JB. Analysis of formaldehyde in the headspace of urine from bladder and prostate cancer


39 Early study identifying role for endothelin in cancer-related pain.


Emerging factors in the progression of cancer-related pain

- Study showing peripheral endothelin B receptor agonism attenuates cancer-related pain by modulating cancer cell-released β-endorphins to act on peripheral opioid receptors in the cancer microenvironment.


• Study shows bone cancer-related pain has a unique neurochemical signature compared with changes that occur in persistent inflammatory or neuropathic pain states.


80 Honore P, Lugner NM, Sabino MA et al. Osteoprotegerin blocks bone cancer-induced skeletal destruction, skeletal pain and...


Four steps to eliminate or reduce pain in children caused by needles (part 1)

Dr Stefan Friedrichsdorf* speaks to Jade Parker, Commissioning Editor: Stefan J Friedrichsdorf, MD, is medical director of the Department of Pain Medicine, Palliative Care and Integrative Medicine at Children’s Hospitals and Clinics of Minnesota, Minneapolis/St Paul, MN, USA, home to one of the largest and most comprehensive programs of its kind in the country. The interdisciplinary pain team is devoted to prevent and treat acute, procedural, neuropathic, psycho-social-spiritual, visceral, and chronic/complex pain for all inpatients and outpatients in close collaboration with all pediatric subspecialties at Children’s Minnesota. The palliative care team also provides holistic care for pediatric patients with life-threatening diseases and adds an extra layer of support to the care of children with serious illness and their families. Integrative medicine provides and teaches integrative (‘non-pharmacological’) therapies, such as massage, acupuncture/acupressure, biofeedback, aromatherapy and self-hypnosis, to provide care that promotes optimal health and supports the highest level of functioning in all individual children’s activities. Children’s Minnesota became the first children’s hospital to system-wide implement a “Children’s Comfort Promise: We promise to do everything to prevent and treat pain,” resulting in decrease or elimination of needle pain caused by vaccinations, blood draws, intravenous access, and injections in more than 200,000 children annually.

First draft submitted: 11 November 2016; Accepted for publication: 17 November 2016; Published online: 30 November 2016

KEYWORDS
• analgesia • integrative strategies • pediatric pain management

*Department of Pain Medicine, Palliative Care & Integrative Medicine, Children’s Hospitals and Clinics of Minnesota, Minneapolis, MN, USA

and

Department of Pediatrics, University of Minnesota, Minneapolis, MN, USA

stefan.friedrichsdorf@childrensmn.org
pain prevention and treatment in babies, toddlers, school kids and teenagers is so much more than just prescribing medication. Thanks to our organization’s leadership and interdisciplinary pediatric care team members, we developed a very unique program at our institution. Now, we are able to utilize multimodal analgesia – that is, many different modalities concurrently, to achieve optimal pain control with the least amount of side effects in children.

At Children’s Minnesota, we are using advanced pharmacology, aiming to use the right amount of the right medication via the best route of administration. This may mean using simple analgesia and/or adjuvants and/or opioids, which not infrequently means rotating from one opioid to another. We have also found that advanced pain control commonly includes the integration of rehabilitation, physical therapy and exercise, occupational therapy, child life, psychology, including cognitive behavioral therapy and, most importantly, active integrative ‘non-pharmacological’ modalities. We are proud to have one of the largest integrative medicine programs in the USA and as such we teach children and their caregivers both inpatient and in our clinic many modalities including deep breathing, progressive muscle relaxation, self-hypnosis and biofeedback. In addition, we offer aromatherapy, massage, acupuncture and acupressure [2]. All in all, this whole package has shown that we can provide much better pain control, and when we started regular audits, we were able to demonstrate how we successfully implemented a system-wide change toward better analgesia and higher patient satisfaction.

In 2013, when we received the Center of Excellence Award from the American Pain Society, I believe the panel recognized that, on the one hand, we are a rather active pain service, which takes care of not only children with acute pain but also with procedural, chronic, psychosocial–spiritual and neuropathic pain. As part of the above-mentioned multimodal analgesia, we are also utilizing pharmacological modalities and anesthetic interventions including neuraxial anesthesia such as epidural or paravertebral analgesia and nerve blocks, as well as using an interdisciplinary pain clinic model.

Additionally, our advocacy and training was recognized. By running the international pediatric pain master class [3], the largest pediatric pain course of its kind annually in Minneapolis and after having trained more than 500 physicians and nurse practitioners from more than 30 countries, we have shown that we are not only interested in providing excellent pain care here in our area but that we are also very interested in teaching and providing this knowledge nationally and internationally. In addition, we have trained more the 450 professional ‘Trainers’ through the comprehensive Education in Palliative and End-of-Life Care (EPEC) – Pediatrics curriculum, made possible by a US$1.6 million grant by the NIH/National Cancer Institute [4].

Children’s Minnesota recently received the prestigious ChildKind designation [5] certifying that we were able to demonstrate an institutional commitment to pain relief and provide the technical support to achieve that goal. Our pain service is fully integrated within the hospital, and all employees including nurses, social workers, clinicians, physicians, physiotherapists, among others, have access to modalities to provide best pain prevention and treatment. Importantly, our hospital leadership has made this a priority in patient care and made it part of the institution’s strategic goals.

Children’s Minnesota, as one of the largest US children’s hospitals, is the first hospital worldwide, which implemented a ‘Comfort Promise: We do Everything Possible to Prevent & Treat Pain’; what are your four ‘non-negotiables’, which are now offered system wide for all children to prevent or reduce needle pain caused by vaccinations, injections, intravenous access or blood draws? To the best of our knowledge, we became the first children’s hospital in the world to implement the Comfort Promise: “We will do everything possible to prevent and treat pain” [6]. The Comfort Promise [7] is applicable system-wide for all pediatric inpatients, as well as in the emergency rooms, outpatient surgical centers, outpatient laboratories and at all of our 29 primary and ambulatory clinics, aiming to eliminate or reduce all needle pain.

We are using ‘lean methodology’ for quality improvement in our institution. Lean improvement systems are focused on removing waste from work processes, and pain was defined as ‘waste’. When a quality improvement process spans multiple areas of authority, such as units and departments, and requires extensive coordination, it is referred to as a ‘Value Stream’. Therefore, the first step was to ask the children we were treating ‘What do we have to
do better?” and of course, if you ask children what are you most afraid of when coming to see a doctor, whether this is in a clinic or emergency room or children’s hospital, hands down the answer is “I am afraid of needle pokes or pricks.” The children in our hospital told us in a system-wide survey that the least well-controlled and most distressing pain was caused by needles [8]. We then found strong evidence to offer four modalities [9–13] concurrently to eliminate or reduce needle pain, modalities we now call ‘the four non-negotiables’. Using this evidence, we became the first hospital which system wide not only offers those four modalities to every child for elective needle procedures, including for vaccinations, blood draws, intravenous cannulation and injections without exception, but also audits this regularly [6].

The first non-negotiable is to ‘numb the skin’ using topical anesthesia. The reason we choose lidocaine 4% cream is that it is available over the counter in the USA without a prescription and it works within 30 min as opposed to other creams such as EMLA cream, which takes around 60 min. Even if the needle stick infiltrates the tissue deeper than the depth of the numbed area, such as in a vaccination, there is clear evidence that numbing the skin already significantly reduces the pain and cannot be omitted.

We offer to numb the skin of any child we are doing injections for. In our critical care areas, when we may not have the time to wait 30 min, we then use a carbon dioxide-powered, needleless lidocaine injector, similar to a ‘hypospray’ in Star Trek, which works within 10 s.

Second, we use a few drops of 24% sucrose, which is sugar water, or we allow breastfeeding while we are undertaking the vaccinations or injections for infants of 0–12 months of age. Excellent evidence has shown that this significantly reduces pain in children for needle procedures.

Third, it is important to not hold children down for needle procedures and vaccinations. If you ask children would they rather be held down or would they like to sit on their mother’s lap, not surprisingly not a single child wants to be held down. Research has shown that the use of restraint is never supportive. Restraining children for procedures makes them feel ashamed, humiliated, powerless, and children report they feel having lost the right to control their own body [14]. In our institution, a posted letter signed by our chief executive officer, chief medical officer, chief nursing officer and chief operating officer states that we are offering the ‘four non-negotiables’ to all children, all of the time. This letter included the sentence “We at Children’s Minnesota will not physically hold children down for routine needle procedures,” indicating tremendous hospital leadership support for the implementation of the Comfort Promise. We are the first hospital in the USA that has not only stated that we are not going to hold down children anymore for elective needle procedures, which affects more than 200,000 children annually in our institution alone, but also undertakes regular audits. Rare exceptions would include injections required to save a child’s life in an emergency. For example, if a child is presenting in the emergency room with a severe meningococcal infection and requires intravenous antibiotics in minutes, then there may not be time to implement all aspects of the Comfort Promise. Of course, in that case we do everything we can to save the life of the child. But 99% of the needle pokes we are performing in our hospital are elective procedures and we have time to implement a protocol. For infants younger than 6 months, who are too young to sit up, we swaddle them in a blanket or use facilitated tucking or parental skin-to-skin contact. Whereas, kids who are older than 6 months, depending on their age, usually want to sit either on their parent’s lap, next to them, or alone by themselves.

Fourth, we always use age-appropriate use distraction. For an infant we may provide sounds, for a small toddler we have electrical toys which spin or make sounds. For slightly older kids we may use bubbles, pin wheels, ‘I spy’ pictures, and many older kids bring smartphones to provide their own form of distraction [15].

What are your results?
Not surprisingly, the ‘Comfort Promise’ represented a significant culture change in our institution. No hospital has undertaken this before on such a large level for all children, all of the time, including vaccinations, with regular audits. Our outcomes have been overwhelmingly positive; our patients’ and their parents’ satisfaction has significantly improved and our waiting times for blood draws have actually decreased. So carrying out all these modalities means that children are usually not crying anymore in the parking lot, in the waiting room and while the blood draw is being carried out. For our institution, and the more than 200,000 children annually who
used to experience needle pain in the past, this is a game changer and it is truly spectacular to watch.

We know that up to 25% of adults are needle-phobic, which does unfortunately translate into increased morbidity and even increased mortality. For instance, needle-phobic teenagers are shown to be hesitant to seek out medical care. Those patients may postpone seeing a physician because they are worried about a blood draw or injection, until for instance a tumor might be too far spread. Several surveys found that a significant number of parents were hesitant to vaccinate their children because they could not stand the pain their child is going through. More than 350 children die of measles every day worldwide, most of them in resource-poor countries, but in my career as a pediatrician I have seen five unvaccinated children die of measles in high-income countries. In other words, children are dying of preventable diseases because they or their parents are afraid of needle pain, yet the pain of a shot can now be prevented.

We now know that if we clinicians hold down a child for stitches, vaccinations, blood draws or other painful procedures, then many of those children need more analgesia, more anesthesia, and more man or woman power during their medical care for exactly the same procedure in future visits. So we in healthcare are creating children who are highly afraid of us and become needle-phobic.

At Children’s Minnesota, we are using lean quality improvement and our goal is to make sure these four ‘non-negotiables’ are offered more than 95% of the time. We have rolled this out over the last 3 years, unit by unit, department by department, meaning that every single time we include the front-line staff we ask them questions such as, “we need to get numbing cream on the child, what is the best way to do this?” We inquire about this, because whenever we want to change practice, the new way must be easier than the old way; otherwise, it will not be successful. This is why we have been successful in integrating all staff and implementing the four modalities [6].

**Have you seen in the field that other pediatric pain centers are also taking this up?**

The evidence supporting the utilization of these four modalities is fairly clear. Much of this evidence has been around for 20 years or more, with a lot of this research coming from Canada. However, as with many things in medicine, there remains a chasm between research and what is put into practice. We recently received a grant from The Mayday Fund, a foundation which supports pediatric pain improvement, in order for us to roll out our initiatives in four other children’s hospitals [16]. We have now trained a team from each of the four children’s hospitals in Montréal, Atlanta, Toronto and Kansas City, and now we are in the process of visiting these hospitals and assisting the teams on the ground, and are using this funding to put this into practice as proof that we can replicate the roll-out of these modalities outside of Children’s Minnesota.

A few hospitals worldwide have implemented versions of our (four non-negotiable) initiatives, but judging from the published literature usually it seems to be implemented only in some clinical areas and not system-wide for all children all of the time, including for vaccinations. Existing protocols often also unfortunately still omit the numbing cream. We feel strongly that right now we do not have enough research to undertake needle pokes without topical anesthesia. But there are several children’s hospitals worldwide, especially the ChildKind certified hospitals, which have done hard work in the last years to really reduce pain system wide.

**The recently opened ‘Healing Environment’ Pain, Palliative & Integrative Medicine Clinic in Minneapolis has won several architecture awards & represents a one-of-a-kind pain clinic; how does the healing space support advanced best clinical care for the large number of children with chronic pain?**

As mentioned earlier, we have learned that taking pain away and providing excellent clinical care for children who are suffering from pain and other distressing symptoms is so much more than just prescribing the right medications. We have noticed that the space the children are in has a huge impact on how families are doing, the level of anxiety and the child’s ability to heal.

A clinic space like ours, the “Kiran Stordalen and Horst Rechelbacher Pediatric Pain, Palliative and Integrated Medicine Clinic,” to the best of our knowledge has never been built before [17]. It is absolutely unique, stunning and provides the means to offer light, sound and nature images so that children, even before
they see the first clinician, can start to heal. In our clinic, at Children’s Minnesota we see kids in pain, at the end of life and/or those who need integrative ‘non-pharmacological’ modalities. Having a well thought-out clinic architecture is yet another way to help children to heal beyond psychology, physical therapy, medications, and other modalities. Our clinic is an example of how we can utilize architecture and space to the best of its ability to create a healing environment. We heard feedback from our patients and their parents how uniquely helpful this is.

Do patients & their parents play a larger role in designing treatment plans than in the past? If yes, what strategies have allowed them to become more involved?

An excellent piece of research explaining why our pain interventions may or may not be effective for an individual patient is from Dr Tracey’s group in Oxford, UK, in 2011, where 22 volunteers were invited to carry out some pain testing [18]. This brilliant British group undertook a four step experiment: Step one, all of those 22 volunteers had an intravenous access receiving saline infusion, while pain testing was conducted. They asked the participants to put their hand on a research-approved hot plate and asked them how painful it was. Unsurprisingly, on average the reported pain was between 7 and 8 out of 10. Next, they told them beforehand that they wanted to find out whether giving the strong opioid remifentanil reduced the pain. They then gave the opioid without telling them that they wanted to find out whether giving the strong opioid remifentanil reduced the pain. They then gave the opioid without telling them and repeated the test, with the pain going down to around a 6 out of 10. This showed that if you give patients a very strong opioid, it reduces the amount of pain. They then told them “I’m giving you the opioid now” and repeated the test; however, they had already given it. The pain went down to a 4 out of 10. In other words, the positive expectation that an intervention is going to work more than doubled the treatment effect of this particular strong opioid. The fourth and last step of this experiment was to tell the volunteers that the research group had discontinued the opioid, and then repeated the hot-plate test and the pain went back to 7–8 out of 10; however, they had not stopped the opioid. In other words, and this is what we see every single day, the patient’s and parent’s expectation of whether or not any of our pain intervention will work will predict to a large degree whether or not it is going to work.

Therefore, the best way to be successful in advanced pain treatment is to develop a plan together with our patients and their parents, which they believe will actually work. We have to be fairly convincing and offer choices. For example, if I expect my patient to do something, I may use some hypnotic language. I might say something like “would it be okay if I sit down and help you to be bothered by this pain less?” Or I might say something along the lines of “As we talked about it, I think you’re ready to stop the intravenous morphine patient controlled analgesia. Do you think we should do this today or tomorrow?” Alternatively, I could suggest “I really expect you to learn one cool integrative modality, it could be hypnosis, biofeedback, deep breathing, etc.” By going through these modalities very commonly you see the eyes of the child light up with a specific modality and they may ask, for instance, “what is hypnosis?” and then I might respond “well it is my favorite thing and you may love it too – would you like learning how to leave this room and go to your favorite place in the world in your imagination right now?” If the children or the parents have the opportunity choosing the integrative modality they believe works best, then it is much more likely to work. We often cannot be successful implementing a care plan for kids and parents without them buying into it.

Do you have any closing comments or messages for our readers?

In the USA we spend more than US$560 billion annually on pain diagnosis and treatment, far more money than on cancer, kidney disease, and on cardiac diseases combined. Yet, some clinicians and especially most hospital administrations still believe incorrectly that pain in hospitalized children or children seeing their doctor is unavoidable and regards appropriate pain prevention as an afterthought. When we ask a child what is his or her number one worry when seeing a doctor would be, the child’s answer would be pain caused by clinicians, especially by needles. If we ask parents, why they chose to go to a hospital with their child and what were their top priorities? For parents, the number one priority is to find and treat the underlying condition. However, the second one on their list was to treat pain. For children, of course, it is the first priority – so pain prevention and treatment is far from an afterthought.

There is nothing worse for a parent to see their child being in pain. There is nothing worse for
a child, than being in pain. We do know that pain has long-term negative consequences. We do know that even babies remember pain. Boys who have been circumcised without appropriate analgesia scream much longer and much harder at their 4–6 months vaccinations than boys who have been circumcised with appropriate analgesia. So of course infants remember this pain from a long time ago. We do know that unrelieved pain in hospitalized children increases their morbidity and even their mortality. We do know that children with unrelieved pain after trauma or burns have a much higher risk of developing post-traumatic stress disorder.

We, as the treating clinicians of children, have the responsibility to treat and prevent pain every single time. We do have knowledge and the resources, and we just need the will to actually do this. Analgesic treatment is mandatory for children when they undergo painful procedures and no avoidable suffering is acceptable nowadays, even for so-called minor interventions.

Disclaimer
The opinions expressed in this interview are those of the interviewee and do not necessarily reflect the views of Future Medicine Ltd.

Financial & competing interests disclosure
S Friedrichsdorf is supported, in part, by the The Mayday Fund, NIH/National Cancer Institute, Children’s Hospitals and Clinics of Minnesota Research Grant Program, NIH/National Institute of Nursing Research, and the Canadian Partnership Against Cancer. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References
2 Integrative medicine. www.childrensmn.org
3 Annual Paediatric Pain Master Class. http://nonneedlespain.org/ppmc/
4 Northwestern University Feinberg School of Medicine, Education in Palliative and End-of-Life Care. www.epec.net/
5 Child Kind International. www.childkindinternational.org
7 Children’s Comfort Promise. www.childrensMN.org/comfortpromise
15 Reducing pain with needle procedures. www.childrensmn.org
16 The May Day Fund. www.maydayfund.org/
17 Kiran Stordalen and Horst Rechelbacher Paediatric Pain, Palliative and Integrative Medicine Clinic Tour. https://vimeo.com/122654881
Chronic postsurgical pain and persistent opioid use following surgery: the need for a transitional pain service

Alexander Huang1,2, Abid Azam1,2,3, Shira Segal1, Kevin Pivovarov1, Gali Katznelson1,2, Salima SJ Ladak1,2, Alex Mu1,2, Aliza Weinrib1,2,3, Joel Katz1,2,3,4 & Hance Clarke1,2,4

Aim: To identify the 3-month incidence of chronic postsurgical pain and long-term opioid use in patients at the Toronto General Hospital. Methods: 200 consecutive patients presenting for elective major surgery completed standardized questionnaires by telephone at 3 months after surgery. Results: 51 patients reported a preoperative chronic pain condition, with 12 taking opioids preoperatively. 3 months after surgery 35% of patients reported having surgical site pain and 13.5% continued to use opioids for postsurgical pain relief. Postoperative opioid use was associated with interference with walking and work, and lower mood. Conclusion: Chronic postsurgical pain and ongoing opioid use are concerns that warrant the implementation of a Transitional Pain Service to modify the pain trajectories and enable effective opioid weaning following major surgery.

First draft submitted: 28 April 2016; Accepted for publication: 11 May 2016; Published online: 6 July 2016

1Department of Anaesthesia, Toronto General Hospital, University of Toronto, Toronto, Ontario, Canada
2Transitional Pain Service, Department of Anesthesia, Toronto General Hospital, Toronto, Ontario, Canada
3Department of Psychology, York University, Toronto, Ontario, Canada
4Department of Anesthesia, University of Toronto, Toronto, Ontario Canada
*Author for correspondence: Tel.: +1 416 340 4800;6649, Fax: +1 416 340 3698, hance.clarke@uhn.ca

Practice points

- The incidence of chronic postsurgical pain (pain that persists for greater than 2 months and is a consequence of the surgical intervention) varies based on type of surgery, but can approach, and even, exceed 50%.
- Chronic postsurgical pain (CPSP) places a significant burden on patient daily life and the healthcare system, and is often misidentified and poorly managed in the postdischarge period.
- Opioid use is common in the CPSP patient population and is associated with significant risk for both morbidity and mortality.
- In total, 35% of the present sample reported ongoing pain at their surgical incision site at 3 months after surgery.
- A total of 13.5% reported ongoing opioid use for management of their surgical site pain at 3 months after surgery.
- The majority of patients still using opioids for postsurgical pain at 3 months reported moderate-to-severe pain (Numeric Rating Scale ≥4).
- Patients who were using opioids reported lower overall global health, and greater pain-related disability in daily life, including interference in walking and mood.
- This study demonstrates the ongoing issues that CPSP presents, and highlights the need and importance of a Transitional Pain Service to identify at-risk patients and optimize pain management for them before, during and after discharge from hospital.
- Our Transitional Pain Service is a multidisciplinary group consisting of pain physicians, nurse practitioners, psychologists, pharmacists and physiotherapists who provide regular support for patients while in hospital and as well as follow up in the postdischarge period to improve pain management, reduce persistent opioid use and lower the risk of developing of chronic postsurgical pain.
As many as 50% of surgical patients develop chronic postsurgical pain (CPSP) 1 year after surgery and a subset of these patients are at an increased risk for persistent opioid use [1–4]. A universal definition of CPSP has not been agreed upon; however, a commonly accepted definition describes it as ‘pain that develops after surgical intervention and lasts for at least 2 months’ [5]. There has been a 402% increase in opioid consumption from 1997 to 2007 in the USA, a significant proportion of which stems from treatment for chronic pain conditions [6]. Opioid exposure after major surgery is often unavoidable. Unfortunately, the initiation of opioid medications for postoperative pain control often leads to their continued use for months and even years after hospital discharge. In Ontario, Canada, our data demonstrate that almost 50% of patients who undergo a major surgical procedure are discharged with an opioid prescription [7]. Furthermore, 3.1% of postsurgical patients who had never taken opioids prior to hospital admission (i.e., opioid-naïve) remained on an opioid medication 3 months after hospital discharge [7]. This problem is not limited to major surgery: a retrospective analysis reported that opioid-naïve patients who received a prescription for opioids within a week of low risk surgery had a 7.7% chance of continued opioid use 1 year later [8]. Complicating the matter is the fact that general practitioners struggle with complex postsurgical pain patients as they transition from hospital to the community and frequently lack the expertise or level of comfort to wean their patients from opioids [9]. Finally, there is a paucity of literature dealing with the management of postoperative pain as patients transition from the hospital setting to the community and even less research into the safe and effective weaning of patients from their postoperative opioid prescriptions.

In most cases, patients will undergo surgery and return to baseline functional status after a few months, but reports have identified that some surgical populations have greater than a 50% risk of developing CPSP [1,10]. CPSP can persist beyond 1 year after surgery [3,14] and has significant impact on quality of life and patient well-being [12–14]. Unfortunately, acute pain management after surgery is frequently suboptimal in hospital settings, and moderate-to-severe postoperative pain can limit postoperative rehabilitation and delay discharge from hospital [15]. A subset of patients describe an increase in pain after hospital discharge [16], and pain disability that ensues as a result of the development of CPSP has been estimated to incur annual direct and indirect costs of US$43,000 annually per patient [13].

Most of the literature in this field deals with the incidence of, and risk factors for, CPSP after particular surgical interventions. There is little in the way of literature on the safe and effective management of postoperative pain as patients transition from the hospital, as well as follow-up and titration of their postdischarge opioids. We recently developed a Transitional Pain Service (TPS) at the Toronto General Hospital [17,18] which aims to modify the pain trajectories of patients who are at increased risk of developing CPSP and to reduce opioid consumption in the long term, which is often overlooked in the typical course of current perioperative care [19]. The purpose of the present study was to determine the need for such a service at our institution prior to implementation of the TPS.

Methods
This was a single center needs assessment conducted by the Pain Research Unit at the Toronto General Hospital Department of Anesthesia and Pain Management that aimed to identify subgroups of surgical patients that warrant interventions to prevent progression to CPSP and prolonged postoperative opioid use. After REB approval and informed consent, researchers conducted brief 10–15-min interviews which included administration of the: Pain Disability Index (PDI), Brief Pain Inventory (Short Form; BPI), EQ-5D-5L Questionnaires and a 3-month follow-up pain questionnaire developed by the researchers. These interviews were conducted over a single telephone call, and all administered 3 months post-surgery. A 3-month follow-up period was selected to meet the commonly accepted time period to define CPSP (2 or more months postoperatively) and to be consistent with the standard reporting time point reflected in the literature of similar studies (3 months postoperatively).

A total of 200 patients were consecutively enrolled in this study using the Department of Anesthesia and Pain Management’s Acute Pain Service (APS) manager tracking system between September 2013 and April 2014. Patients eligible for the study: had undergone major surgery at Toronto General Hospital from the following surgical services: thoracic surgery, cardiac surgery, urological surgery, general surgery,
Chronic postsurgical pain & persistent opioid use following surgery

The Acute Pain Research Unit developed the Follow-up Pain Questionnaire (FUPQ) which assesses CPSP (intensity, duration), as well as medication use and satisfaction with hospital/home pain control. Patients were determined to have chronic postsurgical pain if they reported pain at the surgical incision site within the last week as per Question 2 on the Follow-Up Pain Questionnaire.

We identified patients taking opioids preoperatively based on their medication list obtained during their preoperative/preanesthetic assessment at our pre-admission clinic using our institution’s electronic medical record system in which all preoperative medications are captured. We then identified continuing opioid users by asking patients to provide a list of medications for pain management during our 3-month telephone follow-up. ‘Continuing to use opioids’ refers specifically to patients who reported using opioids during their follow up interview at 3 months either for postsurgical pain, or other pain. However, we also established whether opioid use was for ongoing postsurgical pain, or for another pain condition. Opioid users were defined as those who reported taking opioids for pain management.

Results

Demographics

Two hundred patients were enrolled in this study (98 males; 102 females; mean age = 58.7 years; gynecological surgery and otolaryngology; were cared for by the APS; and were discharged with an opioid-containing prescription. Patients were excluded if they could not speak English well enough to complete the interview and/or questionnaires. Additionally, patients were considered ineligible after a maximum of three unanswered telephone attempts. This study was approved by the Toronto General Hospital Research Ethics Board (REB# 13-6892-AE); there was no financial compensation for participants. Data were collected, maintained and analyzed by the Pain Research Unit at the Toronto General Hospital, Toronto, Canada.

The following data were collected: age, gender, OR date, type of surgery and the surgical service performing the operation. The primary end points were the incidence of postsurgical pain and incidence of persistent opioid use 3 months following surgery. Additionally, pain disability, quality of life measurements and overall patient satisfaction with their pain management while in hospital and after hospital discharge were evaluated through administration of questionnaires.

Measurement tools

Pain Disability Index

The PDI assesses the extent to which persistent pain interferes with an individual’s ability to engage in seven different areas of everyday activity including: family/home responsibilities, recreation, social activity, occupation, sexual behavior, self-care and life-support activity. The PDI has good construct validity, test–retest reliability and internal consistency [20,21].

Brief Pain Inventory

The BPI asks patients to rate the severity of their pain and the degree to which their pain interferes with common aspects of psychosocial function [22]. Initially developed to assess pain related to cancer, the BPI has been shown to be an appropriate measure for pain caused by a wide range of clinical conditions [23].

EQ-5D-5L Health Questionnaire

The EQ-5D-5L questionnaire, an instrument commonly used to assess health outcomes. The difficulty scale assesses difficulties in various health-related areas (‘mobility,’ ‘self-care,’ ‘usual activities,’ ‘pain/discomfort’ and ‘anxiety/depression’), while the current health scale asks respondents to rate their current health from 0 to 100 [24].

Data analysis

Patients were dichotomized into two groups based on 3-month pain scores: those with and those without postoperative pain. Pain intensity scores, questionnaire scores and satisfaction ratings for the two groups are reported as mean ± standard deviation. Demographic variables, presence/absence of pain, and use/nonuse of opioids were compared between the two groups using Wilcoxon’s test for continuous (or ordinal) variables and Fisher’s exact test for categorical variables. One-way ANOVAs were used to test differences in pain interference (on work, walking, and mood) between opioid users and nonusers at 3 months. A one-way ANOVA was performed to determine whether there was a significant effect of pain group (pain at 3 months vs no pain at 3 months) on health outcomes as measured by the EQ-5D-5L questionnaire. All statistical analyses were performed using SAS software version 9.2 (SAS Inc., NC, USA). All tests were two-sided and significance was defined as p < 0.01.
standard deviation = 14.21). All participants had had major surgery at the Toronto General Hospital 3 months prior. Cardiac (31.5%), general (23.5%) and thoracic (20.5%) surgeries reflected the majority of the cohort (Table 1). A total of 51 patients (25.5% of cohort) reported having had a preoperative chronic pain condition. In total, 12 of the 51 patients (23.5%) who reported preoperative chronic pain also reported having used opioids prior to surgery.

- **CPSP & persistent opioid use**
  Seventy patients (35%) reported postsurgical pain at the site of surgery/scar 3 months after surgery and 130 (65%) were pain free. A total of 27 participants (13.5%) reported ongoing opioid use for pain. Of these 27 patients, 19 (70.4%) reported using opioids for management of postsurgical pain. Nine of these 19 patients reported having used opioids preoperatively. Thus, 19 of the 70 patients (27.1%) with persistent postsurgical pain were using opioids 3 months after surgery. Patients who were using opioids at 3 months but who had been opioid-naive preoperatively (ten of the 19 patients) represented 14.3% of patients reporting CPSP. The remaining eight (29.6%) of the 27 patients were using opioids for pain unrelated to their surgery. Three of these patients reported preoperative opioid use. The majority of patients reported using codeine, morphine, oxycodone or hydromorphone for pain relief.

  At 3 months’ time, 52.63% of patients still taking opioids for postsurgical pain reported moderate to severe pain (Numeric Rating Scale ≥4).

- **Global health & pain disability/interference**
  Global health ratings (EQ-5D-5L) and PDI scores are shown in Table 2. For overall global health, non-opioid users (n = 173, mean = 71.27, standard deviation = 20.91) reported significantly higher scores (F = 13.93; p < 0.000) compared with opioid users (n = 27, mean = 55.33, standard deviation = 20.21) at 3 months postsurgery. Opioid users with postsurgical pain (n = 19) reported significantly greater pain-related interference in walking (F = 7.92; p < 0.01) and mood (F = 9.17; p < 0.01), and marginally greater interference in work (F = 5.47; p < 0.05), compared with nonopioid users with postsurgical pain (n = 51). There were no significant differences between groups in terms of pain disability in relation to enjoyment, relationships, activity or sleep.

**Discussion**

In this study, 35% of patients continued to have pain at their surgical incision site 3 months after surgery, therefore meeting the criteria for chronic postsurgical pain. The incidence determined in our sample is consistent with that previously documented in the literature [1–4]. Of significant concern, is the fact that at 3 months after surgery, 27.1% of patients reporting pain remained on opioids to manage their persistent postsurgical pain. This is a distinctly greater incidence than previously published by our group (3.1%) [7]. This difference may be related to differences in presurgical pain, diagnoses and medical complexity found in the present patient sample. We did not specifically look at the role of these factors in this study. Finally, pain scores were lower in the patients continuing to use opioids 3 months postsurgery, with 52.63% reporting pain scores ≥4, compared with 64.7% in the nonopioid using group.

Importantly, the results of the present study show that patients who continued to use opioids at 3 months post-surgery rated their overall global health to be lower compared with nonopioid users. Moreover, opioid users with ongoing postsurgical pain reported significantly more pain-related interference in relation to mobility, mood and ability to work compared with nonopioid users. This may reflect multifactorial influences, including more severe postoperative pain resulting in decreased functioning, as well as a direct effect from opioids themselves. Unfortunately, our study did not further explore this relationship. While the direct implications of pain interference from chronic postsurgical pain are unclear in the literature, it has been shown that chronic noncancer pain is associated with increased health care utilization [25], increased workplace absenteeism [26] and decreased workplace effectiveness [27]. This equates to increased costs to both the healthcare system (Figure 1), and the patient personally. Chronic postsurgical pain has been shown to incur personal costs of up to US$12,000 per year, and indirect costs, such as lost income, of US$30,000 per year [13] and the incremental institutional costs that result from the development of CPSP are staggering.

Acute pain management strategies are typically limited to the immediate perioperative period with preventive, multimodal analgesic regimens and patient-controlled analgesia (PCA) [28] being the main methods employed. The majority of postsurgical patients do not
Chronic postsurgical pain & persistent opioid use following surgery

ResearCh article

future science group
www.futuremedicine.com

develop a significant acute pain problem or an exacerbation of a preexisting pain problem. We estimate that approximately 15% of complex postoperative pain patients develop moderate-to-severe CPSP, experience significant disability and continue to use opioids for pain relief in the long term. These patients will go on to consume 90% of Toronto General Hospital’s pain-related health care resources [18]. Figure 1 outlines the annual projected total cost associated with patients that enter the Toronto General Hospital and go on to develop moderate-to-severe CPSP, pain disability and persistent opioid use. CPSP arising from our institution alone could cost the Canadian healthcare system CAD$2.5–4.1 million in annually. The public health burden, as well as the cost to the healthcare system from each patient who develops CPSP has made identification and treatment of these patients a priority. The above estimates are based on a recent publication that demonstrated the cost for a chronic patient in Ontario to be CAD$5177 annually [29].

Unfortunately, opioid prescriptions occur as a reflex action for many physicians dealing with chronic pain patients, despite clear chronic neuropathic pain guidelines for prescription

Table 1. Patient characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Opioid users for surgery-related pain, n (%)</th>
<th>Opioid users for other pain, n (%)</th>
<th>Nonopioid users, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>58.89 (12.36)</td>
<td>61.25 (16.12)</td>
<td>58.51 (14.37)</td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Male</td>
<td>8 (42.1)</td>
<td>4 (50.0)</td>
<td>86 (49.7)</td>
</tr>
<tr>
<td>– Female</td>
<td>11 (57.9)</td>
<td>4 (50.0)</td>
<td>87 (50.3)</td>
</tr>
<tr>
<td>Patients reporting chronic pain prior to surgery (total n = 51), n</td>
<td>9</td>
<td>3</td>
<td>39</td>
</tr>
<tr>
<td>Surgery procedure:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Cardiac</td>
<td>2 (10.5)</td>
<td>3 (37.5)</td>
<td>58 (33.5)</td>
</tr>
<tr>
<td>– Ear, nose and throat</td>
<td>1 (5.3)</td>
<td>0 (0)</td>
<td>5 (2.9)</td>
</tr>
<tr>
<td>– General</td>
<td>6 (31.6)</td>
<td>3 (37.5)</td>
<td>38 (22)</td>
</tr>
<tr>
<td>– Gynecological</td>
<td>1 (5.3)</td>
<td>0 (0)</td>
<td>13 (7.5)</td>
</tr>
<tr>
<td>– Plastic</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>– Thoracic</td>
<td>7 (36.8)</td>
<td>2 (25.0)</td>
<td>32 (18.5)</td>
</tr>
<tr>
<td>– Urology</td>
<td>1 (5.3)</td>
<td>0 (0)</td>
<td>18 (10.4)</td>
</tr>
<tr>
<td>– Vascular</td>
<td>1 (5.3)</td>
<td>0 (0)</td>
<td>8 (4.6)</td>
</tr>
<tr>
<td>Average surgical site pain score for patients reporting pain at 3 months after surgery:</td>
<td>n = 19</td>
<td>n = 51</td>
<td></td>
</tr>
<tr>
<td>– &lt;4/10 (mild)</td>
<td>9 (47.37)</td>
<td>27 (52.94)</td>
<td></td>
</tr>
<tr>
<td>– 4 to ≤7/10 (moderate)</td>
<td>9 (47.37)</td>
<td>21 (41.18)</td>
<td></td>
</tr>
<tr>
<td>– 7/10 (severe)</td>
<td>1 (5.26)</td>
<td>3 (14.29)</td>
<td></td>
</tr>
</tbody>
</table>

* n = 8 reported opioid use for pain related to other pain conditions.
SD: Standard deviation.

Table 2. Pain disability, pain interference, and global health ratings.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Opioid users (n = 19), mean (SD)</th>
<th>Nonopioid users (n = 51), mean (SD)</th>
<th>Significance (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain Disability Index total</td>
<td>23.21 (17.15)</td>
<td>15.06 (15.92)</td>
<td>0.066</td>
</tr>
<tr>
<td>Brief Pain Inventory interference:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Enjoyment</td>
<td>3.00 (3.42)</td>
<td>1.53 (2.74)</td>
<td>0.066</td>
</tr>
<tr>
<td>– Relationships</td>
<td>3.54 (2.26)</td>
<td>0.90 (2.12)</td>
<td>0.054</td>
</tr>
<tr>
<td>– Work</td>
<td>4.29 (3.54)</td>
<td>2.22 (3.03)</td>
<td>0.022</td>
</tr>
<tr>
<td>– Walking</td>
<td>3.28 (3.41)</td>
<td>1.16 (2.49)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>– Mood</td>
<td>4.05 (3.64)</td>
<td>1.55 (2.85)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>– Activity</td>
<td>3.21 (3.51)</td>
<td>2.08 (2.89)</td>
<td>0.17</td>
</tr>
<tr>
<td>– Sleep</td>
<td>2.74 (3.54)</td>
<td>1.94 (2.94)</td>
<td>0.34</td>
</tr>
<tr>
<td>Global health rating</td>
<td>55.19 (20.21)</td>
<td>71.27 (20.91)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Global health rating was measured by the EQ-5D-5L health questionnaire.
SD: Standard deviation.
Chronic pain as a consequence of surgery at the Toronto General Hospital costs the Ontario Health Care System CAD$2.5–4.1 million annually.

- 4000 patients receiving major surgery at Toronto General Hospital annually.
- 200 new cases of chronic postsurgical pain (5% of all surgeries).
- 300 worsening cases of chronic pain post-surgery (12.5% of all surgeries).
- CAD$5000 annual Ontario estimate, US$13,000 is US published number in direct costs.
- CAD$1.0–2.6 million+
- CAD$1.5 million

Figure 1. Costs associated with the development of chronic postsurgical pain using economic modeling data from the USA and Canada. 6000 surgeries are performed per year at the Toronto General Hospital, of which 4000 are major surgical operations. Using a conservative estimate of a 5% incidence of moderate to severe pain and an annual estimate based on data from the province of Ontario, Canada of CAD$5000 in direct health-related costs, results in a CAD$1.0–2.6 million cost to the healthcare system. The 12.5% of patients who present to our pre-operative consult clinics with a pre-existing chronic pain condition and taking an opioid-based analgesic will leave on 100–300% more opioid medication than when they were admitted to hospital. Assuming a conservative increase in direct costs for 60% of patients (n = 300 vs 100% at n = 500) our data suggest the annual total cost for these patients would be CAD$1.5 million. The total estimated expenditure for all-cause chronic pain after major surgery is between CAD$2.5 and CAD$4.1 million from a single institution.

medications [30]. Pain visits related to chronic noncancer pain increased by 11–14% between 2000 and 2007 and the cost of opioids for the management of chronic pain in the USA has grown to US$3.6 billion per year [31]. This parallels a growth in the literature documenting the potential harm associated with prolonged opioid use. Traditionally, concerns about opioid use in the postoperative period involved side-effects such as nausea, vomiting, constipation, pruritus and respiratory depression. These typically present in the hospital during the immediate postoperative period [15], and can be prevented with prophylactic strategies, or treated with various adjuncts. Often overlooked is the potential for opioid overdose when used in the chronic pain setting. It has been shown that long-term use of 50–99 mg of morphine equivalents per day is associated with a 3.7-fold increase in risk for overdose, which increases to 8.9-fold when doses exceed 100 mg of morphine per day [32]. More recently, an association between opioid use and road trauma has been demonstrated. Compared with individuals consuming 20–49 mg of morphine per day, individuals using 100–199 mg of morphine per day had a twofold increase in odds for road trauma [33]. Furthermore, opioid use has been linked to both overall increase in cardiovascular events [34], and mortality [34,35]. The ongoing challenges with chronic postsurgical pain, as well as the growing body of knowledge concerning the risks and dangers of long-term...
opioid use, highlight the importance of identifying and intervening with patients at risk for the development of CPSP.

Results similar to those of the present study and years of research aimed at identifying risk factors for CPSP provided the impetus for the creation of The Toronto General Hospital TPS to address the needs of at-risk patients. The TPS is composed of a multidisciplinary team of chronic pain specialists, nurse practitioners, psychologists, physiotherapists (with acupuncture and myofascial release training) and patient care coordinators based on the identified needs from this study’s sample and our regional data [7,17]. The TPS is the first of its kind, and works independently, but in conjunction with, the Acute Pain Service and the surgical services at our hospital. The clinical algorithms used by the TPS are detailed elsewhere [17]; however, the goal of the program is to provide regular, comprehensive and multidisciplinary care to patients identified at high risk for developing CPSP and long-term opioid use. The TPS places a special focus on safe, effective and monitored opioid weaning, as well as nonpharmacologic pain management strategies including physiotherapy, acupuncture and most importantly, psychotherapy. In its short time, the TPS has had several positive outcomes in the management of patients with complex postsurgical pain needs [19,36].

The present study has some important limitations. We did not specifically examine whether patients in our sample were being followed by a pain specialist or following a tailored pain management regimen/plan prior to enrolling in the study, or whether they had preoperative pain at the surgical site. Additionally, we did not report patient use of adjuncts such as gabapentinoids, NSAIDs, NMDA antagonists or epidural/regional techniques, as a focus of our study was to specifically evaluate postoperative opioid use after major surgery. We are aware, however, that these adjuncts are important in minimizing opioid use, and modifying the postoperative pain experience. Furthermore, we did not collect data on amount of opioid being consumed at 3 months after surgery, which limits our analysis.

Conclusion
In our cohort, 35% of patients presenting for major elective surgery reported ongoing CPSP at 3 months following the procedure. There was also a significant number of patients persisting on their opioid medications at 3 months. The persistent use of opioid medications was found to be associated with reduced function and low mood.

Future perspective
Tailored perioperative care for patients needs to be extended beyond the hospital setting. Our work continues to highlight the fact that a significant percentage of patients continue to struggle with persistent pain and opioid use following surgery. This is a discussion that needs to occur preoperatively and strategies to identify high-risk patients immediately postoperatively will help to decrease the burden to patients and the healthcare system by providing early and aggressive intervention with aim of modifying the postsurgical pain trajectory. As we await the development of novel therapeutics to treat chronic non cancer pain novel services such as the TPS will hopefully become an integral part of perioperative care and facilitate return to work for some patients as well as enabling patients to manage their pain and lead as meaningful of a life as possible while managing the pain disability that often ensues as a consequence of life saving surgery.

Financial & competing interests disclosure
H Clarke is supported by Merit Awards from the Department of Anaesthesia at the University of Toronto. H Clarke is also supported by a Canadian Institutes of Health Research Fellowship. J Katz is supported by a Canadian Institutes of Health Research Canada Research Chair in Health Psychology at York University. MA Azam is supported by an Ontario Graduate Scholarship. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research
The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Open access
This work is licensed under the Creative Commons Attribution-NonCommercial 4.0 Unported License. To view a copy of this license, visit http://creativecommons.org/licenses/by-nc-nd/4.0/
References

Papers of special note have been highlighted as:

• of interest; •• of considerable interest


• Reviews the risk factors for persistent postsurgical pain and outlines potential strategies for its prevention.


•• Summarizes the known risk factors associated with the transition of acute postoperative pain to chronic postsurgical pain. It reviews the genetic, surgical, anesthetic, individual-difference, psychological and social–environmental risk factors that may contribute to persistent pain and explicitly discusses the implications of acute pain as causal or noncausal modifiable risk factor.


•• Identifies specific risk factors associated with the development of persistent opioid use following major surgery for opioid-naïve patients following non-musculoskeletal-related procedures.


• A systematic review which describes that the prevalence of neuropathic pain among persistent postsurgical pain cases differs in various types of surgery, probably depending on the likelihood of surgical iatrogenic nerve injury.


• Discusses pharmacological candidates and introduces novel nonpharmacological interventions for the treatment of acute postsurgical pain that aim to modify postsurgical pain trajectories and reduce the risk that an acute pain becomes chronic after surgery.


• These are revised Canadian guidelines which provide an updated, step-wise approach to the pharmacological management of neuropathic pain and discuss that treatment should be...
individualized for each patient based on efficacy, side-effect profile and drug accessibility including cost.


The moderating and covarying effects of social support and pain intensity on depressive symptomology among racially and ethnically diverse older adults

Juyoung Park*,1, David Newman2, Gabriella Engstrom3, Lena M Hammar4 & Anna Swall4

Summary points

- Hispanic participants with chronic pain reported the highest prevalence of depressive symptomatology, followed by African–Americans, Afro–Caribbeans and non-Hispanic whites.
- The role of social support is more effective in racially and ethnically diverse older adults with high pain intensity in decreasing depressive symptomatology than in those with moderate or low levels of pain intensity.
- Older adults with high levels of pain intensity who received social support were more likely to be resistant to stressful events, including pain intensity, and more resilient to depressive symptomatology than those with lower levels of social support.

Aim: To examine the interplay of social support, pain intensity and ethnicity as moderators and covariates of relationship on depressive symptomatology. Methods: Racially and ethnically diverse elders responded to measures of depressive symptomatology and social support. Results: Hispanics reported significantly higher prevalence of moderate pain intensity and depressive symptomology, and lower prevalence of high social support compared with other ethnic groups. Although social support showed reduced depressive symptomatology among those with high pain intensity, it did not play a significant role in decreasing depressive symptomatology among those with moderate or low levels of pain intensity. Conclusion: Social support in decreasing depressive symptomatology is more effective in older adults with high pain intensity than those with moderate or low levels of pain intensity.

First draft submitted: 27 June 2016; Accepted for publication: 12 October 2016; Published online: 31 October 2016

Background

- Chronic pain & depressive symptoms among older adults
  Chronic pain is the most common nonmalignant condition in older adults [1]; more than 50% of community-dwelling older adults experience such chronic pain [2]. Aging populations commonly experience musculoskeletal disorders, including osteoarthritis, osteoporosis, low back pain and neuropathic pain resulting from damage to peripheral nerves [3–5]. Untreated chronic pain is associated with impairments in activities of daily living, including limited range of motion and

KEYWORDS

- chronic pain • depressive symptomatology • ethnicity • older adults • social support
impaired walking ability [6,7], which causes long-term disability [8]. Due to long-term disability, older adults with pain are more likely to need assistance with activities of daily living than those without pain, which is likely to deliberate capacity to live independently [9,10]. Dependence on other people and functional impairment associated with untreated chronic pain can lead to psychosocial impairment, such as loneliness and isolation, or lack of social interaction, which further increases depressive symptomatology and decreases quality of life [11,12].

• Depression & pain
Research has identified that chronic pain and depression are often comorbid in older adults [13]. Depression has been found to be directly associated with chronic pain in older adults [13–15]. Older adults with chronic pain and depression reported higher pain levels and functional limitations than those without depression [16,17]. Depression may exacerbate pain intensity and pain interference (level to which pain interferes with productive activities such as house and outside work), with outcomes of negative perceived health and functional limitations [18–21].

A recent study examined the relationship between depressive symptomatology and pain frequency (10-point scale, 1 = very infrequently to 10 = all the time), pain intensity (10-point scale, 1 = very minimal pain to 10 = extremely intense pain) and pain interference (10-point scale, 1 = rarely interferes to 10 = interferes all the time); and prescription analgesic use and relationship with use of psychoactive medications among low-income home-bound individuals (50 years or older) with mild to severe levels of depressive symptomology [15]. The study found that pain frequency and pain interference were significantly associated with depressive symptoms, in particular among depressed community-dwelling older adults. Pain could further limit functioning, which could lead to worsening depressive symptoms [15].

• Pain among racially & ethnically diverse older adults
Ethnicity, a social construct, is defined as shared culture, language, beliefs, behaviors, history and experience [22], while race refers to individual physical characteristics such as skin color, hair texture and bone structure [23]. The Office of Management and Budget (OMB) identified minimum standards for collecting and disseminating data on race and ethnicity [28]. The standards include two ethnic categories: Hispanic or Latino and not Hispanic or Latino [23]. Five minimum categories of race were included: American–Indian or Alaska native, Asian, black or African–American, native Hawaiian or other Pacific Islander and white [23]. However, ethnic and racial categories are not clearly defined and described in the health literature [22–26]. Non-Hispanic white, for example, has been commonly used as either race or ethnicity category in the literature [24]; however, it refers to both race and ethnicity based on the categories defined by the OMB in 1997 [23,24].

Due to the complicated and multifaceted characteristics of race and ethnicity, both race and ethnicity were used in many studies, as in racially and ethnically diverse older adults [26,27].

Studies [27–30] emphasized that racial and/or ethnic minorities report more pain and higher prevalence of pain conditions than non-Hispanic white people [28]. In particular, pain associated with arthritis disproportionately affects ethnic minority groups, with Hispanics and blacks experiencing more activity limitations (43.2% Hispanics, 44.6% blacks, 36.2% whites) and severe pain (36.4% Hispanics, 38.3% blacks, 23.1% whites) than whites [31]. A review study suggested that racial and ethnic differences in pain experience might be due to differences in pain processing, pain coping strategies and cultural factors [29]. Although pain accounts for 80% of all physical healthcare visits, many ethnic and racial minorities receive inadequate pain treatments [38].

A recent study [32] identified that ethnically and racially minority groups (African–Americans, Afro–Caribbeans, Hispanics) reported higher pain intensity than non-Hispanic whites. The study also compared health-related quality of life, including physical health and mental health, by ethnicity, as measured by Medical Outcomes Study Short Form (SF-36) [32,33]. Higher scores indicate a perception of better health, less impairment in physical function and fewer limitations on psychosocial well-being [34]. Hispanics reported the worst emotional distress and best physical health among the four groups, while African–Americans had the best mental health scores and worst physical health [32]. Although few studies [32,35–36] have identified racial and/or ethnic differences in pain research, Hispanic samples are underrepresented, and almost no studies have
Social support in older adults with chronic pain

Social support refers to an interactive process in which emotional, instrumental, informational, or financial support is obtained from a social network [37]. Social support is often assessed as subjective perception of available support and may help to reduce depressive symptoms and other emotional distress in older adults [38]. A number of studies have demonstrated an association between higher levels of social support and lower levels of chronic pain [39,40]. One study [41] showed that the effect of social support on depression varied by ethnic and racial status; for non-Latino Caucasians and African–Americans, sufficient friendship support was critical in reducing the risk of depression. In another study [42], perceived support from friends, rather than family, was associated with reduced depression among Caucasians, whereas a study examined Latino populations [43] found that support from friends was related to better mental health among Latinos. Social support directly contributed to positive health outcomes as an important factor of quality of life in patients with chronic disease [44]. Use of social support could mediate potential consequences of functional impairment and disability related to chronic diseases [37].

Previous studies [39] have reported a relationship between social support and pain; social support can reduce pain perception (i.e., self-reported perceptions of the severity of pain), even when support is minimal. Perceived social support has been linked with pain intensity in older adults. A study [45] examined the relationship between chronic pain and perceived social support and noted that emotional support may buffer deterioration of depression in patients with low pain controllability, while patients preferred significantly more informational and emotional support than instrumental support for both low and high pain controllability levels. Pain studies describe the benefits of social support for chronic pain patients so that those with high levels of social support experience less emotional distress (e.g., depression), display better coping skills [46] and report improved life satisfaction [47].

Studies [45–48] have demonstrated that social support has beneficial effects on depression in older adults; persons with high social support showed lower levels of emotional distress, such as depression. The literature emphasizes the potential role of social support among older adults with chronic pain [49]. However, very few pain studies [45,50] have focused on the relationships among social support, pain intensity and emotional distress in older adults with chronic pain. Also, differences in the relationships among pain intensity, social support and depressive symptomatology among racially and ethnically diverse older adults have not been examined. A recent study [50] urged further investigation of factors associated with depressive symptoms in older persons regarding social support as a source of resilience in the face of stressors from chronic diseases. Therefore, the purpose of this study was to examine racially and ethnically diverse community-dwelling older adults aged 60 years or older to identify ethnic/racial differences in depressive symptomology and the interplay of social support and pain intensity as both moderators and covariates of these differences. In addition, the study was designed to identify the differences in participants with risk of clinical depression and those without risk of clinical depression. Based on the categories defined by the OMB in 1997, the four groups (non-Hispanic white, Hispanic, African–American and Afro–Caribbean) included in the study designated both racial and ethnic categories. Two research questions were addressed:

- Do depressive symptomology, pain intensity and social support differ by race/ethnicity among community-dwelling older adults?
- Are there moderating effects or significant covariates among the independent variables of social support, pain intensity and race/ethnicity related to depressive symptomology?

Methods

- Study procedure

This study was approved by the Institutional Review Board of the participating university. A convenience sample of participants was recruited from the Healthy Aging Research Initiative (HARI) registry, an ongoing study of a racially and ethnically diverse convenience sample of older adults living in south Florida designed to enhance knowledge about aging and to understand the influence of race/ethnicity on healthy aging and life style (for the blind review, the citation is not added). All participants signed an informed consent form.
Participants
Participants were recruited at health fairs, senior centers and community events, and by referrals from other participants. Inclusion criteria for the HARI registry were: age 60 years or older; ability to ambulate independently or with the help of a device (e.g., cane or walker); and an age- and education-adjusted score of 23 or higher on the Mini-Mental State Examination [51]. Persons in the HARI registry were eligible for the current study based on responses to a question about chronic pain intensity and two instruments: Center for Epidemiological Depression Scale (CES-D), and the ENRICHD (Enhancing Recovery in Coronary Heart Disease) Social Support Inventory (ESSI).

Data collection
Consenting participants received written and oral information about the aim of the study and were informed that they could withdraw from the study at any time. A cover letter explaining the study and information about how to contact the research team was provided. Based on participant preference, the interviews were conducted at the collaborating center (i.e., university clinic) or in the participant’s home. All instruments were translated and back translated into Spanish and Creole and administered by bilingual speakers of English–Haitian Creole or English–Spanish.

Instruments
Pain questions
Participants were asked to report pain and pain intensity (in the previous 7 days) by answering the following question: ‘Do you have chronic pain that has persisted for at least 3 months (e.g., knee pain, low back pain, hip pain, arthritis, osteoporosis, fibromyalgia)? 1 = Yes; 2 = No; 3 = Do not know; Please rate your pain by circling the number that best describes your pain on the average (11-point scale, 0 = no pain to 10 = pain as bad as you can imagine’) [52].

CES-D
The CES-D is widely used as a self-report tool in epidemiological and population-based studies to measure depressive symptoms in the previous 7 days [53] with older adults [54,55]. The frequency of each symptom during the previous 7 days is rated on a scale ranging from 0 (rarely/none of the time, less than 1 day) to 3 (most or all of the time, 5–7 days), except Items 4 (‘I felt that I was just as good as other people’), 8 (‘I felt hopeful about the future’), 12 (‘I was happy’) and 16 (‘I enjoyed life’), which are reverse-scored to assess the absence of positive affect. CES-D test scores have shown adequate internal consistency and test-retest reliability, correlated with clinical judgment. CES-D scores range from 0 to 30, with a higher score indicating a higher level of depressive symptoms. A score greater than 16 (cut-off score) identifies individuals at risk for clinical depressive symptomatology, with good sensitivity and specificity as well as high internal consistency [56]. Studies [57,58] have reported that the CES-D is reliable and valid across populations. In the current study, internal consistency was excellent, α = 0.90.

ENRICHD Social Support Inventory
The ESSI was used in the current study to measure social support among older adults [59]. The ESSI was developed to identify three dimensions of support, including: structural (partner), instrumental (tangible help) and emotional (caring) support. The ESSI has a 5-point scale for each item (1 = none of the time to 5 = all of the time) except Item 7 (living with spouse), scored 4 = yes and 2 = no. Scores range from 8 to 34, with higher scores indicating greater social support. Internal consistency was acceptable, α = 0.86 [59]. In the present study, the Cronbach’s α for internal consistency of the ESSI was relatively high (0.84) [59].

Data analysis: univariate, bivariate & multivariate analyses
Data were analyzed with SPSS for Windows (version 24.0). First, univariate analyses were conducted to identify participant demographic and predisposing characteristics of the participants. Second, three chi-square analyses were conducted to examine: the relationship of depressive symptomatology and ethnicity (1 = non-Hispanic whites; 2 = African–Americans; 3 = Hispanics; 4 = Afro–Caribbeans), the relationship of pain intensity and ethnicity and the relationship of social support and ethnicity. The depressive symptomatology was categorized in two levels: depressive (1 = CES-D ≥16) and nondepressive (0 < CES-D <16). Pain intensity (11-point scale) was categorized into three levels – low (0–3), moderate (4–6) and high (7–10). Level of social support was categorized into three levels: low (ESSI score 8–19), medium (20–29) and high (30–34).

Finally, three binary logistic regression analyses were performed to examine the potential role of associating, moderating, and covarying
effects of social support, pain intensity and race/ethnicity on depressive symptomology. Moderating effects for three- and two-way interactions were tested using full and restricted binary logistic regression models [60,61].

In particular, these analyses investigated social support as a moderator to the relationship between pain intensity and depressive symptomatology, and how this moderation differed across the four racial and ethnic groups. The three-way interaction among social support, pain intensity and race/ethnicity was tested, followed by tests of the two-way interactions: between social support and pain intensity; between race/ethnicity and pain intensity; and between race/ethnicity and social support.

An outcome variable was measured by a dichotomous variable (depressive symptomology [CES-D ≥ 16] versus nondepressive symptomology [CES-D < 16]) to identify participants with clinical depression and those without clinical depression, based on CES-D score. In the first step, as independent variables, pain intensity (‘Please rate your pain by circling the number that best describes your pain on the average’; 11-point scale, 0 = no pain to 10 = pain as bad as you can imagine), race/ethnicity and social support were entered into the equation model.

In the second step, the three-way interaction of social support, pain intensity and race/ethnicity was entered. Prior to examining any of the potential main effects, the moderating effects of social support, pain intensity and race/ethnicity were investigated [60]. After examining the three-way interaction, three sets of two-way interactions were conducted to investigate the interactions of: social support and pain intensity; pain intensity and race/ethnicity; and social support and race/ethnicity. Graphs were produced to enhance interpretation of the interaction, using categorized levels.

To test for patterns in any missing data, this study used the Missing Value Analysis function.

Table 1. Comparison of characteristics of participants with and without pain (n = 576).

<table>
<thead>
<tr>
<th>Characteristics of participants</th>
<th>All (n = 576)</th>
<th>With pain (n = 279; 48.4%)</th>
<th>Without pain (n = 297; 51.6%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>f</td>
<td>%</td>
<td>f</td>
</tr>
<tr>
<td>Age (mean, SD); years</td>
<td>74.3</td>
<td>8.3</td>
<td>74.4</td>
</tr>
<tr>
<td>Race/ethnicity:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– African–American</td>
<td>110</td>
<td>19.1</td>
<td>53</td>
</tr>
<tr>
<td>– Afro–Caribbean</td>
<td>140</td>
<td>24.3</td>
<td>68</td>
</tr>
<tr>
<td>– Hispanic</td>
<td>122</td>
<td>21.2</td>
<td>79</td>
</tr>
<tr>
<td>– Non-Hispanic white</td>
<td>204</td>
<td>35.4</td>
<td>79</td>
</tr>
<tr>
<td>Gender:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Male</td>
<td>160</td>
<td>27.8</td>
<td>72</td>
</tr>
<tr>
<td>– Female</td>
<td>416</td>
<td>72.2</td>
<td>207</td>
</tr>
<tr>
<td>Marital status:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Married</td>
<td>198</td>
<td>34.8</td>
<td>90</td>
</tr>
<tr>
<td>– Divorced/separated</td>
<td>158</td>
<td>27.7</td>
<td>83</td>
</tr>
<tr>
<td>– Widowed</td>
<td>180</td>
<td>31.6</td>
<td>87</td>
</tr>
<tr>
<td>Living with family</td>
<td>301</td>
<td>53.0</td>
<td>133</td>
</tr>
<tr>
<td>Physical health:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Excellent</td>
<td>86</td>
<td>15.8</td>
<td>19</td>
</tr>
<tr>
<td>– Very good</td>
<td>154</td>
<td>28.2</td>
<td>60</td>
</tr>
<tr>
<td>– Good</td>
<td>204</td>
<td>37.4</td>
<td>110</td>
</tr>
<tr>
<td>– Fair</td>
<td>88</td>
<td>16.1</td>
<td>60</td>
</tr>
<tr>
<td>– Poor</td>
<td>14</td>
<td>2.6</td>
<td>9</td>
</tr>
<tr>
<td>Health history:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– High blood pressure or hypertension</td>
<td>401</td>
<td>70.7</td>
<td>214</td>
</tr>
<tr>
<td>– Diabetes</td>
<td>193</td>
<td>34.8</td>
<td>94</td>
</tr>
<tr>
<td>– Psychiatric problems</td>
<td>113</td>
<td>19.7</td>
<td>69</td>
</tr>
<tr>
<td>– Cognitive problems</td>
<td>12</td>
<td>2.1</td>
<td>8</td>
</tr>
</tbody>
</table>
in SPSS 24, which assesses the extent of randomness and pattern of missing data. This program allows one to investigate the mechanisms of the missing data by assigning 1 or 0 to a vector R for each variable to test whether the data are missing completely at random, missing at random, or missing not at random. This analysis used maximum likelihood estimated and the expectation–maximization algorithm to test the relationship between missing values across variables. Patterns of missing data were also displayed in tables and figures to facilitate description of the patterns. The results of the missing data analysis classified the missing data in this study as missing completely at random ($\chi^2(9) = 15.4; p = 0.081$). No data imputations were used and missing data resulted in a list-wise deletion for any analysis that used that variable.

Results

Of the 697 participants who were enrolled in the HARI study, 576 (83%) provided complete data on the relevant questions and were included in the analysis. Table 1 presents the characteristics of the participants. Of these 576, 48.4% (n = 279) reported chronic pain for more than 3 months. The majority were women (72.4%; n = 416); non-Hispanic whites were the largest group, with the three racial/ethnic minority groups almost equally distributed. The mean age of the participants was 74.2 years (SD = 8.4). Almost half (48.4%; n = 279) reported having chronic pain at an average intensity of 6.21 (Min. 0 to Max. 10). More than 50% of the participants (53.0%; n = 301) were living with family, and 70.7% (n = 401) were diagnosed with high blood pressure or hypertension. A majority of the members of the Hispanic group (92%) and the Afro–Caribbean (84%) group were born outside of the USA; mean years of living in the USA by Hispanics (M = 33) and Afro–Caribbeans (M = 37) was less than mean years for the other two racial/ethnic groups, particularly less than half of those for the non-Hispanic whites (M = 77.5).

**Depressive symptomology, pain intensity & social support by race/ethnicity**

The prevalence of depressive symptomology by racial/ethnic group is displayed in Table 2. Chi-square analyses showed that Hispanic participants (37.3%; n = 44) reported the highest prevalence of depressive symptomatology (CES-D ≥16) and non-Hispanic white participants (14.0%; n = 18) reported the lowest prevalence of depressive symptomatology ($\chi^2(3; [3] = 29.004; p = 0.005$).

Pain intensity by race/ethnicity is shown in Table 3. Non-Hispanic whites reported a significantly lower level of pain, with an average pain level of 4.7 ($p < 0.001$). There were no significant differences in average pain levels of Hispanics (M = 6.5), African–Americans (M = 6.7) and Afro–Caribbeans (M = 6.7).

The level of social support by race/ethnicity is presented in Table 4. There was an overall significant difference in level of social support by race/ethnicity $\chi^2(6) = 12.66; p = 0.049$. The only statistically significant difference in social support by race/ethnicity was that the Hispanic group reported lower numbers in the high level of social support compared with the other racial/ethnic groups ($p = 0.008$). Even though not statistically significant, more non-Hispanic whites reported high levels of social support and more Hispanics reported low levels of social support ($p = 0.08$ for both groups).

**Three-way interaction: social support, pain intensity & race/ethnicity**

The overall model for the three-way interaction among social support, pain intensity and race/ethnicity showed nonsignificant results, accounting for 18.2% of the total variance in depressive symptomatology ($p = 0.665$, Nagelkerke $R^2 = 0.182$). Because this interaction was not significant, we investigated the three sets of two-way interactions, since one cannot interpret main effects or interactions if there is a significant higher-order interaction [60,61].

---

**Table 2. Depressive symptomology scores on the Center for Epidemiological Depression Scale by race/ethnic group.**

<table>
<thead>
<tr>
<th>Depression</th>
<th>Non-Hispanic white</th>
<th>African–American</th>
<th>Hispanic</th>
<th>Afro–Caribbean</th>
</tr>
</thead>
<tbody>
<tr>
<td>CES-D &lt;16</td>
<td>n=92 (83.6)</td>
<td>n=178 (86.0)</td>
<td>n=74 (62.7)</td>
<td>n=118 (83.7)</td>
</tr>
<tr>
<td>CES-D ≥16</td>
<td>n=18 (16.4)</td>
<td>n=29 (14.0)</td>
<td>n=44 (37.3)</td>
<td>n=23 (16.3)</td>
</tr>
</tbody>
</table>

$p < 0.001; \chi^2(3) = 29.004$. Hispanics were statistically more depressed compared with the three other racial/ethnic groups ($p = 0.005$).
Two-way interaction: social support & pain intensity

The next research question investigated the moderating effects of social support on the positive relationship between pain intensity and depressive symptomatology after covarying race/ethnicity. The results for the final model of two-way interaction between social support and pain intensity were significant ($\chi^2[1] = 3.83$, $p = 0.05$, with Nagelkerke $R^2 = 0.146$), accounting for 14.6% of the total variance in depressive symptomatology. The only independent variables that accounted for a significant proportion of unique variance in this model were social support ($B = -0.07$; OR: 0.93; $p < 0.0005$) and pain intensity ($B = 0.16$; OR: 1.18; $p = 0.014$). The moderation analysis revealed that the effect of the interaction between pain intensity and social support on depressive symptomatology was significant ($B = -0.04$; OR: 0.97; $p = 0.019$; Table 5).

To further investigate these results, pain intensity was trichotomized into older adults with high pain intensity (score 7–10 on the 10-point pain scale), moderate pain intensity (score 4–6) and low pain (score 1–3). As shown in Figure 1, with high pain and when social support was low (ESSI score 8–19), they were more likely to have high levels of depressive symptomatology; when levels of social support increased (ESSI score 20–34), levels of depressive symptomatology were decreased. On the other hand, among older adults with moderate pain intensity (score 4–6) or low pain intensity (score 0–3), once a medium level of social support was reached (ESSI score 20–29), the lowest level of depressive symptomatology was reported. After that, depressive symptoms no longer decreased, even when level of social support increased from medium to high (ESSI 30–34).

Two-way interaction: pain intensity & race/ethnicity

The next research question investigated the moderating effects of pain intensity and race/ethnicity on clinical depressive symptomology after covarying social support. The result of the final model of interaction of race/ethnicity and pain intensity was not statistically significant, accounting for only 1.40% of the unique variance in depressive symptomatology ($p = 0.161$, Nagelkerke $R^2$ total model = 0.15). Although the final model of the interaction of race/ethnicity and Hispanics was significant ($B = -0.21$; OR: 0.81; $p = 0.023$) but that interaction in the other racial/ethnic groups was not significant (Table 6). Figure 2 graphs the difference for the Hispanic group, which indicated no significant change across pain intensity levels.

Two-way interaction: social support & race/ethnicity

The last research question investigated the moderating effects of social support and race/ethnicity on clinical depressive symptomology after covarying pain intensity. There was an overall significant difference in level of reported social support by race/ethnicity $\chi^2(6) = 12.66; p = 0.049)$. The only statistically significant difference in social support by race/ethnicity was that the Hispanic group reported lower numbers in the high level of social support compared with the other racial/ethnic groups ($p = 0.008$).

---

Table 3. Pain intensity by race/ethnicity.

<table>
<thead>
<tr>
<th>Pain intensity</th>
<th>Non-Hispanic white</th>
<th>African–American</th>
<th>Hispanic</th>
<th>Afro–Caribbean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n$</td>
<td>%</td>
<td>$n$</td>
<td>%</td>
</tr>
<tr>
<td>Low (0–3)</td>
<td>151</td>
<td>77.4</td>
<td>63</td>
<td>63.0</td>
</tr>
<tr>
<td>Moderate (4–6)</td>
<td>36</td>
<td>18.5</td>
<td>11</td>
<td>11.0</td>
</tr>
<tr>
<td>High (7–10)</td>
<td>84</td>
<td>4.1</td>
<td>26</td>
<td>26.0</td>
</tr>
</tbody>
</table>

There was an overall significant difference in level of reported social support by race/ethnicity $\chi^2(6) = 56.43, p < 0.001$. The non-Hispanic white group had a significantly higher prevalence of low pain intensity ($p = 0.01$) and lower prevalence of high pain intensity reported ($p < 0.001$) compared with all other groups. Fewer Hispanics reported low pain intensity ($p = 0.006$) and more moderate pain intensity ($p = 0.002$) compared with other groups.

Table 4. Level of social support by race/ethnicity.

<table>
<thead>
<tr>
<th>Social support</th>
<th>Non-Hispanic white</th>
<th>African–American</th>
<th>Hispanic</th>
<th>Afro–Caribbean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n$</td>
<td>%</td>
<td>$n$</td>
<td>%</td>
</tr>
<tr>
<td>Low</td>
<td>28</td>
<td>13.7</td>
<td>17</td>
<td>15.5</td>
</tr>
<tr>
<td>Medium</td>
<td>91</td>
<td>44.6</td>
<td>58</td>
<td>52.7</td>
</tr>
<tr>
<td>High</td>
<td>85</td>
<td>41.7</td>
<td>35</td>
<td>31.8</td>
</tr>
</tbody>
</table>

There was an overall significant difference in level of reported social support by race/ethnicity $\chi^2(6) = 12.66, p = 0.049$.

The only statistically significant difference in social support by race/ethnicity was that the Hispanic group reported lower numbers in the high level of social support compared with the other racial/ethnic groups ($p = 0.008$).
ethnicity on depressive symptomology after covarying pain intensity; the results were not statistically significant, accounting for only 1.41% of the unique variance in depressive symptomology. The result of the final model of interaction of social support and race/ethnicity was not significant, accounting for only 1.41% of the unique variance in depressive symptomology (p = 0.155, Nagelkerke $R^2$ total model = 0.15). No other variables accounted for a significant proportion of unique variance in associating depressive symptomology (Table 7).

Although the final model of the interaction of social support and race/ethnicity was nonsignificant, Figure 3 displays interaction between social support and race/ethnicity. Hispanic participants with low levels of social support reported the highest levels of depressive symptomology. When social support increased to the medium level, Hispanics had the lowest level of depressive symptomology; when Hispanic participants received high levels of social support, levels of depressive symptomology increased slightly. The other three racial/ethnic groups showed higher levels of depressive symptomology when they received low levels of social support. In contrast, when social support increased to medium or high levels, levels of depressive symptomology decreased (Figure 3).

Discussion
The current study identified depressive symptomology, pain intensity and social support among four ethnic and racial groups. Consistent with recent study findings [6], Hispanic participants with chronic pain reported the highest prevalence of depressive symptomatology, followed by African-Americans and Afro-Caribbeans, while non-Hispanic white participants reported the lowest prevalence of depressive symptomatology. Although these three ethnic and racial minority groups remain at great risk for depressive symptomatology, compared with non-Hispanic whites, more than twice as many

<table>
<thead>
<tr>
<th>Table 5. Logistic regression for the interaction of social support and pain intensity predicting depressive symptomology.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Factor</strong></td>
</tr>
<tr>
<td>Social support</td>
</tr>
<tr>
<td>Pain intensity</td>
</tr>
<tr>
<td>Non-Hispanic white (reference):</td>
</tr>
<tr>
<td>– African–American</td>
</tr>
<tr>
<td>– Hispanic</td>
</tr>
<tr>
<td>– Afro–Caribbean</td>
</tr>
<tr>
<td>Social support X pain</td>
</tr>
<tr>
<td>Constant</td>
</tr>
</tbody>
</table>

p = 0.05; $R^2 = 0.146$. OR: Odds ratio; SE: Standard error.
Hispanics (37.3%) reported depressive symptomatology than African–Americans (16.4%) or Afro–Caribbeans (16.3%). A majority of the Hispanics (92%) were immigrants, having lived in the USA for fewer years than the other racial/ethnic groups. It is plausible that perceptions of depressive symptomatology and cultural perspectives on mental health among Hispanics may be different from those of other racial/ethnic groups in rating their own level of depressive symptomatology [62]. Older Hispanic immigrants may be less engaged with mental health services and more susceptible to depressive symptomatology than other racial/ethnic groups [63–65].

However, little is known about how perception of depressive symptomatology and their attitudes toward accessing mental health services among Hispanics influence their decision to seek services [66]. Although this study did not produce data to support that Hispanic older adults feel less prone to seek treatment service, the literature supports this statement. For example, in a population-based study [67], significantly fewer Hispanic participants had visited a physician for pain or to seek mental health services [65]. Thus, more research is needed to examine perceptions of depressive symptomatology and attitude toward mental health services among Hispanic older adults compared with other racial/ethnic groups [66].

With regard to the relationship between pain intensity and social support among four racial/ethnic groups, Hispanics reported significantly lower prevalence of high social support and higher prevalence of moderate pain intensity, compared with other racial/ethnic groups [63–65].

Table 6. Logistic regression for the interaction of race/ethnicity and pain intensity predicting depressive symptomology.

<table>
<thead>
<tr>
<th>Factor</th>
<th>B</th>
<th>SE</th>
<th>OR</th>
<th>95% CI</th>
<th>Wald</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social support</td>
<td>-0.09</td>
<td>0.02</td>
<td>0.92</td>
<td>0.89–95</td>
<td>23.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pain intensity</td>
<td>0.18</td>
<td>0.07</td>
<td>1.19</td>
<td>1.04–1.037</td>
<td>6.24</td>
<td>0.012</td>
</tr>
<tr>
<td>Non-Hispanic white (reference):</td>
<td></td>
<td></td>
<td></td>
<td>17.86</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>– African–American</td>
<td>-0.32</td>
<td>0.43</td>
<td>0.73</td>
<td>0.31–3.169</td>
<td>0.55</td>
<td>0.457</td>
</tr>
<tr>
<td>– Hispanic</td>
<td>-0.13</td>
<td>0.50</td>
<td>0.88</td>
<td>0.33–3.235</td>
<td>0.07</td>
<td>0.793</td>
</tr>
<tr>
<td>– Afro–Caribbean</td>
<td>1.30</td>
<td>0.45</td>
<td>3.67</td>
<td>1.53–5.811</td>
<td>8.46</td>
<td>0.004</td>
</tr>
<tr>
<td>Pain X African–American</td>
<td>-0.11</td>
<td>0.10</td>
<td>0.90</td>
<td>0.74–7.091</td>
<td>1.24</td>
<td>0.267</td>
</tr>
<tr>
<td>Pain X Hispanic</td>
<td>-0.21</td>
<td>0.09</td>
<td>0.81</td>
<td>0.68–6.97</td>
<td>5.19</td>
<td>0.023</td>
</tr>
<tr>
<td>Pain X Afro–Caribbean</td>
<td>-0.12</td>
<td>0.10</td>
<td>0.89</td>
<td>0.74–7.071</td>
<td>1.63</td>
<td>0.202</td>
</tr>
<tr>
<td>Constant</td>
<td>0.36</td>
<td>0.55</td>
<td>1.43</td>
<td>1.36</td>
<td>0.43</td>
<td>0.512</td>
</tr>
</tbody>
</table>

p = 0.161, R² = 0.150.

OR: Odds ratio; SE: Standard error.

Figure 2. Pain intensity by race/ethnicity: interaction with depressive symptomatology (nonsignificant; p = 0.161).
with other racial/ethnic groups. Although not significantly different among racial/ethnic groups, non-Hispanic whites reported a higher prevalence of high social support, compared with other racial/ethnic groups. The three racial/ethnic minority groups, in particular the Hispanic group, reported higher levels of pain intensity and lower levels of social support, compared with non-Hispanic whites. Although the findings confirmed the literature indicating that minority older adults report a higher prevalence of pain intensity than non-Hispanic whites [68], the results of this study add to the literature on level of pain intensity and social support among four racial/ethnic groups.

The results indicated a role of social support in the decreasing level of depressive symptomatology in community-dwelling older adults with chronic pain. The results indicate the moderating and covarying effects of social support and pain intensity on depressive symptomatology across racial/ethnic groups. When considering direct association, older adults with high levels of pain intensity showed greater levels of depressive symptomatology than those with low or moderate levels of pain intensity. This finding is consistent with previous findings regarding pain intensity, social support and depressive symptomatology in older adults with arthritis pain [51].

To our knowledge, this is the first study of four racially and ethnically diverse groups with chronic pain to examine the potential role of associating, moderating and covarying effects of social support, pain intensity and race/ethnicity on depressive symptomatology. Without considering the role of social support in moderating the relationship between pain intensity and depressive symptomatology, one cannot truly understand this complex interrelationship among pain intensity, social support and depressive symptomatology in racially and ethnically diverse older adults. Furthermore, the role of social support seemed to be more effective in racially and ethnically diverse older adults with high pain intensity in decreasing depressive symptomatology than in those with moderate or low levels of pain intensity. Older adults with high levels of pain intensity who received social support were more likely to be resistant to stressful events [69,70], including presence of pain, and more resilient to depressive symptomatology than those with lower levels of social support. Social support can be effective in reducing pain intensity in older adults because it can provide positive experiences and buffer depressive symptomatology associated with chronic pain [71].

Furthermore, the current study found that, for those with low or moderate levels of pain intensity, the lowest level of depressive symptomatology was reported when they received a medium level of social support. However, level of depressive symptomatology did not continue to decrease among those with low or moderate pain intensity, even when social support increased from a moderate level to a high level. The study results indicated that, although social support could be effective for older adults with higher levels of pain intensity to manage depressive symptomatology, it did not play a significant role in decreasing levels of depressive symptomatology among those with low or moderate pain intensity once they had received a medium level of social support. Many of the moderations investigated in this study yielded nonsignificant or small effects. The only statistically significant interaction that accounted for a significant proportion of unique variance in the

### Table 7. Logistic regression for the interaction of social support and race/ethnicity predicting depressive symptomology.

<table>
<thead>
<tr>
<th>Factor</th>
<th>B</th>
<th>SE</th>
<th>OR</th>
<th>95% CI</th>
<th>Wald</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social support</td>
<td>-0.05</td>
<td>0.03</td>
<td>0.95</td>
<td>0.89–1.01</td>
<td>3.37</td>
<td>0.109</td>
</tr>
<tr>
<td>Pain intensity</td>
<td>0.06</td>
<td>0.03</td>
<td>1.06</td>
<td>0.99–1.14</td>
<td>7.45</td>
<td>0.067</td>
</tr>
<tr>
<td>Non-Hispanic white (reference):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– African–American</td>
<td>-2.51</td>
<td>1.29</td>
<td>0.08</td>
<td>0.01–1.03</td>
<td>3.01</td>
<td>0.053</td>
</tr>
<tr>
<td>– Hispanic</td>
<td>-2.46</td>
<td>1.42</td>
<td>0.09</td>
<td>0.01–1.38</td>
<td>0.00</td>
<td>0.083</td>
</tr>
<tr>
<td>– Afro–Caribbean</td>
<td>0.01</td>
<td>1.33</td>
<td>1.01</td>
<td>0.07–13.73</td>
<td>0.00</td>
<td>0.997</td>
</tr>
<tr>
<td>Social support X African–American</td>
<td>0.00</td>
<td>0.05</td>
<td>1.00</td>
<td>0.90–1.1</td>
<td>1.75</td>
<td>0.057</td>
</tr>
<tr>
<td>Social support X Hispanic</td>
<td>-0.06</td>
<td>0.05</td>
<td>0.94</td>
<td>0.86–1.03</td>
<td>3.84</td>
<td>0.186</td>
</tr>
<tr>
<td>Social support X Afro–Caribbean</td>
<td>-0.10</td>
<td>0.05</td>
<td>0.90</td>
<td>0.082–1.0</td>
<td>3.58</td>
<td>0.050</td>
</tr>
<tr>
<td>Constant</td>
<td>1.91</td>
<td>1.01</td>
<td>6.76</td>
<td></td>
<td></td>
<td>0.058</td>
</tr>
</tbody>
</table>

OR: Odds ratio; SE: Standard error.

$p = 0.155, R^2 = 0.150$. 

---

RESEARCH ARTICLE  Park, Newman, Engstrom, Hammar & Swall

---

Pain Manag. (2017) 7(1)
moderation models was with pain intensity and social support. Further research may examine these interactions as well as potential interactions with variables other than social support to decrease depressive symptomatology among those with low or moderate pain intensity.

When pain interferes in daily activities, it is a factor associated with depressive symptomatology [72]. Social support (i.e., instrumental support) can offer help with daily chores and housekeeping services, as well as assistance with instrumental activities of daily living such as grocery shopping, preparing meals and medication management [73]. The study results imply that interventions to reduce and prevent depressive symptomatology in older adults with chronic pain must be designed to reduce pain interference.

Limitations & implications

The cross-sectional nature of this study limits inference of directionality. Future longitudinal work may improve assessment of temporal relationships. Although four racial/ethnic groups were recruited, participants in the current study were all listed in the HARI registry at the university. Thus, the findings may not be generalized to other populations of the same racial/ethnic groups.

As another limitation, several studies have shown that the effect of race/ethnicity on health outcomes tends to decrease significantly when socioeconomic characteristics are controlled for. This raises the question whether racial and ethnic disparities in healthcare are due to race or ethnicity, socioeconomic factors such as income level or educational status, or a combination of the two factors [74]. However, in this study, we did not measure socioeconomic factors such as income level.

Further research is needed to develop appropriate interventions that address the needs of racially and ethnically diverse older adults with chronic pain for obtaining social support or the ways in which support networks encourage and respond to their adaptive ways to cope with pain. Healthcare providers may consider providing services to older patients with chronic pain to maintain adequate levels of social support in an effort to minimize the effect of pain on levels of depressive symptomatology.

Social support could include concrete assistance with daily living tasks for older adults suffering from high pain intensity [55]. Healthcare professionals could assess social support in depressed older patients with chronic pain and refer them to appropriate treatment (e.g., counseling services or pain support group) or provide interventions to improve support [55]. Healthcare professionals may help older adults to connect to formal support resources, including transportation (e.g., transportation by local government) to visit healthcare providers, assistance with personal care, Meals on Wheels and informal social networks from family and friends. Specifically, healthcare providers may assist older patients to learn effective ways to express their emotional needs to significant others to gain appropriate social support.

Social support from family or community and

---

Figure 3. Social support by race/ethnicity: interaction with depressive symptomatology (nonsignificant; p = 0.155).
resources to manage chronic pain in older adults are associated with lower levels of depressive symptomatology.

Although Hispanic older adults with chronic pain reported the highest level of depressive symptomatology compared with the other racial/ethnic groups, no appropriate intervention to decrease pain intensity and level of depressive symptomatology has been identified to date. Thus, further research is needed to identify effective interventions to address the needs of older adults with pain in obtaining social support or the ways in which support networks respond to older adults’ adaptive ways to cope with pain. Primary healthcare providers should be aware that social support may help older adults with chronic pain to manage depressive symptomatology; they can assess patients’ need for social support and refer them to local recourses, such as housekeeping or chore services and counseling services.

Conclusion
The study fills a gap in research regarding social support and depressive symptomatology among older adults with chronic pain by examining racial/ethnic differences. The results indicate that social support may be a buffer that decreases the relationship between pain intensity and depressive symptomatology in older adults. Outcomes among older adults who live with chronic pain may be enhanced by building resources through increasing social support.

Acknowledgements
The authors acknowledge Dr Joseph Ouslander of the College of Medicine and Dr Ruth Tappen of the College of Nursing, Florida Atlantic University, for helping the corresponding author to gain access to the HARI registry and for providing support and guidance in completing the project.

Financial & competing interests disclosure
This study is a part of Healthy Aging Research Initiative (HARI) project that was funded by Florida Atlantic University. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research
The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

References
Papers of special note have been highlighted as:
• of interest; •• of considerable interest
16 Eggermont L, Penninx B, Jones R et al. Depressive symptoms, chronic pain, and falls

**A longitudinal population-based study of risk factors for falls in older community-dwelling adults.**


23 Office of Management and Budget. Revision to the standard for classification of federal data on race and ethnicity. www.whitehouse.gov


**Provides data of prevalence of chronic pain and the association of physical and mental health associated with chronic pain among four ethnically diverse groups of older adults.**


**Examines the role of social support in coping among patients with rheumatoid arthritis.**


**Examines the influence of active and passive pain coping strategies and social support characteristics on the change in functional status in patients with rheumatoid arthritis.**


**Persons with higher social support and cognitive functioning reported lower levels of depressive symptoms.**

51 Folsom MF, Folsom SE, McHugh PR. Mini-Mental State: a practical method for
- Describes Hispanic immigrants’ perceptions of depression and attitudes toward treatment and examines how cultural factors were associated with their perceptions and attitudes.
69 Ringdal GI, Ringdal K, Jordhøy MS et al. Does social support from family and friends work as a buffer against reactions to stressful life events such as terminal cancer? Palliat. Support Care 5, 61–69 (2007).
70 Thoits PA. Mechanisms linking social ties and support to physical and mental health. J. Health Soc. Behav. 52(2), 145–161 (2011).
Abuse-deterrent formulations of prescription opioid analgesics in the management of chronic noncancer pain

Martin E Hale*,1, Derek Moe2, Mary Bond3, Maciej Gasior3 & Richard Malamut3

Practice points

- Opioid analgesics are effective therapies for the management of chronic noncancer pain; however, the potential for misuse, abuse and diversion of these medications is a global public health concern.
- Strategies to minimize misuse, abuse and diversion of prescription opioid analgesics include educational and regulatory initiatives, as well as the development of novel formulations or delivery systems with abuse-deterrent properties.
- Both immediate-release and extended-release prescription opioid analgesics can be abused in their original formulation or after manipulation of the original formulation to change the drug-delivery characteristics.
- Abuse-deterrent formulations aim to hinder extraction of the active ingredient, prevent administration through alternative routes and/or make abuse of the manipulated product less attractive, less rewarding or even aversive.
- Approaches to abuse deterrence include physical and chemical barriers, agonist/antagonist combinations, aversion technologies, use of new molecular entities or prodrugs and novel delivery systems; different approaches can be combined to further reduce the potential for abuse by different routes.
- The science of abuse deterrence and the regulatory landscape are still relatively new and evolving.
- There are currently six opioid analgesics with a US FDA abuse-deterrent label, and a number of other products are under review.
- Although opioid abuse-deterrent formulations may still be abused via the intended route of administration by increasing the dose and/or dosing frequency, a growing body of evidence suggests that introduction of these formulations has been associated with decreased rates of abuse and diversion of these medications in the USA.

Misuse, abuse and diversion of prescription opioid analgesics represent a global public health concern. The development of abuse-deterrent formulations (ADFs) of prescription opioid analgesics is an important step toward reducing abuse and diversion of these medications, as well as potentially limiting medical consequences when misused or administered in error. ADFs aim to hinder extraction of the active ingredient, prevent administration through alternative routes and/or make abuse of the manipulated product less attractive, less rewarding or even aversive. However, opioid ADFs may still be abused via the intended route of administration by increasing the dose and/or dosing frequency. The science of abuse...
deterrence and the regulatory landscape are still relatively new and evolving. This paper reviews the current status of opioid ADFs, with particular focus on different approaches that can be used to deter abuse, regulatory considerations and implications for clinical management.

First draft submitted: 18 November 2015; Accepted for publication: 18 February 2016; Published online: 6 April 2016

Chronic noncancer pain is one of the most common reasons for seeking medical care worldwide. It has a significant impact on patients’ quality of life and represents a major public health burden [1]. Data from the USA, Europe, Australia and Japan suggest that approximately 20% of the general population have chronic noncancer pain [2–8]. The Institute of Medicine estimates that 100 million North Americans have chronic noncancer pain, with associated annual direct and indirect costs exceeding US$600 billion [9]. Low back pain – the most common cause of chronic noncancer pain – was ranked highest in terms of years lived with disability in the most recent analysis from the Global Burden of Disease Study; neck pain and other chronic musculoskeletal disorders were the fourth and tenth most common causes of years lived with disability, respectively [10].

Prescription opioid analgesics are an important treatment option for patients with chronic noncancer pain [11]. However, misuse, abuse and diversion of these medications represent a global public health concern. Misuse is defined as the intentional therapeutic use of a prescription opioid analgesic in an inappropriate way, but excluding events that meet the definition of abuse [12]. Abuse is the intentional, nontherapeutic use of a prescription opioid analgesic for the purpose of achieving a desirable psychological or physiological effect [12]. Diversion is any intentional act that results in transferring a prescription opioid analgesic from lawful to unlawful distribution or possession [12].

Abuse and misuse of prescription opioid analgesics can lead to serious consequences, including addiction, physical dependence, overdose, drug-related suicide, drug-related road traffic accidents, spreading of serious infectious diseases via shared drug paraphernalia or death [13,14]. Out of the 22,134 drug-overdose deaths involving pharmaceuticals (not including overdose of illegal drugs) that occurred during 2010 in the USA, 75.2% involved prescription opioid analgesics, frequently with concomitant use of benzodiazepines and/or alcohol [15]. Prescription opioid analgesic abuse has been independently related to risky injection behaviors, such as sharing syringes [16]. Intravenous drug users who inject prescription opioid analgesics have been shown to be more likely than those who do not inject these drugs to become infected with hepatitis C virus and/or human immunodeficiency virus [17–20].

Balancing the benefits of prescription opioid analgesics against their abuse liability can be challenging for clinicians. Thus, the development of abuse-deterrent formulations (ADF) of prescription opioid analgesics is an important step toward reducing abuse and diversion of these medications, while ensuring access to these drugs for patients with legitimate medical need. ADFs may also limit the potential medical consequences if misused (e.g., if the drug is overingested, crushed or chewed before ingestion, or administered with alcohol) or taken in error. Abuse-deterrent properties are defined as those properties shown to meaningfully deter abuse, even if they do not fully prevent it. The term ‘tamper-resistant’ is sometimes used to describe these formulations (e.g., in Canada, where it is the preferred term), but is in fact more accurately used to describe packaging requirements applicable to certain classes of drugs, devices and cosmetics.

This paper aims to review the current status of opioid ADFs, including the different approaches used to deter abuse, regulatory considerations and available products, with implications for their use in the management of chronic noncancer pain in routine clinical practice.

Scale of the problem

Nonmedical use of prescription opioid analgesics is continuing to increase worldwide [21]. It is estimated that approximately 33 million people—or 0.7% of the world’s adult population—currently abuse prescription or nonprescription opioids [22]. In the USA, approximately 4.3 million individuals aged 12 years or older (1.6% of the population) used prescription pain medications for nonmedical purposes in 2014 [22]. Prescription
Prescription opioid analgesics were the second most commonly abused drug class after marijuana [22]. Indeed, it is estimated that nonmedical use of prescription opioid analgesics contributes to over 16,500 deaths annually (i.e., 46 deaths/day) in the USA [23]. In insured individuals, healthcare costs have been shown to be higher among those with a history of abuse of prescription opioid analgesics compared with those without this history [24,25]. The total societal cost associated with prescription opioid analgesic misuse, abuse and diversion in the USA has been estimated to range from US$55.7 to US$72.5 billion annually, depending on the data source [26,27]. The use of opioid ADFs would be expected to reduce, but not eradicate, this cost. Immediate-release (IR) hydrocodone is the most frequently prescribed opioid analgesic in the USA and is associated with higher rates of abuse and diversion than any other prescription opioid analgesic [28].

Although most prevalent in the USA, nonmedical use of prescription opioid analgesics is recognized to be a problem in many other parts of the world, including Canada, Australia, Europe and Japan [21,29–33]. For example, 6% of the adult population and 15.5% of secondary school students in Ontario, Canada, reported nonmedical use of prescription opioid analgesics in 2010–2011 [31]. In Australia, 7.7% of individuals reported having used painkillers or analgesics for nonmedical purposes at some point in their lifetime [34]. Data concerning nonmedical use of prescription opioid analgesics in Europe are recognized to be scarce [35], with authorities, such as the EMA and the European Monitoring Centre on Drugs and Drug Abuse, tending to focus on rates of abuse of heroin rather than prescription opioid analgesics [33]. Nevertheless, available data indicate that nonmedical use of prescription opioid analgesics is an increasing cause for concern in this region as well [30,33]. In Japan, the lifetime prevalence of nonmedical use of prescription opioid analgesics has been reported to be 2.4% [36].

Prescription opioid analgesic abuse is seen in almost all age groups, from young adolescents to the elderly [22]. Diversion through family and friends appears to be the most common source of prescription opioid analogues for abuse [37]. In most cases, these relatives and friends had obtained their prescriptions from a single doctor [37]. It should be noted that opioid abuse is a complex, multifactorial problem and ADFs are only one potential tool to address this problem.

**Routes of abuse**

Prescription opioid analgesics can be abused in their original formulation or after manipulation of the original formulation to change the drug-delivery characteristics [38–40]. The aim of altering an extended-release (ER) formulation is to create a ‘dose-dumping’ effect (i.e., to achieve an increased maximum concentration of the opioid in the shortest time within the brain reward pathway that includes the ventral tegmental area, nucleus accumbens and cortex), which results in a rapid ‘high’ and other reinforcing effects that drive further abuse potential [41]. Possible routes of abuse are ingestion (including chewing or ingesting more than the usual dose), inhalation (e.g., snorting or smoking) and parenteral administration (intravenous, intramuscular or subcutaneous injection). Manipulation methods include crushing or grinding into a powder or small particles, dissolving in a solvent (e.g., alcohol), and extracting through exposure to hot or cold temperatures. To achieve enhanced CNS effects, abusers may also often co-administer prescription opioid analogues with other psychoactive substances (e.g., alcohol, benzodiazepines, barbiturates or antidepressants) [42,43].

Data suggest that ingestion (intact or following manipulation by chewing, crushing or dissolving) is the most prevalent route of abuse for prescription opioid analogues, followed by inhalation (snorting or smoking) and injection [38–40]. However, reported routes of abuse vary considerably between prescription opioid analgesic formulations [44]. The preferred route of abuse most likely reflects what the individual abuser finds attractive and/or unattractive about a specific formulation. ER formulations are generally more attractive to abusers than IR formulations due to the greater dose of opioid contained in the product [40]. Initial oral abuse may progress to more invasive non-oral abuse in more experienced abusers or addicted individuals [40]. Routes of abuse associated with the highest morbidity are injection and inhalation [40].

**Current approaches to abuse deterrence**

The goal of opioid ADFs is to maintain effective pain relief while reducing the potential for abuse by manipulation of the ER formulation. This can be achieved by hindering extraction of the active ingredient, preventing administration through alternative routes and/or making abuse of the manipulated product less attractive or less rewarding. Approaches to abuse deterrence include
physical and chemical barriers, agonist/antagonist combinations, aversion technologies, use of new molecular entities or prodrugs and novel delivery systems (Table 1). Different approaches can be combined to further reduce the potential for abuse by different routes [45–48].

Physical and chemical barriers aim to prevent chewing, crushing, cutting, grating or grinding of the opioid formulation, and to prevent extraction of the opioid using solvents. Examples of ADFs that use physical and chemical barriers include crush-resistant pills and tablets, high-viscosity gelatin capsules and extruded pellets. Formulations with these barriers may prevent multiple routes of abuse. Physical and chemical barriers have the potential to deter manipulation for abuse without the risk of adverse effects in compliant patients or those who may accidentally chew or crush their medication. However, such barriers generally do not prevent abuse of intact tablets through overingestion.

With agonist/antagonist combinations, an opioid antagonist (such as naloxone or naltrexone) is added to the formulation. Naloxone has negligible absorption after oral administration, but higher bioavailability for blockade of euphoric effects of opioids following intranasal administration or injection. Naltrexone is orally bioavailable and therefore needs to be sequestered in an oral formulation to minimize or prevent absorption from the GI tract during normal use. When used as prescribed – that is, when the product is swallowed whole or the pellets are sprinkled on food, there is no notable antagonistic effect. However, if the formulation is manipulated (e.g., crushed or chewed), the sequestered naltrexone is released, mixes with the opioid and, after being absorbed, blocks opioid receptors, which decreases the opioid euphoric and other reinforcing effects sought by the abuser. However, this may result in opioid withdrawal symptoms in opioid-dependent individuals [49–52]. Inadvertent manipulation, for example, accidental chewing, can also release the antagonist and precipitate withdrawal symptoms and reduce analgesic efficacy in compliant patients.

The aim of aversive agents is to induce unpleasant effects if the formulation is manipulated before administration or if multiple doses are consumed. Proposed aversive agents include laxatives, emetics, nauseants and bittering agents to discourage manipulation and oral overconsumption; and mucous membrane irritants to deter snorting, inhalation and/or parenteral administration. An IR formulation of oxycodone with niacin (Acurox®, Acura Pharmaceuticals, Inc.) was not approved by the US FDA due to concerns about the ease with which it was possible to circumvent the potential abuse-deterrant

<table>
<thead>
<tr>
<th>ADF technology</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical and chemical barriers</td>
<td>May prevent chewing, crushing, grating or grinding</td>
<td>Does not deter abuse of intact tablets</td>
</tr>
<tr>
<td></td>
<td>May prevent accidental crushing or chowing in compliant patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td>May resist extraction by solvents</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No adverse effects in compliant patients</td>
<td></td>
</tr>
<tr>
<td>Agonist/antagonist combinations</td>
<td>Antagonist may be formulated to be clinically active only when manipulated</td>
<td>Inadvertent chewing or crushing may reduce analgesic effects and/or precipitate side effects or opioid withdrawal symptoms</td>
</tr>
<tr>
<td></td>
<td>May curb euphoria when formulation is compromised</td>
<td></td>
</tr>
<tr>
<td>Aversion</td>
<td>Aversive agents may be combined with the opioid to create unpleasant side effects when manipulated or taken at higher doses</td>
<td>Potential for unpleasant adverse effects in compliant patients who take product as intended</td>
</tr>
<tr>
<td></td>
<td>May prevent abuse by chewing or crushing</td>
<td>Adverse effects with intact tablets may prevent legitimate dose increases</td>
</tr>
<tr>
<td></td>
<td>May limit abuse of intact tablets</td>
<td>Adverse effects may not be sufficient to deter a motivated abuser</td>
</tr>
<tr>
<td>Delivery system</td>
<td>The method of drug delivery can offer resistance to abuse (e.g., depot formulations or subcutaneous implants)</td>
<td>It may still be possible to extract the opioid from the formulation</td>
</tr>
<tr>
<td>Prodrug</td>
<td>A prodrug that lacks opioid activity until transformed in the GI tract may be unattractive for intravenous or intranasal routes of abuse</td>
<td></td>
</tr>
<tr>
<td>Combination</td>
<td>A combination of two or more of the above approaches</td>
<td></td>
</tr>
</tbody>
</table>

ADF: Abuse-deterrent formulation.

Data taken from [45].

Table 1. Advantages and limitations of current ADF technologies.
effects of niacin, as well as the risk of side effects at therapeutic doses when used as prescribed [53]. The niacin was included to induce unpleasant flushing and other adverse reactions at excess doses; however, co-administration of food, aspirin and NSAIDs was found to attenuate these effects. A modified formulation containing an irritant instead of niacin to deter nasal administration was subsequently approved by the FDA (Oxecta™, Pfizer, Inc.).

Prodrugs are biologically inactive substances that are metabolized inside the body to their active form. A prodrug that lacks opioid activity until it has been metabolized in the GI tract may prevent abuse via other routes of administration [53]. No currently available opioid ADFs use this approach; however, stimulant medications formulated as prodrugs are available (e.g., Vyvanse® [lisdexamfetamine], Shire Pharmaceuticals). Large-scale, postmarketing data concerning the abuse liability of this formulation are beginning to emerge, with available data showing the rate of nonmedical use of the prodrug formulation to be lower than that of short-acting stimulants and lower than or equivalent to long-acting stimulant formulations [54].

It may also be possible to formulate opioids for delivery in ways that may deter abuse, for example, as subcutaneous implants, depot injectable formulations, beads within a capsule and erodible matrix technology. Such drug delivery systems are intended to release the opioid slowly over time and are inherently difficult to manipulate.

**Current regulatory guidelines for ADF evaluation**

Regulatory authorities recognize that the availability of ADFs represents an important component of programs developed to address prescription opioid analgesic abuse [45,55]. The FDA guidance policy on abuse-deterrent opioid analgesics provides guidance on studies that should be conducted to demonstrate that a formulation has abuse-deterrent properties, details how those studies will be evaluated, and outlines what labeling claims may be proposed based on the results of those studies [45]. Four categories of studies are required for comprehensive product evaluation (Table 2): laboratory-based *in vitro* manipulation and extraction studies (Category 1), pharmacokinetic studies (Category 2), clinical abuse potential studies (Category 3) and postmarketing epidemiologic studies to determine whether use of the ADF results in a significant reduction in abuse in the community compared with conventional opioid analgesic formulations (Category 4).

The aim of Category 1 studies is to assess the ease with which the potential abuse-deterrent properties of the formulation can be overcome or compromised. These studies should consider not only how abusers may attempt to overcome the abuse-deterrent properties of the medication, but also the ways in which patients may intentionally or unintentionally alter the formulation in order to change the rate or amount of opioid released (e.g., dose dumping may occur when taking the product with alcohol or when the product is cut, chewed or crushed). The routes of abuse most likely to be used and the manipulation methods that would yield the greatest release of opioid should be used for Category 2 and 3 assessments. The effects of food and alcohol on the pharmacokinetic properties of the formulation should also be assessed. Category 4 studies represent the ultimate demonstration of ADF effectiveness; however, it may take several years to collect sufficient data to demonstrate epidemiologic impact for an individual ADF.

The FDA guidance recognizes the importance of including information on abuse-deterrent properties in the product label in order to appropriately inform healthcare professionals and the patient. The FDA suggests that the product label should not only detail the results of *in vitro*, pharmacokinetic, clinical abuse potential and formal postmarketing studies, but also describe the specific abuse-deterrent product features in order to appropriately characterize the abuse-deterrent properties of the product.

The draft guidelines for regulation of tamper-resistant formulations issued by Health Canada are broadly similar to those from the FDA [55]. Other countries have not yet issued written guidance despite increasing awareness of the problem of abuse of prescription opioid analgesics worldwide [21,29-33].

**Current status of opioid analgesic ADFs**

There are currently six opioid pain medications with an FDA ADF label (Table 3). In April 2013, OxyContin® (Purdue Pharma LP) was the first opioid pain medication to be given an ADF label in the USA; it has also been available in Canada as OxyNEO® since August 2011 and in Australia as OxyNEO® since April 2014. This product is a reformulation of a controlled-release
formulation of oxycodone and has physical and chemical properties intended to deter manipulation for the purposes of oral and intranasal abuse by making tablet crushing both more difficult and less effective. The formulation is also resilient to ethanol dose dumping and other chemical extraction techniques. If attempts are made to dissolve the tablet, it gradually forms a viscous gel that resists passage through a hypodermic needle, thus deterring intravenous abuse. Studies have shown this ADF to be less attractive to recreational drug abusers than the original ER formulation [56–58]. Both rate and extent of oxycodone absorption have been shown to be reduced following intranasal administration of reformulated OxyContin compared with the original formulation [57]. The reformulated OxyContin provides the same therapeutic benefits as the original formulation, which was approved by the FDA in 1995. Shipping of the original controlled-release formulation of OxyContin to wholesalers stopped in August 2010. The FDA withdrew the new drug application (NDA) for the original formulation for reasons of safety in April 2013, thereby preventing generic ER oxycodone products without an ADF from entering the market.

Approved with ADF labeling in July 2014, Targiniq™ ER (Purdue Pharma LP) contains oxycodone combined with naloxone – an antagonist that blocks the euphoric effects of oxycodone if the tablet is crushed for snorting or manipulated for injection [59]. The safety and effectiveness of Targiniq ER have been demonstrated in three large, 12-week, randomized, double-blind Phase III trials in patients with moderate-to-severe chronic noncancer pain [60]. However, Targiniq ER has not yet been marketed.

In October 2014, Embeda® (Pfizer, Inc.) became the third opioid analgesic to meet FDA requirements for ADF labeling. Embeda was first approved in 2009, but was voluntarily withdrawn from the market in March 2011 due to testing that found stability concerns in the manufacturing process; it was relaunched in the USA in 2015. Embeda comprises pellets of morphine sulfate, each containing a core of sequestered naltrexone that is intended to remain sequestered when the product is taken as prescribed [61]. Studies performed in nondependent recreational opioid users have indicated that the quantity of naltrexone released upon manipulation is sufficient to attenuate the desired subjective effects of morphine following oral, intranasal or intravenous administration [52,62,63].

Hysingla® ER (Purdue Pharma LP) is a once-daily formulation of hydrocodone that does not contain acetaminophen; overdose of acetaminophen is a leading cause of acute liver failure [64]. Approved in November 2014, this formulation has physical and chemical properties that render it difficult to crush, break or dissolve; these abuse-deterrent properties are expected to deter misuse and abuse via chewing, snorting and injection. Phase III studies have demonstrated the efficacy and safety of this ADF in individuals previously receiving hydrocodone/acetaminophen combination therapy for chronic pain [65]. This formulation was also shown to be well tolerated and effective for the long-term treatment of moderate-to-severe chronic noncancer pain in a 12-month open-label study [66].

MorphaBond™ ER (Inspirion Delivery Technologies), an ER formulation of morphine, is designed to present multiple barriers to abuse through widely used methods of physical and chemical manipulation without the use of antagonists or aversive agents. Laboratory test data show that, relative to morphine sulfate ER

<table>
<thead>
<tr>
<th>Category</th>
<th>Study type</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Laboratory-based in vitro manipulation and extraction studies</td>
<td>To assess the ease with which the potential abuse-deterrent properties of the formulation can be overcome or compromised</td>
</tr>
<tr>
<td>2</td>
<td>Pharmacokinetic studies</td>
<td>To evaluate the in vivo properties of the formulation by comparing the pharmacokinetic profiles of intact versus manipulated formulations using one or more routes of administration</td>
</tr>
<tr>
<td>3</td>
<td>Clinical abuse potential studies</td>
<td>To assess the relative abuse potential of the formulation to predict how attractive it is likely to be to abusers; usually conducted in a drug-experienced population</td>
</tr>
<tr>
<td>4</td>
<td>Postmarketing epidemiologic studies</td>
<td>To determine whether use of the potential ADF results in a significant reduction in abuse in the community compared with conventional opioid formulations</td>
</tr>
</tbody>
</table>

ADF: Abuse-deterrent formulation.
Data taken from [45].
Abuse-deterrent formulations of prescription opioid analgesics

Review

In November 2015, the FDA granted tentative approval of Xtampza ER for the management of patients with moderate-to-severe chronic low back pain, with significant improvement in pain scores in patients with moderate-to-severe osteoarthritis or chronic low back pain [70]. In November 2015, the FDA granted tentative approval of Xtampza ER for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate [71].

The microsphere design is also intended to enable patients with difficulty in swallowing to open the capsule and administer the contents sprinkled on food or via a feeding tube, while maintaining the ER properties of the drug [68]. Studies have shown that this formulation maintains its ER profile when crushed, making it less attractive to potential abusers [69]. In a Phase III study in opioid-naïve and opioid-experienced adults with moderate-to-severe chronic low back pain, patients receiving Xtampza ER had statistically significantly lower pain scores after 12 weeks [70]. In November 2015, the FDA approved Xtampza ER [67].

Xtampza ER™ (Collegium Pharmaceuticals) is an ER oxycodone microsphere-in-capsule formulation utilizing proprietary DETERx® technology. It has been developed primarily as an ADF to protect against common methods of manipulation such as chewing, crushing, insufflation and extraction for intravenous injection. The microsphere design is also intended to enable patients with difficulty in swallowing to open the capsule and administer the contents sprinkled on food or via a feeding tube, while maintaining the ER properties of the drug [68]. Studies have shown that this formulation maintains its ER profile when crushed, making it less attractive to potential abusers [69]. In a Phase III study in opioid-naïve and opioid-experienced adults with moderate-to-severe chronic low back pain, patients receiving Xtampza ER had statistically significantly lower pain scores after 12 weeks [70].

The FDA is currently reviewing a number of other potential opioid ADFs (Table 4). ALO-02 (Pfizer, Inc.) comprises pellets of ER oxycodone surrounding sequestered naltrexone, similar to Embeda. Crushed ALO-02 administered intranasally to nondependent recreational opioid users resulted in significantly lower drug-liking scores versus crushed IR oxycodone, suggesting lower potential for abuse [72]. ALO-02 has been shown to be effective in patients with chronic noncancer pain or chronic low back pain, with a safety profile similar to other opioids [73,74].

CEP-33237 (TEVA Pharmaceutical Industries, Ltd) is an acetaminophen-free ER formulation of hydrocodone incorporating proprietary CIMA® abuse-deterrence technology utilizing multiple polymers in three mechanisms of protection via a granulation and particle-coating process [75]. CEP-33237 is designed to deter abuse via milled or crushed oral, nasal and intravenous administration and prevents dose dumping when co-administered with alcohol [76]. CEP-33237 has yielded positive results in oral and intranasal human abuse-liability studies in nondependent, recreational opioid users [77,78]. In Phase III clinical trials, CEP-33237 was shown to provide significant improvement in pain scores in patients with moderate-to-severe osteoarthritis or chronic low back pain [79,80]. CEP-33237 demonstrated a safety profile in these studies that was consistent with the known safety profile of hydrocodone and other opioid pain medications.

NKTR-181 (Nektar Therapeutics) is a μ-opioid receptor agonist with a novel molecular structure, engineered using small molecule polymer–conjugate technology. It appears to enter the CNS at a substantially lower rate than

Table 3. Currently available opioid analgesics with a US FDA abuse-deterrent formulation label (as of January 2016).

<table>
<thead>
<tr>
<th>Drug</th>
<th>ADF approach</th>
<th>Abuse-deterrent properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>OxyContin® (oxycodone)</td>
<td>Physical and chemical barriers</td>
<td>Difficult to crush or break; resistant to ethanol dose dumping and other chemical extraction techniques; forms a viscous gel when dissolved</td>
</tr>
<tr>
<td>Targiniq™ ER (oxycodone/naltrexone)</td>
<td>Agonist/antagonist combination</td>
<td>Naloxone exhibits extremely low oral bioavailability due to significant first-pass hepatic metabolism, and therefore has very little effect if the product is taken orally as prescribed. Naloxone is absorbed if administered intranasally or intravenously, blocking the euphoric effects of oxycodone</td>
</tr>
<tr>
<td>Embeda® (morphine/naltrexone)</td>
<td>Agonist/antagonist combination</td>
<td>Upon manipulation, naltrexone is released and blocks the euphoric effects of morphine</td>
</tr>
<tr>
<td>Hysingla® ER (hydrocodone)</td>
<td>Physical and chemical barriers</td>
<td>Difficult to crush or break; resistant to ethanol dose dumping and other chemical extraction techniques; forms a viscous gel when dissolved</td>
</tr>
<tr>
<td>MorphaBond™ ER (morphine sulfate)</td>
<td>Physical and chemical barriers</td>
<td>Designed to present multiple barriers to abuse through widely used methods of physical and chemical manipulation, as well as various routes of administration; does not contain an opioid antagonist</td>
</tr>
<tr>
<td>Xtampza ER™ (oxycodone)</td>
<td>Physical and chemical barriers</td>
<td>Designed to protect against common methods of manipulation, such as chewing, rushing, insufflation, and extraction for intravenous injection</td>
</tr>
</tbody>
</table>

ADF: Abuse-deterrent formulation; ER: Extended release.
Table 4. Potential opioid analgesic abuse-deterrent formulations under review by the US FDA (as of January 2016).

<table>
<thead>
<tr>
<th>Drug</th>
<th>ADF approach</th>
<th>Abuse-deterrent properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALO-02 (oxycodeone/naltrexone)</td>
<td>Agonist/antagonist combination</td>
<td>Upon manipulation, naltrexone is released and blocks the euphoric effects of morphine</td>
</tr>
<tr>
<td>CEP-33237 (hydrocodone)</td>
<td>Physical and chemical barriers</td>
<td>Designed to deter abuse via crushed oral, nasal and intravenous administration; prevents dose dumping when co-administered with alcohol</td>
</tr>
</tbody>
</table>

ADF: Abuse-deterrent formulation.

A growing body of evidence suggests that introduction of opioid ADFs has been associated with decreased rates of abuse and diversion of these formulations in the USA [56,58,82–89]. In one study, an 87% reduction in overdose deaths was reported during the 3-year period following introduction of the abuse-deterrent reformulation of OxyContin [90]. Cost savings have also been reported to be associated with reductions in abuse following the introduction of the abuse-deterrent reformulation of OxyContin in the USA [89,91,92]. It has been estimated that reformulated oxycodone is associated with annual medical cost savings of US$430 million and indirect cost savings of US$605 million, giving total annual societal cost savings of approximately US$1.0 billion [91]. The societal cost savings associated with reductions in prescription opioid analgesic abuse may be expected to increase with the introduction of other ADFs.

In some studies, however, these benefits appear to have been accompanied by a significant increase in abuse of other opioids, most notably heroin [84,87,88,93,94]. In one recent study, although the estimated overdose rate attributed to prescription opioid analgesics decreased by 20% during the 2 years after introduction of the abuse-deterrent reformulation of OxyContin, heroin overdose rates increased by 23% during the same period of time [88]. In another study utilizing Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) System data, rates of heroin-related deaths during 2011–2013 appeared to be inversely related to the availability of prescription opioid analgesics [88]. Such findings suggest that there is a risk that individuals may switch to abusing other prescription opioid analgesics without abuse-deterrent properties or to abusing illicit heroin. ADFs are not a treatment for addiction and it is to be expected that individuals who are addicted to opioids would switch to other opioids if their drug of choice was reformulated. However, it should be noted that rates of heroin abuse in the USA began to rise before the introduction of opioid ADFs [95]. This suggests that other factors such as increased availability and reduced costs may also have contributed to this increase, particularly since non-ADFs of prescription opioid analgesics remain widely available. Early findings from the Australian NOMAD study show that introduction of the abuse-deterrent reformulation of OxyContin in Australia was associated with a reduction in abuse by injection, with no clear switch to other drugs [96].

Conclusion & future perspective
Opioid analgesics are effective therapies for the management of chronic noncancer pain; however, the potential for abuse and diversion of these medications is a major public health concern worldwide. Strategies to minimize abuse and diversion of prescription opioid analgesics include educational and regulatory initiatives, as well as the development of novel formulations with abuse-deterrent properties.

The science of abuse deterrence and the regulatory landscape are still relatively new and evolving. Currently available opioid ADFs have been shown to be associated with significant reductions in rates of abuse and diversion of these formulations in real-world settings, although in
some studies, this has been accompanied by an increase in rates of heroin abuse and overdose. Furthermore, although currently available ADFs may prevent patients progressing to abuse via non-oral routes of administration, abuse by over-ingestion of the intact formulation is still possible. Concerns have also been expressed that the potential additional costs associated with opioid ADFs could impede access to these medications for patients with legitimate medical needs [95]. Payers may be reluctant to give preferential formulary status to branded ADFs over existing non-AD generic formulations.

ADFs clearly have particular potential benefits for certain groups of patients, such as those with a history of addiction or substance abuse, and those who live with current or recovering addicts, or with individuals who may be more likely to seek opioids for recreational use (e.g., teenagers or young adults). However, clinicians may decide to be nonselective when prescribing ADFs so as not to appear to discriminate between patients.

Financial & competing interests disclosure
M Hale is a principal investigator on clinical trials sponsored by TEVA Pharmaceutical Industries and has served as a consultant to TEVA Pharmaceutical Industries. D Moe is an employee of CIMA Labs, Inc., a subsidiary of TEVA Pharmaceutical Industries. M Bond, M Gasior and R Malamut are employees of TEVA Pharmaceutical Industries. Other TEVA personnel provided a single medical accuracy review of the final draft. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing assistance was utilized in the production of this manuscript and was provided by Jennifer Coward of Anhemis Consulting, funded by TEVA Pharmaceutical Industries, Frazer, PA, USA.

Open access
This work is licensed under the Creative Commons Attribution-NonCommercial 4.0 Unported License. To view a copy of this license, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

Consensus recommendations on classification and definition of abuse terminology.

References
Papers of special note have been highlighted as:
• of interest; •• of considerable interest
Systematic review on the misuse of analgesics, opioid substitution medicines and sedatives/hypnotics in Europe between 2001 and 2011.


Substance Abuse and Mental Health Services Administration. Results from the 2013 national survey on drug use and health: summary of national findings (2014). www.samhsa.gov


Recent comprehensive review on methods and routes of abuse of prescription opioid analgesics.

Abuse-deterrent formulations of prescription opioid analgesics


• Draft Canadian guidelines concerning the development and labeling of abuse-deterrent opioid formulations.


• Analysis of data from the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS) System to describe trends in the diversion and abuse of prescription opioid analgesics from January 2002 through December 2013.


• Analysis of the impact of the availability of an abuse-deterrent formulation of oxycodone on abuse rates and routes of abuse.
• Overview of abuse-deterrent formulations as a method to reduce prescription opioid abuse, including policy recommendations for transitioning the market.