

EVENT REPORT FORM

Project title	Strengthening Capacities for Higher Education of Pain Medicine in Western Balkan countries
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Event	Modern approaches to the diagnosis and treatment of pain
Type of event	WP5 (Project dissemination) WP5.3. Promotion of HPMP Program: Seminars
Venue	Banja Slatina, Banjaluka
Date	11.05.2019. godine
Organizer	Faculty of Medicine, Banjaluka
Reporting date	05.07.2020.
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EVENT DESCRIPTION

with special reference to goals and outcomes

Number of participants at the event	30
Participants (organisations)	University Clinical Center Banjaluka, Institute for Rehabilitation “Dr Miroslav Zotović” Banjaluka, Primary Health Care Center Banjaluka
Event description:	

The main objective was to point out new guidelines in the diagnosis and treatment of acute and chronic pain and deliver it to health care professionals in Primary and Higher levels of Health Care Centers in Banjaluka, Republic of Srpska. The participants of the seminar are family doctors, surgeons, physiatrists, anesthesiologists and psychologists. After the development of the training material, selection of trainees, and accreditation of the course by The Ministry of Health and Social Welfare, the course was held for the purpose to give modern guidelines regarding acute and chronic pain management considering that undergraduate studies do not include modules of pain medicine.

Objectives of the course:

- A historical review of pain
- Understanding and importance of treatment of acute and chronic pain
- Teach participants how to treat acute and chronic pain
- Teach participants how to treat cancer pain
- Learn the mechanism of action of oral opioids and their administration
- Get acquainted with non-pharmacological methods of pain treatment
- Learn what are the invasive procedures for treating acute postoperative and chronic pain

Description of activities -

After drawing up a draft of educational material, eight lectures were selected who, each in the area for which they were delegated, wrote the material and made a presentation. The overall educational material is systematized, prepared in a demanding format and sent for the printing of the handbook received by all participants. Educational event was accredited as a first category seminar with the high number of CME points. The accreditation notice is posed by mail, the pdf version of which is enclosed with this document. A flyer was prepared in which a Program of events was presented, as well as decision on accreditation. In addition, the leaflet was sent in the form of a call to potential participants. In addition to Banja Luka, the lecturers were from Osijek (Croatia) and Novi Sad (Serbia).

The Seminar started from 10,00 p.m. by the participants registration. The Project Coordinator of the University of Banjaluka, professor Bucma, welcomed the audience and announced a session on acute and chronic pain and emphasized the importance of the course and understanding of the issues related to the treatment of acute and chronic pain. He highlighted the importance of the participation of the Faculty of Medicine in Banjaluka in this project, as well as the importance of the topic being dealt with. Prof. Bucma, said that he welcomed all the people present

and stressed the importance of the project and the implementation of health care education activities on the issue of pain, which is very significant but often insufficiently understood. Then there was an introductory lecture through which the participants were introduced to the HEPMP project, its goals and tasks.

Mira Fingler: Clinical approach to diagnosis, pathophysiology and treatment of neuropathic pain.

The lecture emphasizes the modern approach in the diagnosis and treatment of neuropathic pain, with special emphasis on clinical significance. Neuropathic pain is associated with impaired quality of life, and is often poorly managed. Around 7–8% of adults have pain with neuropathic characteristics. A quarter of people with diabetes and 35% of people with HIV have neuropathic pain.

The management of neuropathic pain can be challenging and, as with all pain, should be approached with a biopsychosocial framework. There are several options for drug treatment as part of an overall approach to improve patients' quality of life and function.²

International guidelines have clarified the definition of neuropathic pain and updated their recommendations for drug treatment based on evidence from a systematic review and meta-analysis. Being aware of these changes is important in the clinical assessment and treatment.

Neuropathic pain is now defined by the International Association for the Study of Pain (IASP) as 'pain caused by a lesion or disease of the somatosensory nervous system'. This replaces the older definition of 'pain initiated or caused by a primary lesion, dysfunction or transitory perturbation of the peripheral or central nervous system'.

The definition was reviewed and updated because the term dysfunction in the old definition was thought to be over-inclusive and did not reflect the pathophysiology. Additionally, neuropathic pain is not one disease entity but a number of diseases or lesions with a cluster of symptoms and signs, where understanding of pathophysiology is evolving.

Proponents of the change believe it has greater scientific rigour. It removes confusion around pain arising as a result of disease within the nervous system but outside the somatosensory system, for example pain from muscle spasticity. It now excludes syndromes where pathophysiology is unclear, such as fibromyalgia or complex regional pain syndrome, which is controversial and has been perceived by some to be overly restrictive.

The primary disease management of neuropathic pain needs to consider the individual as a whole. For instance, in patients with diabetic neuropathy, erratic glycaemic control worsens symptoms and improving glycaemic control may reduce progression of neuropathy. However, there is increased mortality with intensive insulin regimens in patients with established diabetic neuropathy compared to

patients without neuropathy.⁷ HIV associated neuropathy presents an even more complex picture – starting antiretrovirals may initially improve symptoms although nerve damage may progress. Some antiretrovirals can cause neuropathy, and neurotoxicity may be a feature of concomitant medicines such as isoniazid for tuberculosis.

The IASP’s Neuropathic Pain Special Interest Group (NeuPSIG) has recently undertaken a systematic review of medicines for neuropathic pain.⁸ Fibromyalgia, atypical facial pain, complex regional pain syndrome and chronic low back pain without radiculopathy were not included in the review as they do not meet the current criteria for the definition of neuropathic pain.

The review included tricyclic antidepressants, serotonin and noradrenaline reuptake inhibitors (SNRIs), antiepileptic drugs, opioids, topical lidocaine (lignocaine), capsaicin high-concentration patches and oromucosal cannabinoids. A number of overarching themes were identified:

- most studies were conducted in diabetic neuropathy or postherpetic neuralgia
- publication bias accounted for approximately 10% of the treatment effect
- placebo effect was large
- drug effects were modest⁴
- data did not identify that one particular drug or drug class was superior in any particular neuropathic pain syndrome
- the majority of studies were for 12 weeks or less
- data were limited to non-cancer pain in adults.

Recommendation	Drugs
First-line	SNRI - duloxetine, venlafaxine Tricyclic antidepressants Gabapentin, pregabalin
Second-line	Capsaicin 8% patches Lidocaine (lignocaine) patches Tramadol
Third-line	Strong opioids

SNRI serotonin noradrenaline reuptake inhibitors

Tricyclic antidepressants and SNRIs were effective in reducing pain. Amitriptyline was the most studied tricyclic antidepressant (daily doses 25–150 mg) and did not show a dose-response effect. Seven of nine studies with duloxetine 20–120 mg were positive, while two of four studies identified efficacy with venlafaxine 150–225 mg daily. The negative venlafaxine studies were at lower doses. Most trials with pregabalin (18/25) showed improvement in neuropathic pain, and the effect was greater with larger doses. Pregabalin in HIV neuropathy was no better than placebo. However, the placebo was very effective. Gabapentin was also found to be effective, although no dose response was identified. The number needed to harm was 13.9 for pregabalin and 25.6 for gabapentin. Other antiepileptic

drugs had minimal evidence of efficacy, and topiramate, carbamazepine and oxcarbazepine had a poor safety profile.

Tramadol consistently showed efficacy, while tapentadol had very limited supporting data. With morphine or oxycodone, 10 of 13 trials showed benefit, with no benefit in increasing the dose beyond 180 mg daily oral morphine equivalents.

There were some limited data suggesting the efficacy of lidocaine (lignocaine) 5% patches, with good safety and tolerability. Although registered, this product is not available on the Pharmaceutical Benefits Scheme (PBS) so may be prohibitively expensive for patients.

For postherpetic neuralgia and HIV neuropathy, a high-concentration (8%) capsaicin patch demonstrated efficacy over a low-dose (0.04%) patch.

Darko Golić: Opioid in pain therapy

The promotion pointed out the importance of opioids in the treatment of pain, but also the importance of abuse.

Opioids have been regarded for millennia as among the most effective drugs for the treatment of pain. Their use in the management of acute severe pain and chronic pain related to advanced medical illness is considered the standard of care in most of the world. In contrast, the long-term administration of an opioid for the treatment of chronic non-cancer pain continues to be controversial. Concerns related to effectiveness, safety, and abuse liability have evolved over decades, sometimes driving a more restrictive perspective and sometimes leading to a greater willingness to endorse this treatment. The past several decades in the United States have been characterized by attitudes that have shifted repeatedly in response to clinical and epidemiological observations, and events in the legal and regulatory communities. The interface between the legitimate medical use of opioids to provide analgesia and the phenomena associated with abuse and addiction continues to challenge the clinical community, leading to uncertainty about the appropriate role of these drugs in the treatment of pain. This narrative review briefly describes the neurobiology of opioids and then focuses on the complex issues at this interface between analgesia and abuse, including terminology, clinical challenges, and the potential for new agents, such as buprenorphine, to influence practice.

The term *opioid* refers to all compounds that bind to opiate receptors. Conventionally, the term *opiate* can be used to describe those opioids that are alkaloids, derived from the opium poppy; these include morphine and codeine. Opioids include semi-synthetic opiates, i.e., drugs that are synthesized from naturally occurring opiates (such as heroin from morphine and oxycodone from thebaine), as well as synthetic opioids such as methadone, fentanyl, and propoxyphene. The term *narcotic* is a legal designation and should not be used in the clinical setting; it refers to opioids and a few other drugs that are grouped with the opioids by law enforcement.

In the United States, numerous opioids have been commercialized for oral, transdermal and intravenous administration. Oral and transdermal formulations are usually administered for

pain in the ambulatory setting. These include combination products, such as those containing hydrocodone and acetaminophen (Vicodin®, Lorset®) or ibuprofen (Vicoprofen®), tramadol and acetaminophen (Ultracet®), oxycodone and acetaminophen or aspirin (Percocet® or Percodan®), and those containing codeine and acetaminophen or aspirin. The single entity formulations on the market include those containing morphine (Avinza®, Kadian®, MS Contin®, MSIR®), oxycodone (OxyContin®), fentanyl (Duragesic®, Actiq®, Fentora®), hydromorphone (Dilaudid®), oxymorphone (Opana®), and methadone.

Opioids act by binding to specific proteins, called opioid receptors. Receptors are widely distributed. Those involved in pain modulation are situated in both the central nervous system and the peripheral nervous system. These receptors also bind endogenous opioid peptides (endorphins), which are involved in pain modulation and numerous other functions in the body. Among these functions are those mediated by deep structures of the brain, which are involved in the modulation of reinforcement and reward mechanisms, mood and stress. Opioid receptors are also found on cells from the immune system ([Bidlack, 2000](#)). In studies with rats, activation of these receptors with morphine is associated with varied effects, including sensitization of afferent nerves to noxious stimuli ([Raghavendra, Rutkowski, & DeLeo, 2002](#)).

When an opioid given for pain binds to receptors, analgesia may be accompanied by any of a diverse array of side effects related to the activation of receptors involved in other functions. These may include effects mediated by peripheral or by peripheral and central mechanisms, such as reduced peristalsis (leading to constipation) and itch, or primary central nervous system effects, such as miosis, (pupillary constriction) somnolence, mental clouding, and respiratory depression ([Jaffe & Jaffe, 2004](#); [Jaffe & Martin, 1990](#)). Central mechanisms also lead to changes associated with hyperalgesia and decreased responsiveness to opioids (tolerance) and it has been speculated that opioid-induced hyperalgesia may be a clinically-relevant phenomenon leading to increased pain in some situations ([Deleo, Tanga, & Tawfik, 2004](#)). Activation of other central nervous system pathways by opioids also may produce mood effects, either dysphoria or euphoria.

Presumably, binding to those receptors involved in reinforcement and reward also occurs whenever an opioid is taken. In most individuals, when opioids are taken to treat pain, there appears to be no overt effect from change in these systems. In some cases, however, powerful reinforcement occurs, expressed as efforts to repeat the administration and these reinforcing outcomes may be associated with craving and with positive mood effects such as euphorogenic or pleasurable effects ([Di Chiara, 2002](#); [Koob & Bloom, 1988](#)). These outcomes, which are uncommon but potentially serious when they occur (driving the development of an addictive pattern of use), can occur in the presence or absence of pain. Although these effects could be associated with iatrogenic addiction, they appear to be rare in patients who do not have risk factors suggesting the existence of the biological substrate for opioid-induced craving (see below).

Although several types of opioid receptors exist (e.g., mu, kappa and delta), opioid drugs largely produce their analgesic and reinforcing effects via activation of the mu opioid receptor; thus, opioids used for pain are often described as, “mu agonists”. Mu drugs that have the ability to fully activate opioid receptors (e.g., higher doses produce greater receptor activation in a dose-dependent manner) are referred to as opioid agonists or full mu agonists (such as morphine, oxycodone and methadone). Those opioids that occupy, but do not activate, receptors are referred to as opioid antagonists (e.g., naltrexone, naloxone); they can reverse the effects of mu opioid agonists. Those opioids that either have a low intrinsic

activity at the mu receptor, or are agonists at another receptor and antagonists at the mu receptor are called agonist-antagonist drugs. Those with a low intrinsic activity are called partial opioid agonists and are characterized by a ceiling on most agonist activity, such that increases in dose will increase the drug's physiological and subjective effects only to a certain level and further dose increases produce no additional effects ([Jaffe & Martin, 1990](#)).

These differences in mu receptor interactions are clearly related to the clinical use of opioid drugs and their abuse liability. Agonist-antagonist drugs are less attractive than pure mu agonists to individuals with addiction and no pain. Although other biochemical and molecular processes are presumably relevant to variation in these effects, relatively little is known about the interactions among these processes in humans.

The clinical use of opioid drugs is influenced by a variety of other characteristics, including pharmacokinetics. With the notable exception of methadone and buprenorphine, most opioids have relatively short half-lives and this has necessitated the development of new delivery systems designed to provide prolonged effects and a longer dosing interval.

Clinically-relevant physical dependence and tolerance (see below) may occur with short-term or long-term use of an opioid compound, particularly a pure mu agonist. These phenomena, which vary greatly in the clinical setting, represent neuroadaptational processes. The neurophysiology of physical dependence and tolerance are closely related to each other and to the phenomenon of opioid-induced hyperalgesia ([Mao, 2002](#)). The possibility that opioid administration, particularly at relatively high doses, may lead to increased pain has contributed to the controversy about opioid therapy for non-cancer pain, notwithstanding the limited evidence that this phenomenon occurs in clinical settings.

Concerns that addiction is a frequent iatrogenic consequence of the medical use of opioids may partially be attributed to confusion over terminology, as well as failure to recognize that both addiction and chronic pain have a multifactorial etiology. In an effort to develop universal agreement on terminology related to addiction, the American Academy of Pain Medicine (AAPM), the American Pain Society (APS), and the American Society of Addiction Medicine (ASAM) approved a consensus document that clarified this terminology ([ASAM, 2001](#); [Savage, 2003](#)).

According to the consensus document, *tolerance* is defined as a decreased subjective and objective effect of the same amount of opioids used over time, which concomitantly requires an increasing amount of the drug to achieve the same effect. Although tolerance to most of the side effects of opioids (e.g., respiratory depression, sedation, nausea) does appear to occur routinely, there is less evidence for clinically significant tolerance to opioid-analgesic effects ([Collett, 1998](#); [Portenoy et al., 2004](#)). For example, there are numerous studies that have demonstrated stable opioid dosing for the treatment of chronic pain (e.g., [Breitbart, et al., 1998](#); [Portenoy et al., 2007](#)) and methadone maintenance for the treatment of opioid dependence (addiction) for extended periods ([Strain and Stitzer, 2006](#)). However, despite the observation that tolerance to the analgesic effects of opioid drugs may be an uncommon primary cause of declining analgesic effects in the clinical setting, there are reports (based on experimental studies) that some patients will experience worsening of their pain in the face of dose escalation ([Ballantyne, 2006](#)). It has been speculated that some of these patients are not experiencing more pain because of changes related to nociception (e.g. progression of a tissue-injuring process), but rather, may be manifesting an increase in pain as a result of the opioid-induced neurophysiological changes associated with central

sensitization of neurons that have been demonstrated in preclinical models and designated opioid-induced hyperalgesia ([Mao, 2002](#); [Angst & Clark, 2006](#)). Analgesic tolerance and opioid-induced hyperalgesia are related phenomena, and just as the clinical impact of tolerance remains uncertain in most situations, the extent to which opioid-induced hyperalgesia is the cause of refractory or progressive pain remains to be more fully investigated. *Physical dependence* represents a characteristic set of signs and symptoms (opioid withdrawal) that occur with the abrupt cessation of an opioid (or rapid dose reduction and/or administration of an opioid antagonist). Physical dependence symptoms typically abate when an opioid is tapered under medical supervision. Unlike tolerance and physical dependence which appear to be predictable time-limited drug effects, *addiction* is a chronic disease that “represents an idiosyncratic adverse reaction in biologically and psychosocially vulnerable individuals” ([ASAM, 2001](#)).

The distinction between physical dependence and addiction is not always made clear in the pain literature ([Ferrell, McCaffery, Rhiner, 1992](#)). Most patients who are administered opioids for chronic pain behave differently from patients who abuse opioids and do not ever demonstrate behaviors consistent with craving, loss of control or compulsive use (e.g., [Cowan et al., 2001](#)). Of course, pain and addiction are not mutually exclusive and some patients who are treated for pain do develop severe behavioral disturbances indicative of a comorbid addictive disorder.

Some patients who are treated with opioids for pain display problematic behaviors that, on careful assessment, do not reflect addiction, but rather, appear to relate to a different process. This may be another psychiatric disorder associated with impulsive drug-taking, an unresolved family issue, a disorder of cognition, or criminal intention. In addition, there appear to be some patients who engage in problematic behaviors related specifically to desperation about unrelieved pain. The term *pseudoaddiction* was coined to describe the latter phenomenon ([Weissman & Haddox, 1989](#)).

Behaviors that may represent pseudoaddiction and behaviors that reflect addiction or some other serious psychopathology can occur simultaneously, and presumably, one type of phenomenon may incite the others. The diagnosis of these and other conditions may be challenging and requires a careful assessment of clinical phenomenology, specifically a range of drug-related behaviors during treatment with a potentially abusable drug ([Portenoy, 1994](#), Lue, Passik, & Portenoy, 1998).

The term *aberrant drug-related behaviors* has been used to indicate the broad array of problematic nonadherence behaviors ([Passik, Kirsh, Donaghy, & Portenoy, 2006](#)), the nature of which is uncertain until a diagnosis can be developed based on astute clinical assessment. Some aberrant drug-related behavior strongly suggests the existence of addiction. These may include the use of alternative routes of administration of oral formulations (e.g., injection or sniffing), concurrent use of alcohol or illicit drugs, and repeated resistance to changes in therapy despite evidence of adverse effects; examples of aberrant behavior less suggestive of addiction are drug hoarding during periods of reduced symptoms, occasional unsanctioned dose escalation, and aggressive complaining about the need for more drugs ([Portenoy, 1994](#)).

Go to:

[Distinction between Withdrawal and Chronic Pain](#)

Because addiction is associated with psychological distress and physical discomfort in the form of opioid withdrawal symptoms, it may be difficult to distinguish primary chronic pain complaints from withdrawal pain. Withdrawal also may have the potential to increase baseline pain related to other processes. For example, based on anecdotal evidence from chronic pain patients, withdrawal from opioids can greatly increase pain in the original pain site. These phenomena suggest the need to carefully assess the potential for withdrawal during long-term opioid therapy (e.g., at the end of a dosing interval or during periods of medically-indicated dose reduction).

These phenomena notwithstanding, there also is evidence that experienced drug abusers are able to distinguish withdrawal pain from chronic pain. For example in studies of methadone maintenance patients, both the phenomenology and correlates of chronic pain were different than for withdrawal pain ([Karasz et al., 2004](#); [Rosenblum et al., 2003](#)). Chronic pain is typically localized (e.g., back pain, headache) and persists (although with varying degrees of severity) for long periods of time ([Gureje, Von Korff, Simon & Gater, 1998](#)). Although certain subjective experiences of withdrawal (e.g., muscle ache) are similar to some distinct pain syndromes, other withdrawal experiences such as yawning, sweating and hot and cold flashes are likely to be more commonly associated with subjective drug withdrawal than with primary pain conditions. Moreover, the constellation of words used to describe withdrawal pain is likely to be different than words used to describe other painful disorders. Qualitative studies of addicts going through withdrawal typically refer to the experience as “being sick” (similar to a moderate to severe flu-like illness) and not as representing a distinct pain ([Farrell, 1994](#)). The subjective experience of withdrawal can be validly measured with an instrument such as the Subjective Opiate Withdrawal Scale (SOWS; [Handelsman, et al., 1987](#)). Withdrawal from short-acting opioids, such as heroin, is typically short-lived; physical symptoms are likely to reach their maximum intensity over a 36–72 hour period and to reduce in intensity after that ([Farrell, 1994](#)).

Go to:

Co-occurring Chronic Pain and Opioid Addiction

The prevalence of addictive disorders among chronic pain patients is difficult to determine ([Covington and Kotz 2003](#)). One 1992 literature review found only seven studies that utilized acceptable diagnostic criteria and reported that estimates of substance use disorders among chronic pain patients ranged from 3.2% – 18.9% ([Fishbain, Rosomoff, & Rosomoff, 1992](#)). A Swedish study of 414 chronic pain patients reported that 32.8% were diagnosed with a substance use disorder ([Hoffmann, Olofsson, Salen, & Wickstrom, 1995](#)). In two US studies, 43 to 45% of chronic pain patients reported aberrant drug-related behavior; the proportion with diagnosable substance use disorder is unknown ([Katz et al., 2003](#); [Passik et al., 2004](#)). All these studies evaluated patients referred to pain clinics and may overstate the prevalence of substance abuse in the overall population with chronic pain.

A relatively high prevalence of substance abuse disorders among persons with chronic pain can also be inferred by the high co-occurrence of these two disorders. There have been several reports that the prevalence of chronic pain among persons with opioid and other substance use disorders is substantially higher than the pain prevalence found in the general population ([Breitbart, et al., 1996](#); [Brennan, Schutte, & Moos, 2005](#); [Jamison, Kauffman, & Katz, 2000](#); [Rosenblum et al., 2003](#); [Sheu, et al., 2008](#)).

Go to:

Opioid Treatment for Chronic Pain

Opioid therapy is the mainstay approach for the treatment of moderate to severe pain associated with cancer or other serious medical illnesses ([Patt & Burton, 1998](#); [World Health Organization, 1996](#)). Although the use of opioid analgesics for the treatment of CNMP has been increasing in recent years ([Joranson, Ryan, Gilson & Dahl, 2000](#)) and has been endorsed by numerous professional societies ([AAPM, APS, 1997](#); [American Geriatric Society, 1998](#); [Pain Society, 2004](#)), the use of opioids remains controversial due to concerns about side effects, long-term efficacy, functional outcomes, and the potential for drug abuse and addiction. The latter concerns are especially evident in the treatment of CNMP patients with substance use histories ([Savage, 2003](#)).

Other concerns that may contribute to the hesitancy to prescribe opioids may be related to perceived and real risks associated with regulatory and legal scrutiny during the prescribing of controlled substances ([Office of Quality Performance, 2003](#)). These concerns have propelled extensive work to develop predictors of problematic behaviors or frank substance abuse or addiction during opioid therapy. Questionnaires to assist in this prediction and monitoring have been developed and used in research and field trials. Examples include the Prescription Drug Use Questionnaire (PDUQ; [Compton et al., 1998](#)); the Pain Assessment and Documentation Tool (PADT; [Passik et al., 2004](#)) and the Current Opioid Misuse Measure (COMM; [Butler et al., 2007](#)). These instruments are not used in practice settings at this time.

Narrative reports on the use of opioids for CNMP have underscored the effectiveness of opioid therapy for selected populations of patients and there continues to be a consensus among pain specialists that some patients with CNMP can benefit greatly from long-term therapy ([Ballantyne & Mao, 2003](#); [Trescot et al., 2006](#)). This consensus, however, has received little support in the literature. Systematic reviews on the use of opioids for diverse CNMP disorders report only modest evidence for the efficacy of this treatment ([Trescot et al., 2006](#); [2008](#)). For example, a review of 15 double-blind, randomized placebo-controlled trials reported a mean decrease in pain intensity of approximately 30% and a drop-out rate of 56% only three of eight studies that assessed functional disturbance found improvement ([Kalso, Edwards, Moore, & McQuay, 2004](#)). A meta-analysis of 41 randomized trials involving 6,019 patients found reductions in pain severity and improvement in functional outcomes when opioids were compared with placebo ([Furlan, Sandoval, Mailis-Gagnon, & Tunks, 2006](#)). Among the 8 studies that compared opioids with non-opioid pain medication, the six studies that included so-called “weak” opioids (e.g., codeine, tramadol) did not demonstrate efficacy, while the two that included the so-called “strong” opioids (morphine, oxycodone) were associated with significant decreases in pain severity. The standardized mean difference (SMD) between opioid and comparison groups, although statistically significant, tended to be stronger when opioids were compared with placebo (SMD = 0.60) than when strong opioids were compared with non-opioid pain medications (SMD = 0.31). Other reviews have also found favorable evidence that opioid treatment for CNMP leads to reductions in pain severity, although evidence for increase in function is absent or less robust ([Chou, Clark, & Helfand, 2003](#); [Eisenberg, McNicol, & Carr, 2005](#)). Little or no support for the efficacy of opioid treatment was reported in two systematic reviews of chronic back pain ([Deshpande, Furlan, Mailis-Gagnon, Atlas, & Turk, 2007](#); [Martell, et al., 2007](#)). Because patients with a history of substance abuse typically are excluded from these studies, they provide no guidance whatsoever about the effectiveness of opioids in these populations.

Adding further to the controversy over the utility of opioid analgesics for CNMP is the absence of epidemiological evidence that an increase in the medical use of opioids has resulted in a lower prevalence of chronic pain. Noteworthy is a Danish study of a national random sample of 10,066 respondents ([Eriksen, Sjøgren, Bruera, Ekholm, & Rasmussen, 2006](#)). Denmark is known for having an extremely high national usage of opioids for CNMP and this use has increased by more than 600% during the past two decades ([Eriksen, 2004](#)). Among respondents reporting pain (1,906), 90% of opioid users reported moderate to very severe pain, compared with 46% of non-opioid users; opioid use was also associated with poor quality of life and functional disturbance (e.g., unemployment).

Although this epidemiological study may be interpreted as demonstrating that opioid treatment for CNMP has little benefit, the authors acknowledge that these disquieting findings do not indicate causality and could be influenced by the possibility of widespread undertreatment, leading to poorly managed pain. This latter interpretation is supported by a commentary on the Eriksen et al. study ([Keane, 2007](#)). Keane notes that among the 228 pain patients receiving opioids only 57 (25%) were using strong opioids, while the remainder was using weak opioids. European (as well as United States) clinical guidelines generally recommend long-acting formulations of strong opioids for the treatment of chronic moderate to severe pain, which may be supplemented with short-acting opioids for breakthrough pain ([Pain Society, 2004](#); [OQP, 2003](#); [Gourlay, 1998](#); [Vallerand, 2003](#); [Fine & Portenoy, 2007](#)).

The possibility of inappropriate opioid treatment is further supported by another Danish study that assigned pain patients who were on opioid therapy to either a multidisciplinary pain center (MPC) or to general practitioners (GP) who had received initial supervision from the MPC staff ([Eriksen, Becker, & Sjøgren, 2002](#)). At intake, a substantial number of patients in both groups were apparently receiving inappropriate opioid therapy for chronic pain (60% were being treated with short-acting opioids and 49% were taking opioids on demand). At the 12 month follow-up, 86% of MPC patients were receiving long-acting opioids and 11% took opioids on demand. There was no change in the administration pattern in the GP group. These findings suggest that a significant proportion of opioid-treated CNMP patients may be receiving inappropriate opioid treatment and that educating general practitioners in pain medicine may require more than initial supervision.

Opioids are among the most effective medications for moderate to severe pain. Although there is a consensus on their utility as a treatment for chronic cancer pain, their long-term use for chronic non-malignant pain remains controversial. Several medical professional organizations acknowledge the utility of opioid therapy and many case series and large surveys report satisfactory reductions in pain, improvement in function and minimal risk of addiction. However, the clinical trials that have been conducted do not provide adequate evidence of long-term effectiveness. Despite the consensus of pain specialists, and the eminently ethical and medically justified commentaries to consider opioid therapy in the armamentarium of treatments for moderate to severe pain ([Brennan, Carr, & Cousins, 2007](#)), there is concern that the pendulum has swung from undertreatment to overtreatment ([White & Kehlen, 2007](#)). This controversy is enhanced by the increased prevalence of prescription opioid abuse, which has developed concomitantly with an increase in opioid administration in the clinic. The resolution of this controversy will require much more research and the acceptance of treatment guidelines that recognize the dual obligations of the prescriber: to optimize the balance between analgesia and side effects, and promote other favorable outcomes, while concurrently assessing and managing the risks associated with abuse,

addiction and diversion. At this juncture, it is important that the opioid treatment debate evolve from a discussion focused on “too little” or “too much” to one focused on identification and training of best treatment practices. Improvement in opioid therapy can occur through research and training to aid practitioners to determine the appropriate patient subpopulations and treatment protocols to achieve satisfactory outcomes.

Finally, it is imperative to advance a research agenda that leads to the identification of methods that would enhance pain relief while reducing the likelihood of addiction and other adverse events when opioids are selected for therapy. This should include the testing of novel medications that may be safer or more differentially effective for select treatment populations (as the proposal to test buprenorphine with high risk patients, discussed above) and the evaluation of treatment protocols incorporating risk management techniques.

Gordana Ljubojević:Adjuvant analgesic

To date, clinical pain practice relies on opioids as the primary analgesics for the management of moderate to severe pain. Adjuvant analgesics use has become increasingly important especially in the management of mild to moderate pain. Adjuvants act on either the excitatory (e.g., substance P, and glutamate), inhibitory neurotransmitters (e.g., GABA), or on neurotransmitters that modulate pain experience (e.g., serotonin, norepinephrine).

Traditional Adjuvant Analgesics

Traditional adjuvant analgesics such as the NSAIDs, acetaminophen, and muscle relaxants will be briefly described first before discussing the newer adjuvants.

- **NSAIDs and Acetaminophen.** Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used. It is important to note that Acetaminophen is not an anti-inflammatory medication. Along with mild narcotics, NSAIDs remain the mainstay of treating mild pain. They are usually well tolerated and are often used to address inflammatory processes, such as muscle aches, strains, or sprains. NSAIDs, as a class, have analgesic, antipyretic, and anti-inflammatory effects although not all of them are FDA-approved for analgesia use. They have the advantage of a very low short-term side-effect profile that does not impact the patient’s lifestyle. They are called non-steroidal because no steroid agent is present in them. Aspirin, for decades now, remains the prototypical agent. Other examples include ibuprofen (Advil, Motrin), naproxen (Naprosyn), and indomethacin (Indocin). NSAIDs can be used synergistically with opioids and for pain not responsive to opioids alone—especially in patients with bone pain and incidental pain. Unlike opioids, NSAIDs do not cause ileus or sedation. Acetaminophen is recommended by the American Geriatrics Society (AGS) as the drug of choice for mild to moderate musculoskeletal pain. It has an excellent safety profile at therapeutic doses that can be up to 4000 mg/day. Toradol (Ketorolac) is an injectable NSAID that is a potent analgesic (30 mg is roughly equivalent to 7-10 mg of morphine) but has the potential for gastric irritation and possible bleeding.¹
- **COX-2 Inhibitors.** Celecoxib (Celebrex) and rofecoxib (Vioxx) mainly inhibit the enzyme cyclo-oxygenase-2 (COX-2) and thereby result in anti-

inflammatory effects with no, or much less, gastric and renal side effects. They reportedly have fewer drug interactions and have no effect on platelet aggregation or bleeding time commonly found with traditional NSAIDs. COX-2 inhibitors are not free of side effects and package inserts should be read thoroughly before prescribing these drugs. Both rofecoxib and valdecoxib (Bextra) have been taken off the market because of concerns of potential side effects. Meloxicam (Mobic) is not a typical COX-2 inhibitor although some have called for re-classifying it as such.

- **Muscle Relaxants.** Skeletal muscle relaxants are used to ‘relax muscles,’ relieve stiffness, and decrease pain and discomfort caused by strains, sprains, or other injury to muscles or joints. However, they do not take the place of rest, exercise, physical therapy, or other modalities. Commonly used drugs in this class include: baclofen (Lioresal), carisoprodol (Soma), cyclobenzaprine (Flexeril), diazepam (Valium), methocarbamol (Robaxin), orphenadine (Norflex), metaxalone (Skelaxin), and tizanidine (Zanaflex). They all act on the central nervous system (CNS) to produce their depressant effect. It is important to note that, since muscle relaxants act centrally, they indiscriminately relax all muscles and leave the injured area exposed to reinjury if used for long term. It is strongly recommended they be used for a short-term basis only. Note that sudden cessation of the use of baclofen has been associated with withdrawal symptoms and signs.

Tizanidine (Zanaflex) is a centrally acting agent and also is an alpha2-adrenergic agonistic that may contribute some analgesic properties. It is used for acute low back pain, acute musculoskeletal neck pain, and chronic tension headache. This agent has a reversible liver toxicity and should be used with caution. Carisoprodol (Soma) is a popular muscle relaxant with an active byproduct metabolite, meprobamate—a barbiturate—that is potentially addictive. The use of alprazolam (Xanax) as a muscle relaxant is not clinically warranted.

Psychotropic Medications

Psychotropic drugs have increasingly been used in the management of chronic pain. The value of psychotropic medications lie in their capacity to modulate pain experience and to treat symptoms which trigger, exacerbate, or compound the effects of pain—notably depression, anxiety, sleep disturbance, anger, and other states of neural excitation. Classes of psychotropic medications commonly used in pain management include: antidepressants (ADs) and anti-epileptic drugs (AEDs). Other psychotropic drugs that are used clinically include anti-anxiety agents, stimulants, and major tranquilizers.

Antidepressants (ADs). Current research suggests that several antidepressant effects on pain are mediated by the blockade of norepinephrine and serotonin reuptake thereby resulting in increased levels of these neurotransmitters and enhancing the activation of the descending inhibitory neurons.² Serotonin, acetylcholine, and histamine have been identified as pain mediators.³ In addition to activating primary afferent nerve pathways via 5-HT₃ receptors, serotonin produces mechanical hyper-algesia by acting at a different receptor in the periphery—most likely the 5-HT_{1a} receptor subtype.⁴ Beta-adrenoceptors have been demonstrated to mediate the analgesic effects of desipramine and nortriptyline.⁵ ADs have been successfully used to treat chronic headaches (migraine, cluster, and tension), peripheral neuropathies, facial neuralgias (herpes zoster etc.), and neuropathic

lower back pain.⁶ Excellent reviews of the use of ADs in pain management are available.^{2,7} Tricyclic anti-depressants (TCAs) are the most tested including amitriptyline, desipramine, imipramine, and nortriptyline. Among 48 adequately-controlled trials on TCAs, 46 resulted in a statistically significant benefit in pain relief when compared to placebo.⁸ Although amitriptyline or other TCAs with similar pharmacological profile are most widely used, randomized controlled trials have not demonstrated consistent differences between these agents.⁹ They have been most effective in relieving neuropathic pain and headache syndromes, with analgesic activity independent of effects on mood.⁵ Randomized controlled trials and meta-analysis have concluded that TCAs are the only agents proven to benefit Post-herpetic Neuralgia.¹⁰ A recent double-blinded controlled trial of nortriptyline for chronic low back pain patients without depression resulted in significant reduction in pain intensity.¹¹ Unlike opioids and NSAIDs, therapeutic benefit of TCAs and other ADs may often require several weeks to take effect. Over 60% patients reported improvement in the third week of treatment with serum level in the lower end of the therapeutic range for depression (100-250 mg of mean daily dosing).¹² Desipramine and nortriptyline have fewer anti-cholinergic and cardiac side effects leading to better compliance as compared to clomipramine, amitriptyline and doxepin.¹³

Selective Serotonin-Reuptake Inhibitors (SSRI) have been studied for a variety of pain conditions but the results are equivocal to date.^{14,15} Clinical trials do not support the use of SSRIs as first line adjuvant analgesics in pain management and should generally be considered only when other reasons preclude the use of TCAs.¹⁶ Other classes of ADs show good potential for pain management even though they have been less studied. Norepinephrine and dopamine reuptake inhibitors such as bupropion can produce anti-thermal nociception.¹⁷ Buspirone has been found effective as prophylaxis for chronic tension-type headaches.¹⁸ Monoamine oxidase inhibitors have been found to decrease frequency and intensity of migraine.¹⁹ Venlafaxine, a serotonin, and norepinephrine reuptake inhibitor, having fewer side effects, actually reverses hyperalgesia and even prevents its development.²⁰ Nefazodone has both analgesic and opioid potentiation effects.²¹ In general, TCAs are used as first line medications among the ADs. Venlafaxine, nefazodone, mirtazapine and SSRIs may be used as second line agents when tricyclics are not a good option due to excessive anti-cholinergic or other side effects or contraindications (cardiac issues, advanced age, risk of falls). Other intended treatment effects could determine choice of AD. The clinician should not strictly rely on the authors' recommendations but instead should use his/her judgment in picking the right agent for patients; individualizing management is key.

Anti-epileptic drugs (AEDs). Like ADs, AEDs have a role in pain management but, due to safety and side effects, their use has been limited to situations where it is most indicated, namely, in the management of neuropathic pain. The newer agents are much safer and, with few exceptions, preclude the necessity of monitoring blood levels. AEDs act by blocking sodium channels in order to provide pain relief.²² AEDs can also be used as mood stabilizers which, in turn, may have beneficial effects on pain management. Mood stabilization is accomplished via anti-kindling effects, enhancement of GABAergic transmission, diminished excitatory amino acids, and inhibition of voltage-sensitive Na⁺ channels.²³

Carbamazepine (Tegretol), is the most widely studied AED and demonstrates effective treatment of neuropathic pain.²⁴ AEDs have many other pharmacological actions that may produce analgesia thus making them potential treatments for a

variety of chronic pain conditions. Unfortunately, use of carbamazepine is limited by intolerable side effects such as sedation, ataxia, aplastic anemia, agranulocytosis, leukopenia, nausea, and vomiting. Neurotoxicity can lead to acute overdose, stupor, coma, seizures, respiratory depression, vertigo, and blurred vision.²⁵ Drug interactions of carbamazepine with other drugs are also common. For instance, propoxyphene will decrease carbamazepine metabolism while phenytoin (Dilantin) and TCAs will increase it. Similarly, phenytoin has multiple side effects with a profile worse than carbamazepine and should only be used as a second choice.

Valproate is used prophylactically for chronic migraine but is ineffective for acute migraine.²⁶ Although generally well tolerated, valproate requires regular monitoring due to potential hepatotoxicity and bone marrow suppression.²⁷

Gabapentin (Neurontin) has been reported in open trials to reduce the pain of neuropathic states such as diabetic neuropathy, multiple sclerosis, migraine, post-herpetic neuralgia, and sympathetically-mediated pain.²⁸ It may also be useful for phantom limb pain. Gabapentin has a wide therapeutic window and comparable efficacy with other AEDs and can be prescribed without the need for blood monitoring. Sedation can be reduced by starting therapy at 100 mg tid and titrating 100mg up to 3,600 mg/d. Studies have shown that gabapentin can reverse cold and tactile allodynia as well as heat hyperalgesia.²⁹ In contrast to gabapentin, lamotrigine (Lamictal) reversed cold but not tactile allodynia.³⁰ Other newer AEDs, including zonisamide (Zonagran); felbamate (Felbatol); topiramate (Topomax); levetiracetam (Keppra); tiagabine (Gabatril); and oxcarbazepine (Trilipol), may have a role in difficult to treat pain cases. The newer AEDs have not been as well tested for humans and most of the efficacy data has been based on animal studies. Until there is more human data, it is best to avoid agents like felbamate that have the risk of aplastic anemia and liver dysfunction. A better side effect profile agent in this class is oxcarbazepine, which is a keto-analog of carbamazepine, allows twice daily dosing, has no autoinduction, and is better tolerated than carbamazepine. Topiramate (Topomax) works via sodium channel blockade, GABA potentiation, and glutamate antagonism and has the added potential benefit of weight reduction.³¹ Tiagabine (Gabatril) blocks GABA reuptake but there is currently little data on its utility with chronic pain. A multi-center trial is currently ongoing.³²

Pregabalin. This recently launched medication binds, with high affinity, to the alpha2-delta site in central nervous system tissues. In vitro, Pregabalin reduces the calcium-dependent release of several neurotransmitters, possibly by modulation of the calcium channel function. It has been FDA-approved for use in the treatment of diabetic peripheral neuropathic pain and post-herpetic neuralgia, but many clinicians have already started using it for other forms of neuropathic pain, and even as a mood-stabilizing agent. It is also indicated for use in adults with partial onset seizures.³³

Anti-anxiety medications. Despite the paucity of efficacy data, benzodiazepines (BZs) have been widely prescribed for pain management—primarily for anxiety reduction and sleep improvement in patients with chronic pain.³⁴ BZs bind to the “benzo”-GABA-chloride receptor complex, facilitating the action of GABA on CNS excitability.³⁵ BZs possess anxiolytic as well as antispasmodic, sedative/hypnotic, and anticonvulsant effects. Valium and other BZs have been used as muscle relaxants. All BZs are equally effective for reducing anxiety. The selection is determined by the desire for short, intermediate, or long acting effects. Clonazepam has been used to treat neuropathic pain and myoclonus, and the episodic lancinating variety of phantom limb pain.³⁶ BZs have also been used to detoxify

patients from sedative/hypnotic medications. An extensive review of BZs indicated that they were found to be effective in only a small number of chronic pain conditions such as trigeminal neuralgia, tension headaches, and temporomandibular disorders.³⁷ Whereas the benefits of BZs are difficult to document, the negative effects have been well researched. They extend beyond the usual concerns of abuse, dependence, withdrawal, and secondary effects on mood. The elderly are particularly sensitive to the adverse effects of sedation and cognitive compromise.³⁸ BZs have also been associated with exacerbation of pain and interference with opioid analgesia.³⁹ Alprazolam (Xanax) is a very fast acting BZ with short half-life that poses high potential for abuse and withdrawal. It should be avoided except when a temporary fast-acting anxiolytic effect is desired.

Anti-anxiety agents that are not BZs are also available and should be considered. These include buspirone (Buspar), hydroxyzine (Atarax), diphenhydramine (Benadryl) and beta-blockers such as propranolol (Inderal) and atenolol (Tenormin). These medications can produce anxiolytic effects without the cognitive, sedating, and addiction potential of BZ's.

Amphetamine. Amphetamine has been used to enhance morphine analgesia, and to decrease morphine-related side effects such as nausea, sedation, constipation, and loss of alertness. As a class, amphetamine is not widely used due to the risk of increased tolerance and dependence in chronic use, and the potential for withdrawal. Amphetamines can increase blood pressure and exacerbate an underlying coronary artery disease.

Hypnotics/Sedatives. A common problem associated with chronic pain is the inability to have a restful sleep. The resulting decreased capacity for the body to recuperate and to rejuvenate inevitably adds to the suffering of patients with chronic pain. Sleep management is, therefore, an essential part of pain management. Most commonly prescribed hypnotics include the benzodiazepines, chloral hydrate, zopiclone, and zolpidem. Hypnotics suppress the reticular formation of the midbrain resulting in sedation, sleep, or anesthesia. BZs bind to the BZ-GABA-chloride receptor complex in the brain while zolpidem binds selectively to GABA A1 receptors. There are multiple categories and etiology for sleep disorders. Use of hypnotics is not recommended for treating sleep irregularities for more than one or two weeks. Adverse side effects may include daytime sedation, anterograde amnesia, rebound insomnia and, for high dosage, impaired respiration, and blood pressure. Discontinuation may produce withdrawal, rebound, and relapse. Drug interaction profiles should be considered when prescribing hypnotics. Sleep problems, which persist after the pain is treated, should be referred to a mental health clinician and/ or sleep laboratory. Provigil (Modafinil), a novel wake-promoting agent, has recently been added to the list of adjuvants for treating sleep-wake problem. Modafinil has been shown to subjectively and objectively improve wakefulness, vigilance, mood, and cognitive performance.

- To date, clinical pain practice relies on opioids as the primary analgesics for the management of moderate to severe pain. Adjuvant analgesics use has become increasingly important especially in the management of mild to moderate pain. Adjuvants act on either the excitatory (e.g., substance P, and glutamate), inhibitory neurotransmitters (e.g., GABA), or on neurotransmitters that modulate pain experience (e.g., serotonin, norepinephrine).
- Traditional Adjuvant Analgesics

- Traditional adjuvant analgesics such as the NSAIDs, acetaminophen, and muscle relaxants will be briefly described first before discussing the newer adjuvants.
- NSAIDs and Acetaminophen. Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used. It is important to note that Acetaminophen is not an anti-inflammatory medication. Along with mild narcotics, NSAIDs remain the mainstay of treating mild pain. They are usually well tolerated and are often used to address inflammatory processes, such as muscle aches, strains, or sprains. NSAIDs, as a class, have analgesic, antipyretic, and anti-inflammatory effects although not all of them are FDA-approved for analgesia use. They have the advantage of a very low short-term side-effect profile that does not impact the patient's lifestyle. They are called non-steroidal because no steroid agent is present in them. Aspirin, for decades now, remains the prototypical agent. Other examples include ibuprofen (Advil, Motrin), naproxen (Naprosyn), and indomethacin (Indocin). NSAIDs can be used synergistically with opioids and for pain not responsive to opioids alone—especially in patients with bone pain and incidental pain. Unlike opioids, NSAIDs do not cause ileus or sedation. Acetaminophen is recommended by the American Geriatrics Society (AGS) as the drug of choice for mild to moderate musculoskeletal pain. It has an excellent safety profile at therapeutic doses that can be up to 4000 mg/day. Toradol (Ketorolac) is an injectable NSAID that is a potent analgesic (30 mg is roughly equivalent to 7-10 mg of morphine) but has the potential for gastric irritation and possible bleeding.¹
- COX-2 Inhibitors. Celecoxib (Celebrex) and rofecoxib (Vioxx) mainly inhibit the enzyme cyclo-oxygenase-2 (COX-2) and thereby result in anti-inflammatory effects with no, or much less, gastric and renal side effects. They reportedly have fewer drug interactions and have no effect on platelet aggregation or bleeding time commonly found with traditional NSAIDs. COX-2 inhibitors are not free of side effects and package inserts should be read thoroughly before prescribing these drugs. Both rofecoxib and valdecoxib (Bextra) have been taken off the market because of concerns of potential side effects. Meloxicam (Mobic) is not a typical COX-2 inhibitor although some have called for re-classifying it as such.
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- Psychotropic Medications
- Psychotropic drugs have increasingly been used in the management of chronic pain. The value of psychotropic medications lie in their capacity to modulate pain experience and to treat symptoms which trigger, exacerbate, or compound the effects of pain—notably depression, anxiety, sleep disturbance, anger, and other states of neural excitation. Classes of psychotropic medications commonly used in pain management include: antidepressants (ADs) and anti-epileptic drugs (AEDs). Other psychotropic drugs that are used clinically include anti-anxiety agents, stimulants, and major tranquilizers.
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- Carbamazepine (Tegretol), is the most widely studied AED and demonstrates effective treatment of neuropathic pain.²⁴ AEDs have many other pharmacological actions that may produce analgesia thus making them potential treatments for a variety of chronic pain conditions. Unfortunately, use of carbamazepine is limited by intolerable side effects such as sedation, ataxia, aplastic anemia, agranulocytosis, leukopenia, nausea, and vomiting. Neurotoxicity can lead to acute overdose, stupor, coma, seizures, respiratory depression, vertigo, and blurred vision.²⁵ Drug interactions of carbamazepine with other drugs are also common. For instance, propoxyphene will decrease carbamazepine metabolism while phenytoin (Dilantin) and TCAs will increase it. Similarly, phenytoin has multiple side effects with a profile worse than carbamazepine and should only be used as a second choice.
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- Anti-anxiety agents that are not BZs are also available and should be considered. These include buspirone (Buspar), hydroxyzine (Atarax), diphenylhydramine (Benedryl) and beta-blockers such as propranolol (Inderal) and atenolol (Tenormin). These medications can produce anxiolytic effects without the cognitive, sedating, and addiction potential of BZ's.
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- Hypnotics/Sedatives. A common problem associated with chronic pain is the inability to have a restful sleep. The resulting decreased capacity for the body to recuperate and to rejuvenate inevitably adds to the suffering of patients with chronic pain. Sleep management is, therefore, an essential part of pain management. Most commonly prescribed hypnotics include the benzodiazepines, chloral hydrate, zopiclone, and zolpidem. Hypnotics suppress the reticular formation of the midbrain resulting in sedation, sleep, or anesthesia. BZs bind to the BZ-GABA-chloride receptor complex in the brain while zolpidem binds selectively to GABA A1 receptors. There are multiple categories and etiology for sleep disorders. Use of hypnotics is not recommended for treating sleep irregularities for more than one or two weeks. Adverse side effects may include daytime sedation, anterograde amnesia, rebound insomnia and, for high dosage, impaired respiration, and blood pressure. Discontinuation may produce withdrawal, rebound, and relapse. Drug interaction profiles should be considered when prescribing hypnotics. Sleep problems, which persist after the pain is treated, should be referred to a mental health clinician and/ or sleep laboratory. Provigil (Modafinil), a novel wake-promoting agent, has recently been added to the list of adjuvants for treating sleep-wake problem. Modafinil has been shown to subjectively and objectively improve wakefulness, vigilance, mood, and cognitive performance.⁴⁰

Snežana-Tomašević-Todorović Pain in the elderly - a special challenge in rehabilitation

S.Todorović Tomašević

Currently, elderly patients comprise the fastest growing segment of the world's population. The number of people worldwide 65 years and older was estimated at 506 million as of 2008 and by 2040 will increase to 1.3 billion. The United States Census Bureau asserts that there were 38.9 million people 65 and older in 2008, making up 12.8% of the total population. Of this population segment, 5.7 million are 85 years old and older, and this number is growing.

Chronic geriatric pain may be defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage, for persons who are either aged (65 to 79 years old) or very aged (80 and over) and who have had pain for greater than 3 months.”¹ The consequences of this pain include impaired activities of daily living (ADLs) and ambulation, depression, and strain on the health care economy. Pain may also be related to complications associated with deconditioning, gait abnormalities, accidents, polypharmacy, and cognitive decline.

The prevalence of persistent pain increases with age³; increases in joint pain and neuralgias are particularly common. A majority of elderly persons have significant pain problems and are undertreated. Between 25% and 40% of older cancer patients studied had daily pain. Among these patients, 21% who were between 65 and 74 years of age received no pain medication; of patients who were 75 to 84 years old, 26% received no pain medication; and for those above the age of 84, 30% were left untreated.⁵ Moreover, detection and management of chronic pain remain inadequate.⁶ In one study, 66% of geriatric nursing home residents had chronic pain, but in almost half of the cases (34%) it was not detected by the treating physician.

The treatment of pain begins with the assessment of what instigated the pain, how it can be terminated, and what management modalities are most effective for a particular patient. However, assessment is rarely that simple. Clinical manifestations of persistent pain are often complex and multifactorial in the older population. Even the perception of pain may differ from that perceived by those of less advanced years. Issues of physical accessibility to treatment, cost of drugs, the presence of coexisting illness, the use of concomitant medication, and the ability to understand the complaints of the patient who has cognitive impairment are only some of the factors that contribute to the complexity of the situation. Furthermore, the elderly patient's condition is often complicated by depression, psychosocial concerns, denial, poor health, and poor memory. Without a thorough assessment, pain that is causing severe impairment may not be revealed for an array of personal, cultural, or psychological reasons.

Pain may be underreported because some elderly patients incorrectly believe that pain is a normal process of aging. In other cases, such as with cancer pain, it is underreported because of fear of disease progression. Further, the caregivers and relatives are often the most reliable source of information.⁸ To address the need to adequately identify and diagnose pain, an increasing number of articles are being written on pain assessment in patients with dementia as well as research focusing on the measurement of pain.^{9–11}

The complexity of pain assessment in geriatric patients often requires a multidisciplinary approach to diagnosis and to management. The pain physician should work together with a psychologist or psychiatrist as depression is oftentimes present in the patient with chronic pain. A physical therapist should be part of the team as well, to help with functionality. Laboratory and imaging studies may be ordered to help pinpoint a diagnosis if a detailed history and physical examination is not enough.

Evaluation of the patient's level of function is important as it affects the degree of independence, level of need for caregivers, as well as overall quality of life. Activities of daily living—eating, bathing, dressing—and instrumental ADLs—light housework, shopping, managing money, preparing meals—should be assessed. After a diagnosis is

made, a consensus treatment plan should be outlined that includes modalities to decrease pain perception and increase patient function.¹²

The visual analogy scale (VAS), verbal descriptor scale, and numerical rating scale are frequently used to assess pain intensity. Available data support the use of these methods; however, the VAS should be used with caution as it is associated with a higher frequency of responses from the elderly that are incomplete or unable to be given a score.^{13,14} Moreover, elderly patients report difficulty in completing the VAS.^{13,15,16} It has, however, proven reliability in clinical and research settings, and offers the advantages of simplicity, ease of administration, and minimal intrusiveness.¹²

The McGill Pain Questionnaire has evidence for validity, reliability, and discriminative abilities that are not age-related. The McGill Pain Questionnaire can be used to assess the sensory, affective, evaluative, and miscellaneous components of pain.¹⁷

After assessing the intensity of pain, one should perform a thorough examination. An overview is discussed here:

1. Complete history and physical examination, with focus on most pressing pain issues
2. Review of location of pain, intensity, exacerbating and/or alleviating factors, and impact on mood and sleep
3. A screen for cognitive impairment such as the Folstein minimal examination
4. A screen for depression
5. A review of the patient's ADLs (bathing, dressing, toileting, transfers, feeding, and continence) and instrumental ADLs (use of phone, travel, shopping, food preparation, housework, laundry, taking medicine, handling finances)
6. Assessment of gait and balance
7. A screen for sensory depression to examine basic visual and auditory function

The pain physician should assess for evidence of chronic pain. The pain should be considered significant if it is persistent, recurrent, and affecting the patient's functional capacity and/or quality of life. Because pain may be manifested in multiple ways, a variety of terms should be used to screen for symptoms in older patients, such as burning, aching, soreness, tightness, discomfort, sharp, dull, and throbbing. One may also use vocalizations or changes in function as cues to underlying pain, especially in those patients with cognitive or language impairments. These cues may manifest as crying, groaning, changes in gait or posture, or withdrawn/agitated behavior. Furthermore, if cognitive or language impairments are present, the pain physician should seek reports from a caregiver or close relative. The underlying reason for this impairment should be optimally treated, and consultations for skilled procedures or knowledge should be sought when appropriate. A multidisciplinary approach is always recommended.

The examination continues with a comprehensive pain assessment including thorough medical history and physical examination, review of systems and pertinent laboratory results, imaging studies, and diagnostic tests. Noting the temporal relationships among events, medical interventions, and complaints helps elucidate the diagnosis and likely prognosis. The intensity, character, frequency, location, and duration of the pain should be probed. Ameliorating and exacerbating factors help show the nature of the pain as well.

Afterward, the medication history should be reviewed, as well as over-the-counter herbal supplementation. A list of adverse effects should be noted. The physical examination should focus on neuromuscular systems with attention to impairments, weakness, hyperalgesia/hypoalgesia, hyperpathia, allodynia, numbness, and tingling. There may be trigger points, bony deformities, or local inflammation at certain sites that may suggest certain pathologies.

Physical function may be determined by assessing the ability of the patient to perform ADLs. Range of motion testing, gait, and balance testing are appropriate at this stage. The patient's psychosocial function may be determined by assessment of mood, social support groups, family relationships, and any appointed caregivers. Next, a quantitative assessment of the patient's pain may be ascertained with a VAS, numerical rating scale, or other pain scale. Finally, a pain log or diary may help keep track of how different treatment modalities are affecting the patient's pain intensity and function.

The follow-up interval should be determined by the severity of pain and dysfunction. This may be anywhere from 1 to 4 weeks depending on the patient's situation and compliance with medication. Regular visits help to reassess improvement or worsening of the condition, complications with medications, and patient compliance. Some patients who may be unable to drive to meet a physician may require house calls or the assistance of home health care for follow-up. Positive and negative effects of analgesics and therapeutic modalities should be noted, then the treatment plan modified.¹⁸

[Go to:](#)

PATHOPHYSIOLOGIC CHANGES IN THE ELDERLY

A steady decline of homeostatic mechanisms and organ system function occurs during normal aging. The most important organ systems affected are described in the following sections.

Central Nervous System

Many elderly patients may present with neurologic disease and dysfunction, including transient ischemic attacks, strokes, dementia, or movement disorders. The pain physician should be aware that these problems may affect accurate assessment of pain as well as the efficacy of treatment.¹⁹

Although the mechanisms are not totally clear, symptoms of CNS and peripheral nervous system dysfunction may occur as early as 50 years of age. Heredity, concomitant disease, and stress from daily activities may play a role.²⁰ The neurons of elderly patients are not rejuvenated when these cells die and are instead replaced by proliferating glial cells.²¹ Furthermore, the number of dendritic synapses, cell receptors, and intracellular enzymes is decreased.²²

Alzheimer disease constitutes approximately 60% of all cases of dementia, although one must also look for other causes such as idiopathic degenerative processes, vascular disorders, normal-pressure hydrocephalus, neoplastic diseases, CNS infections, metabolic disorders, and pseudodementia.²³ Parkinson disease is another common pathology in the elderly.

Hepatic

An aged liver may prolong the clearance of drugs from the body secondary to prehepatic, intrahepatic, or posthepatic causes ([Table 1](#)). Prehepatic dysfunction includes decreased first-pass and blood extraction, which may be secondary to lower gastrointestinal absorption or decreased portal and arterial blood flow. Intrahepatic dysfunction may be caused by hepatocellular pathology such as cirrhosis. Posthepatic dysfunction is usually due to either biliary tree or enterohepatic circulation blockage or pathology. Liver function tests are often normal despite these changes in the elderly liver.

Renal System

The decline in renal function begins after the age of 40 at a rate of approximately 1% per year, or a 1 mL/min per year decline in creatinine clearance.²⁴ Although the structure and function of the kidney declines, clinically the function of the kidney seems to be maintained in healthy elderly patients.

PAIN THRESHOLD

Multiple studies have been undertaken to determine the effect of aging on pain threshold. Gibson²⁶ conducted a meta-analysis of over 50 studies that examined age differences in sensitivity to induced pain. The effect size was 0.074 ($P < .0005$), indicating that there is definite evidence of an increase in pain threshold with advancing age. There may be a difference in pain threshold depending on the type of pain, as well. Moreover, a study by Latienbacher et al²⁷ compared pain perception in 40 men, half with a mean age of 27.1 years and the other with a mean age of 71.6 years. The results demonstrated that somatosensory thresholds for nonnoxious stimuli increase with age, whereas pressure pain thresholds decrease and heat pain thresholds show no age-related changes, which confirm previous studies as well.

Pharmacokinetic Changes

Elderly patients present with increased fat mass, decreased muscle mass, and decreased body water, which have important ramifications on drug distribution.^{29,30} Blood volume may be decreased as well, secondary to diuretic use. Lipophilic medications such as fentanyl and lidocaine may have an increased duration of effect as more of these medications are absorbed by fat mass and will have an increased volume of distribution. Water-soluble drugs, however, are less efficiently distributed and result in higher plasma concentrations at equivalent doses, and therefore result in a higher frequency of side effects.

Decreases in serum albumin increase the amount of free drug availability. This is even more accentuated in patients with chronic disease and malnutrition, leading to higher levels of adverse effects when using highly protein-bound analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) and antiepileptic drugs.

Drug half-life, the ratio of the volume of distribution to clearance, is notably increased for several benzodiazepines and tricyclic antidepressants related to decreased kidney and liver clearance. Dose-related side effects from analgesics that undergo significant first-pass metabolism will be increased. These drugs, such as lidocaine and opioids, should be initiated slowly and at lower doses to avoid complications.³¹

Hepatic phase I reactions involving oxidation, hydrolysis, and reduction appear to be more altered by age than phase II conjugation such as acetylation, glucuronidation, sulfation, and glycine conjugation. There is a predictable age-related decline in cytochrome P-450 function and, combined with the polypharmacy that much of the elderly population experiences, this may lead to a toxic reaction of medications. Selective serotonin reuptake inhibitors and the newer serotonin-norepinephrine reuptake inhibitors both inhibit the cytochrome system and can lead to a buildup of other drugs. Narcotic accumulation when concurrently administered with other medications—specifically the aforementioned selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors—is always a risk, especially in the elderly population with declining liver function. High doses of narcotics may also act as cytochrome enzyme inhibitors. Although a drug like acetaminophen is metabolized at an equal rate at older ages, a drug like diazepam is metabolized at a reduced rate in the elderly. Further, carbamazepine, lidocaine, and fentanyl are subject to reduced metabolism by the same enzyme systems in older patients even though they are metabolized by the same enzymes. Glucuronidation of morphine and glutathione conjugation of acetaminophen are examples of reduced and unaltered phase II reactions, respectively. The frequency of slow and rapid metabolizing genetic polymorphisms seems to be unaffected by age. Reduction in renal clearance, however, seems to have the largest pharmacodynamic effect on the elderly. Caution should be taken when using drugs that primarily undergo renal metabolism and clearance, such as gabapentin, to avoid side effects.³²

Pharmacodynamic Changes

Generally speaking, geriatric patients usually have increased sensitivity to centrally acting drugs such as benzodiazepines and opioids. The adrenergic and cholinergic autonomic nervous systems, however, generally have decreased sensitivity to receptor-specific drugs such as beta blockers.³³ These changes are strongly coupled with age-related decline in CNS function.

PAIN MANAGEMENT MODALITIES IN THE ELDERLY

Treatment modalities for pain in the elderly may be categorized into the following areas. A multidisciplinary approach is recommended to investigate all possible options for optimal management: (1) pharmacotherapy (most commonly employed), (2) psychological support, (3) physical rehabilitation, and (4) interventional procedures

Pharmacotherapy

Drug treatment is generally the first and most widely used treatment modality to control geriatric pain. It is relatively simple to implement and consists of NSAIDs, muscle relaxants, opioids, and other adjuvant therapy. Prescribing these medications is not without risks, however. The patient's cognitive, physiological, and functional status may be affected. The American Geriatric Society and the World Health Organization (WHO) have put together counsel to arrive at some form of consensus as to the best approach in this patient population.³⁷

Summary of 2009 American Geriatric Society Recommendations

Nonopioids

1. Acetaminophen should be considered as initial and ongoing pharmacotherapy in the treatment of persistent pain, particularly musculoskeletal pain, owing to its demonstrated effectiveness and good safety profile (high quality of evidence, strong recommendation).
 - A. Absolute contraindications: liver failure (high quality of evidence, strong recommendation)
 - B. Relative contraindications and cautions: hepatic insufficiency, chronic alcohol abuse or dependence (moderate quality of evidence, strong recommendation)
 - C. Maximum daily recommended dosages of 4 g per 24 hours should not be exceeded and must include “hidden sources” such as from combination pills (moderate quality of evidence, strong recommendation)
2. Nonselective NSAIDs and cyclooxygenase 2 (COX-2) selective inhibitors may be considered rarely, and with extreme caution, in highly selected individuals (high quality of evidence, strong recommendation).
 - A. Patient selection: other (safer) therapies have failed, evidence of continuing therapeutic goals not met, ongoing assessment of risks and complications outweighed by therapeutic benefits (low quality of evidence, strong recommendation)
 - B. Absolute contraindications: current active peptic ulcer disease (low quality of evidence, strong recommendation); chronic kidney disease (moderate level of evidence, strong recommendation); heart failure (moderate level of evidence, weak recommendation)
 - C. Relative contraindications and cautions: hypertension, *Helicobacter pylori*, history of peptic ulcer disease, concomitant use of corticosteroids or selective serotonin reuptake inhibitors (moderate quality of evidence, strong recommendation)
3. Older persons taking nonselective NSAIDs should use a proton pump inhibitor or misoprostol for gastrointestinal protection (high quality of evidence, strong recommendation).
4. Patients taking a COX-2 selective inhibitor with aspirin should use a proton pump inhibitor or misoprostol for gastrointestinal protection (high quality of evidence, strong recommendation).
5. Patients should not take more than one nonselective NSAID or COX-2 selective inhibitor for pain control (low quality of evidence, strong recommendation).
6. Patients taking aspirin for cardioprophylaxis should not use ibuprofen (moderate quality of evidence, weak recommendation).
7. Patients taking nonselective NSAIDs and COX-2 selective inhibitors should be routinely assessed for gastrointestinal and renal toxicity, hypertension, heart failure, and other drug-drug and drug-disease interactions (weak quality of evidence, strong recommendation).

Opioids

1. Patients with moderate to severe pain, pain-related functional impairment, or diminished quality of life because of pain should be considered for opioid therapy (low quality of evidence, strong recommendation).
2. Patients with frequent or continuous pain on a daily basis may be treated with around-the-clock time-contingent dosing aimed at achieving steady-state opioid therapy (low quality of evidence, weak recommendation).
3. Clinicians should anticipate, assess for, and identify potential opioid-associated adverse effects (moderate quality of evidence, strong recommendation).
4. Maximal safe doses of acetaminophen or NSAIDs should not be exceeded when using fixed-dose opioid combination agents as part of an analgesic regimen (moderate quality of evidence, strong recommendation).
5. When long-acting opioid preparations are prescribed, breakthrough pain should be anticipated, assessed, and prevented or treated using short-acting immediate-release opioid medications (moderate quality of evidence, strong recommendation).
6. Clinicians well versed in the use and risks of methadone should initiate it and titrate it cautiously (moderate quality of evidence, strong recommendation).
7. Patients taking opioid analgesics should be reassessed for ongoing attainment of therapeutic goals, adverse effects, and safe and responsible medication use (moderate quality of evidence, strong recommendation).

Adjuvant Analgesic Drugs

1. All patients with neuropathic pain are candidates for adjuvant analgesics (strong quality of evidence, strong recommendation).
2. Patients with fibromyalgia are candidates for a trial of approved adjuvant analgesics (moderate quality of evidence, strong recommendation).
3. Patients with other types of refractory persistent pain may be candidates for certain adjuvant analgesics (eg, back pain, headache, diffuse bone pain, temporomandibular disorder) (low quality of evidence, weak recommendation).
4. Tertiary tricyclic antidepressants (amitriptyline, imipramine, doxepin) should be avoided because of higher risk for adverse effects such as anticholinergic effects and cognitive impairment (moderate quality of evidence, strong recommendation).
5. Agents may be used alone, but often the effects are enhanced when used in combination with other pain analgesics and nondrug strategies (moderate quality of evidence, strong recommendation).
6. Therapy should begin with the lowest possible dose and increase slowly based on response and side effects, with the caveat that some agents have a delayed onset of action and therapeutic benefits are slow to develop. For example, gabapentin may require 2 to 3 weeks for onset of efficacy (moderate quality of evidence, strong recommendation).

7. An adequate therapeutic trial should be conducted before discontinuation of a seemingly ineffective treatment (weak quality of evidence, strong recommendation).

Other Drugs

1. Long-term systemic corticosteroids should be reserved for patients with pain-associated inflammatory disorders or metastatic bone pain. Osteoarthritis should not be considered an inflammatory disorder (moderate quality of evidence, strong recommendation).
2. Patients with localized neuropathic pain are candidates for topical lidocaine (moderate quality of evidence, strong recommendation).
3. Patients with localized nonneuropathic pain may be candidates for topical lidocaine (low quality of evidence, weak recommendation).
4. Patients with other localized nonneuropathic persistent pain may be candidates for topical NSAIDs (moderate quality of evidence, weak recommendation).
5. Other topical agents, including capsaicin or menthol, may be considered for regional pain syndromes (moderate quality of evidence, weak recommendation).
6. Many other agents for specific pain syndromes may require caution in older persons and merit further research (eg, glucosamine, chondroitin, cannabinoids, botulinum toxin, alpha-2 adrenergic agonists, calcitonin, vitamin D, bisphosphonates, ketamine) (low quality of evidence, weak recommendation).

Overview of the WHO Recommendations: Analgesic Ladder Significant overlap occurs between chronic geriatric pain and cancer pain. For this reason, following the WHO recommendations for pain management is appropriate. In order to maintain freedom from pain, WHO recommends (1) administration of drugs “by the clock” (eg, every 3–6 hours), (2) medication by mouth individualized for the patient, and lastly (3) following the “analgesic ladder” (which was modified from ref. 38 and follows):

1. For mild pain, the most appropriate first choice for relatively safe analgesia is acetaminophen.
2. For mild to moderate pain or pain uncontrolled with acetaminophen, the use of NSAIDs is appropriate.
3. For pain refractory to NSAIDs, or pain rated as moderate initially, a weaker opioid (eg, codeine) is the appropriate first choice. Other weak opioids that may be used include hydrocodone, propoxyphene, and oxycodone in combination with acetaminophen.
4. For pain refractory to the previous plan, or pain rated as severe, a pure opioid agonist (eg, morphine) is selected. Other pure opioids to consider include hydromorphone, fentanyl, levorphanol, and oxycodone.
5. Adjuvant medication may be used to relieve fear and anxiety in the patient as well as for synergism with the previously named medications.

Adjuvants

Adjuvant drug therapy should be considered at all times to enhance the analgesic effects of other medications. It is often necessary to try different drugs to determine the best regimen

for a particular patient. Some of the adjuvant drugs used to treat pain include but are not limited to the following:

1. Antidepressants
2. Anticonvulsants
3. Alpha-2 adrenergic agonists
4. Local anesthetics
5. Corticosteroids
6. Baclofen
7. *N*-methyl-D-aspartate receptor agonists
8. Muscle relaxants
9. Topical creams and gels
10. Neuroleptics
11. Antihistamines
12. Psychostimulants
13. Calcitonin

Newer Opiates and the Elderly

As new guidelines are released discussing the adverse reactions of NSAIDs and the elderly and there is a move toward opiate conversion, the search for new and safer opiates is inevitable. Most of the older opiates have a known efficacy and safety profile when used in an older population. One of the newer opiates, oxycodone, has recently been studied as it is metabolized in a non-cytochrome P-450 pathway and therefore bypasses many of the drug-drug interactions common to the elderly. Moreover, the drug is still renally excreted, so it should be used with caution in elderly patients who already have a decreased glomerular filtration rate. The problem arises as it is not as familiar as many of the other opiates typically used; however, indications suggest that it is safe in the elderly and should be used in the same way as the other opiates, starting with a low dose and increasing it slowly.³⁷

Psychological Support

Because pain is a complex sensory and emotional experience, psychological modalities should be employed in the pain management model. The psychological branch of pain also explains why some patients with minimal disease may have excruciating pain, whereas others with severe disease may have minimal complaints. Pain-coping strategies may include relaxation, prayer, and attention-diversion techniques. Depression and anxiety in the geriatric patient must be addressed with psychotherapy, meditation, and medication. Furthermore, the socioenvironmental variables of each patient should be adjusted to help the patient cope with pain. A solid support system including relatives and caregivers should be established.

Physical Rehabilitation

The rehabilitative aspect of pain management may help the patient live a more independent and functional life. Rehabilitation may involve adapting to loss of physical, psychological, or social skills. The assessment of ADLs can help assess the level of function and direct treatment. The objectives of rehabilitation include stabilizing the primary disorder, preventing secondary injuries, decreasing pain perception via a multidisciplinary approach, treating functional deficits, and promoting adaptations to current disabilities.³⁹

Interventional Modalities

Interventional pain modalities may help to determine the underlying cause of pain and help to arrive at a precise diagnosis. It often alleviates the need for heavy medication use, thereby sparing the patient from unwanted side effects associated with larger doses of drugs. Nerve blocks are some of the most commonly used interventional procedures employed by pain physicians; these help not only with diagnosis but also prognosis, preemptive analgesia, and sometimes definitive therapy. Other interventions that may be used include chemical neurolysis, radiofrequency lesioning, cryoneurolysis, neuroaugmentation, and neuraxial drug delivery.

After the lecture, there was a discussion about specific clinical painful conditions and their diagnosis and therapy.

Ivan Radoš Interventional procedures in pain therapy

Interventional pain management uses injections of drugs to reduce pain. Besides its therapeutic benefit, interventional pain management can play a role in identifying the source of the pain. Interventional procedures are commonly done with the use of fluoroscopy (live x-ray guidance). This allows the physicians to perform injections with increased accuracy and safety.

To ensure patient comfort during minimally invasive procedures, the patient has the option of "twilight" sedation, which makes the procedure virtually pain free. Procedures usually last less than an hour, and the patient is able to walk away from the treatment center the same day.

Common Interventional Procedures

Epidural Steroid Injection

This is the most commonly done procedure to relieve pain. The injection delivers a powerful steroid solution directly into the spinal canal, which reduces the swelling and irritation around a nerve or part of the spinal cord. Most patients who receive

epidural injections will experience less pain for a number of weeks or months, thus allowing them to participate in a [rehabilitation program](#). When severe symptoms flare-up, epidural injections are usually repeated.

Facet Joint Injection

Linking the bones (vertebrae) of our spines to each other, facet joints are paired (one on the right and one on the left side of the spine) on each vertebra. Facet joint injections are used to help the doctor locate the source of back pain. Injecting medication directly into the facet joint also helps to relieve the source of the pain.

NERVE BLOCKS

Nerve blocks, or neural blockades, are procedures that can help prevent or manage many different types of intractable pain. They're often injections of medicines that block pain from specific nerves. They're meant to bring pain relief rather than total loss of feeling.

RADIOFREQUENCY ABLATION (RFA)

Used to treat chronic pain caused by spinal injury or deterioration due to conditions relating to vertebrae and intervertebral discs which may in turn affect the nerves in the area. The most common condition treated is degenerative arthritis of the facet joints in the neck or back. RFA uses thermal energy to deaden tiny nerve endings.

SPINAL CORD STIMULATORS

Spinal cord stimulation is one treatment for chronic pain. A small medical device sends signals to your spinal cord. These signals keep the chronic pain messages from being sent to your brain. Instead, you may feel tingling from the electrical signals.

SYMPATHETIC BLOCKS

The sympathetic nervous system is controlled by nerves called ganglions. One large ganglion, called the stellate ganglion, helps control nerves in the upper body. In the lower body, nerves are controlled by several ganglions that make up the sympathetic chain.

TRIGGER POINT INJECTIONS

The cause of your muscle pain or spasms may be one or more trigger points. Your healthcare provider may decide to inject the painful spots to relax the muscle. This can help relieve your pain. Relaxing the muscle can also make movement easier. You may then be able to exercise to strengthen the muscle and help it heal.

Tatjana Bućma: Spinal cord stimulation in the treatment of chronic pain

Spinal cord stimulation therapy masks pain signals before they reach the brain. A small device, similar to a pacemaker, delivers electrical pulses to the spinal cord. It helps people better manage their chronic pain and reduce their use of opioid medications. It may be an option if you suffer chronic back, leg or arm pain and have not found relief with other therapies.

A spinal cord stimulator (SCS) device is surgically placed under your skin and sends a mild electric current to your spinal cord (Fig. 1). Thin wires carry current from a pulse generator to the nerve fibers of the spinal cord. When turned on, the SCS stimulates the nerves in the area where your pain is felt. Pain is reduced because the electrical pulses modify and mask the pain signal from reaching your brain.

Stimulation does not eliminate the source of pain, it simply interferes with the signal to the brain, and so the amount of pain relief varies for each person. Also, some patients find the tingling sensation unpleasant. For these reasons a trial stimulation is performed before the device is permanently implanted. The goal for spinal cord stimulation is a 50-70% reduction in pain. However, even a small amount of pain reduction can be significant if it helps you to perform your daily activities with less pain and reduces the amount of pain medication you take. Stimulation does not work for everyone. If unsuccessful, the implant can be removed and does not damage the spinal cord or nerves.

Some SCS devices use a low-frequency current to replace the pain sensation with a mild tingling feeling called paresthesia. Other SCS devices use high-frequency or burst pulses to mask the pain with no tingling feeling. A paresthesia-free setting is an option on most devices.

Stimulation does not eliminate the source of pain. It simply changes the way the brain perceives it. As a result, the amount of pain relief varies for each person. The goal for SCS is a 50 to 70% reduction in pain. However, even a small amount of pain reduction can be significant if it helps you perform daily activities and reduces the amount of pain medication you take. SCS does not improve muscle strength.

Stimulation does not work for everyone. Some people may find the sensation unpleasant. Other people may not get relief over the entire pain area. For these reasons a trial stimulation allows you to try it for a week. If it doesn't work for you, the trial wires can be removed, leaving no damage to the spinal cord or nerves.

There are several types of SCS device systems. However, all have three main parts:

A pulse generator with a battery that creates the electrical pulses.

A lead wire with a number of electrodes (8-32) that delivers electrical pulses to the spinal cord.

A hand-held remote control that turns the device on and off and adjusts the settings.

Systems with a non-rechargeable battery need to be surgically replaced every 2 to 5 years, depending on the frequency of use. Rechargeable battery systems may last 8 to 10 years or longer, but you must remember to charge the system daily.

The pulse generator has programmable settings. Some SCS devices are able to sense a change in body position (sitting vs. lying down) and adapt the stimulation level to your activity. Other systems have leads that can be independently programmed to cover multiple pain areas. Some send a sub-perception pulse with no tingling. Your doctor will select the best type of system for you.

Who is a candidate?

An evaluation of your physical condition, medication regime, and pain history will determine whether your goals of pain management are appropriate for SCS. A neurosurgeon, physiatrist, or pain specialist will review all previous treatments and surgeries. Because chronic pain also has emotional effects, a psychologist will assess your condition to maximize the probability of a successful outcome.

Patients selected for SCS usually have had chronic debilitating pain for more than 3 months in the lower back, leg (sciatica), or arm. They also typically have had one or more spinal surgeries.

You may be a candidate for SCS if :

Conservative therapies have failed.

You would not benefit from additional surgery.

The pain is caused by a correctable problem and should be fixed.

You do not want further surgery because of the risks or long recovery. Sometimes SCS may be chosen over a large, complex spine surgery.

You do not have untreated depression or drug addiction; these should be treated prior to having a SCS.

You have no medical conditions that would keep you from undergoing implantation.

You have had a successful SCS trial.

SCS works better in the earlier stages of a chronic condition, before a cycle of pain-suffering-disability-pain is established.

An SCS can help lessen chronic pain caused by:

Chronic leg (sciatica) or arm pain: ongoing, persistent pain caused by arthritis, spinal stenosis, or by nerve damage.

Failed back surgery syndrome: failure of one or more surgeries to relieve persistent arm or leg pain, but not a technical failure of the original procedure.

Complex regional pain syndrome: a progressive disease in which patients feel constant, chronic burning pain, typically in the foot or hand.

Arachnoiditis: painful inflammation and scarring of the protective lining of the spinal nerves.

Other: stump pain, angina, peripheral vascular disease, multiple sclerosis, or spinal cord injury.

Neurosurgeons and doctors who specialize in pain management (an anesthesiologist or physiatrist) implant spinal cord stimulators.

Determining whether a spinal cord stimulator will be a good option for you is a two-step process. First, you must undergo a temporary trial to see if the device decreases your level of pain.

Stage 1. Trial "test drive"

Trial stimulation is a "test drive" to determine if an SCS will work for the type, location, and severity of your pain. It is performed at an outpatient center.

If you take blood-thinners, you are required to stop the medication 3 to 7 days prior to the trial.

A local anesthetic is given to numb the area in the lower back. Using X-ray fluoroscopy, a hollow needle is inserted through the skin into the epidural space between the bone and spinal cord. The trial lead is inserted and positioned over specific nerves. The wires are attached to an external generator worn on a belt (Fig. 2).

You will be sent home with instructions on how to use the trial stimulator and care for your incision site. Keep a written log of the stimulation settings during different activities and the level of pain relief. After 4 to 7 days, you will return to the doctor's office to discuss permanently implanting the stimulator or removing the trial leads.

Stage 2. Surgical implant

If the trial is successful and you felt greater than 50% improvement in pain, surgery can be scheduled to implant the SCS device in your body.

What happens before surgery?

You may be scheduled for presurgical tests (e.g., blood test, electrocardiogram, chest X-ray) several days before surgery. In the doctor's office, you will sign consent and other forms so that the surgeon knows your medical history (allergies, medicines/vitamins, bleeding history, anesthesia reactions, previous surgeries). Inform your healthcare provider about all the medications (over-the-counter, prescription, herbal supplements) that you are taking.

Stop taking all non-steroidal anti-inflammatory medicines (Naprosyn, Advil, Motrin, Nuprin, Aleve, etc.) and blood thinners (Coumadin, Plavix, etc.) 1 to 2 weeks before surgery as directed by the doctor. In addition, stop smoking, chewing tobacco, and drinking alcohol 1 week before and 2 weeks after surgery, because these activities can cause bleeding problems. No food or drink is permitted past midnight the night before surgery.

Morning of surgery

Shower using antibacterial soap. Dress in freshly washed, loose-fitting clothing.

Wear flat-heeled shoes with closed backs.

If you have instructions to take regular medication the morning of surgery, do so with small sips of water.

Remove make-up, hairpins, contacts, body piercings, nail polish, etc.

Leave all valuables and jewelry at home (including wedding bands).

Bring a list of medications (prescriptions, over-the-counter, and herbal supplements) with dosages and the times of day usually taken.

Bring a list of allergies to medication or foods.

Arrive at the hospital 2 hours before your scheduled surgery time (1 hour before at the outpatient surgery center) to complete the necessary paperwork and pre-procedure work-ups. An anesthesiologist will talk with you and explain the effects of anesthesia and its risks. An intravenous (IV) line will be placed in your arm.

The surgery generally takes 1 to 2 hours.

Step 1: prepare the patient

You will lie on your stomach on the table and be given light anesthesia. Next, the areas of your back and buttock are prepped where the leads and generator are to be placed.

Step 2: place the leads

The electrode leads are inserted with the aid of fluoroscopy (a type of X-ray). A small skin incision is made in the middle of your back (Fig. 3), and the bony vertebra is exposed.

Step 3: test stimulation (optional)

Depending on the SCS device being implanted, you may be awakened to help the doctor test how well the stimulation covers your pain areas. However, modern SCS device leads can be positioned based on anatomy or electric monitoring of the nerves. Settings from the trial will be used to program the pulse generator at the end of surgery, so your feedback is important to ensure the best pain relief.

In some cases, if the leads implanted during the trial are positioned perfectly, there is no need to reposition or insert new leads.

Step 4. tunnel the wire

Once the lead electrodes are in place, the wire is passed under the skin from the spine to the buttock, where the generator will be implanted.

Step 5. place the pulse generator

A small skin incision is made below the waistline. The surgeon creates a pocket for the generator beneath the skin (Fig. 5). The lead wire is attached to the pulse generator. The generator is then correctly positioned within the skin pocket.

The results of SCS depend on careful patient selection, successful trial stimulation, proper surgical technique, and patient education. Stimulation does not cure the condition that is causing pain. Rather, it helps patients manage the pain. SCS is considered successful if pain is reduced by at least half.

Published studies of spinal cord stimulation show good to excellent long-term relief in 50 to 80% of patients suffering from chronic pain [1-6]. One study reports that 24% of patients improved sufficiently to return to gainful employment or

housework with stimulation alone or with the addition of occasional oral pain medication [7].

SCS therapy is reversible. If a patient decides at any time to discontinue, the electrode wires and generator can all be removed.

After the lecture, the experiences of the Institute for Rehabilitation "Dr Miroslav Zotović" were presented, where 7 stimulators were installed. Then a discussion started with many questions, because this is a new method in the treatment of pain in this area.

Spinal cord stimulation therapy masks pain signals before they reach the brain. A small device, similar to a pacemaker, delivers electrical pulses to the spinal cord. It helps people better manage their chronic pain and reduce their use of opioid medications. It may be an option if you suffer chronic back, leg or arm pain and have not found relief with other therapies.

A spinal cord stimulator (SCS) device is surgically placed under your skin and sends a mild electric current to your spinal cord (Fig. 1). Thin wires carry current from a pulse generator to the nerve fibers of the spinal cord. When turned on, the SCS stimulates the nerves in the area where your pain is felt. Pain is reduced because the electrical pulses modify and mask the pain signal from reaching your brain.

Stimulation does not eliminate the source of pain, it simply interferes with the signal to the brain, and so the amount of pain relief varies for each person. Also, some patients find the tingling sensation unpleasant. For these reasons a trial stimulation is performed before the device is permanently implanted. The goal for spinal cord stimulation is a 50-70% reduction in pain. However, even a small amount of pain reduction can be significant if it helps you to perform your daily activities with less pain and reduces the amount of pain medication you take. Stimulation does not work for everyone. If unsuccessful, the implant can be removed and does not damage the spinal cord or nerves.

Some SCS devices use a low-frequency current to replace the pain sensation with a mild tingling feeling called paresthesia. Other SCS devices use high-frequency or burst pulses to mask the pain with no tingling feeling. A paresthesia-free setting is an option on most devices.

Stimulation does not eliminate the source of pain. It simply changes the way the brain perceives it. As a result, the amount of pain relief varies for each person. The goal for SCS is a 50 to 70% reduction in pain. However, even a small amount of pain

reduction can be significant if it helps you perform daily activities and reduces the amount of pain medication you take. SCS does not improve muscle strength.

Stimulation does not work for everyone. Some people may find the sensation unpleasant. Other people may not get relief over the entire pain area. For these reasons a trial stimulation allows you to try it for a week. If it doesn't work for you, the trial wires can be removed, leaving no damage to the spinal cord or nerves.

There are several types of SCS device systems. However, all have three main parts:

A pulse generator with a battery that creates the electrical pulses.

A lead wire with a number of electrodes (8-32) that delivers electrical pulses to the spinal cord.

A hand-held remote control that turns the device on and off and adjusts the settings.

Systems with a non-rechargeable battery need to be surgically replaced every 2 to 5 years, depending on the frequency of use. Rechargeable battery systems may last 8 to 10 years or longer, but you must remember to charge the system daily.

The pulse generator has programmable settings. Some SCS devices are able to sense a change in body position (sitting vs. lying down) and adapt the stimulation level to your activity. Other systems have leads that can be independently programmed to cover multiple pain areas. Some send a sub-perception pulse with no tingling. Your doctor will select the best type of system for you.

Who is a candidate?

An evaluation of your physical condition, medication regime, and pain history will determine whether your goals of pain management are appropriate for SCS. A neurosurgeon, physiatrist, or pain specialist will review all previous treatments and surgeries. Because chronic pain also has emotional effects, a psychologist will assess your condition to maximize the probability of a successful outcome.

Patients selected for SCS usually have had chronic debilitating pain for more than 3 months in the lower back, leg (sciatica), or arm. They also typically have had one or more spinal surgeries.

You may be a candidate for SCS if :

Conservative therapies have failed.

You would not benefit from additional surgery.

The pain is caused by a correctable problem and should be fixed.

You do not want further surgery because of the risks or long recovery. Sometimes SCS may be chosen over a large, complex spine surgery.

You do not have untreated depression or drug addiction; these should be treated prior to having a SCS.

You have no medical conditions that would keep you from undergoing implantation.

You have had a successful SCS trial.

SCS works better in the earlier stages of a chronic condition, before a cycle of pain-suffering-disability-pain is established.

An SCS can help lessen chronic pain caused by:

Chronic leg (*sciatica*) or arm pain: ongoing, persistent pain caused by arthritis, spinal stenosis, or by nerve damage.

Failed back surgery syndrome: failure of one or more surgeries to relieve persistent arm or leg pain, but not a technical failure of the original procedure.

Complex regional pain syndrome: a progressive disease in which patients feel constant, chronic burning pain, typically in the foot or hand.

Arachnoiditis: painful inflammation and scarring of the protective lining of the spinal nerves.

Other: stump pain, angina, peripheral vascular disease, multiple sclerosis, or spinal cord injury.

Neurosurgeons and doctors who specialize in pain management (an anesthesiologist or physiatrist) implant spinal cord stimulators.

Determining whether a spinal cord stimulator will be a good option for you is a two-step process. First, you must undergo a temporary trial to see if the device decreases your level of pain.

Stage 1. Trial "test drive"

Trial stimulation is a "test drive" to determine if an SCS will work for the type, location, and severity of your pain. It is performed at an outpatient center.

If you take blood-thinners, you are required to stop the medication 3 to 7 days prior to the trial.

A local anesthetic is given to numb the area in the lower back. Using X-ray fluoroscopy, a hollow needle is inserted through the skin into the epidural space between the bone and spinal cord. The trial lead is inserted and positioned over specific nerves. The wires are attached to an external generator worn on a belt (Fig. 2).

You will be sent home with instructions on how to use the trial stimulator and care for your incision site. Keep a written log of the stimulation settings during different activities and the level of pain relief. After 4 to 7 days, you will return to the doctor's office to discuss permanently implanting the stimulator or removing the trial leads.

Stage 2. Surgical implant

If the trial is successful and you felt greater than 50% improvement in pain, surgery can be scheduled to implant the SCS device in your body.

What happens before surgery?

You may be scheduled for presurgical tests (e.g., blood test, electrocardiogram, chest X-ray) several days before surgery. In the doctor's office, you will sign consent and other forms so that the surgeon knows your medical history (allergies, medicines/vitamins, bleeding history, anesthesia reactions, previous surgeries).

Inform your healthcare provider about all the medications (over-the-counter, prescription, herbal supplements) that you are taking.

Stop taking all non-steroidal anti-inflammatory medicines (Naprosyn, Advil, Motrin, Nuprin, Aleve, etc.) and blood thinners (Coumadin, Plavix, etc.) 1 to 2 weeks before surgery as directed by the doctor. In addition, stop smoking, chewing tobacco, and drinking alcohol 1 week before and 2 weeks after surgery, because these activities can cause bleeding problems. No food or drink is permitted past midnight the night before surgery.

Morning of surgery

Shower using antibacterial soap. Dress in freshly washed, loose-fitting clothing. Wear flat-heeled shoes with closed backs.

If you have instructions to take regular medication the morning of surgery, do so with small sips of water.

Remove make-up, hairpins, contacts, body piercings, nail polish, etc.

Leave all valuables and jewelry at home (including wedding bands).

Bring a list of medications (prescriptions, over-the-counter, and herbal supplements) with dosages and the times of day usually taken.

Bring a list of allergies to medication or foods.

Arrive at the hospital 2 hours before your scheduled surgery time (1 hour before at the outpatient surgery center) to complete the necessary paperwork and pre-procedure work-ups. An anesthesiologist will talk with you and explain the effects of anesthesia and its risks. An intravenous (IV) line will be placed in your arm.

The surgery generally takes 1 to 2 hours.

Step 1: prepare the patient

You will lie on your stomach on the table and be given light anesthesia. Next, the areas of your back and buttock are prepped where the leads and generator are to be placed.

Step 2: place the leads

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Ana Grubišić: Biopsychosocial assessment and treatment of pain

The experience of pain is among the most ubiquitous of humankind and is commonly understood to be a signal of harm to the integrity of the body. Pain is an expected consequence of acute illness, injury, and surgery, and it most often resolves with healing. The experience of chronic pain is an entirely different matter. Pain that persists beyond the expected period of healing or resolution of the source of pain serves little or no useful purpose and can emerge as a devastating blow to one's sense of well-being. Despite widespread beliefs to the contrary, even in the case of arthritis and other degenerative musculoskeletal disorders, pain is unreliably associated with disease severity and does not apparently serve an instrumental role in protecting the sufferer or in otherwise promoting adaptation and adjustment.

Unfortunately, evidence suggests that a majority of persons living in Western societies may suffer from persistent pain at some point in their lives, and some have suggested that chronic pain be considered a public health crisis. On average, reports estimate that the global prevalence of chronic pain is currently at 20% (**Boris-Karpel 2010**). Recent evidence suggests that the prevalence of chronic low back pain, the most common pain condition, is increasing at alarming rates

(**Sinnott & Wagner 2009**). For many, chronic pain contributes to declines in physical and social role functioning and to untold emotional suffering. Beyond its human costs are the estimated billions of dollars associated with persons' interactions with the healthcare system in efforts to find relief and costs associated with lost work productivity, including unemployment and disability benefits. In 2003, the American Productivity Audit reported that lost productive time from common chronic pain conditions such as headache, back pain, arthritis, and other musculoskeletal problems alone cost \$61.2 billion (**Stewart et al. 2003**).

On a more positive note, numerous important advocacy, legislative, and policy efforts can be cited as direct efforts to address the apparent crisis, at least in the United States. Over the past several decades, the field of pain medicine and science has rapidly developed, as demonstrated by the increased volume of pain-related content in the scientific literature, pain curricula development, and the availability of clinical practice guidelines (**Am. Pain Soc. Quality Care Comm. 1995, Gordon et al. 2005, Jacox et al. 1994**). The U.S. Congress designated the period from 2001–2010 as the Decade of Pain Control and Research, and in 2001, the Joint Commission, the major healthcare accreditation organization in the United States, promulgated standards for pain assessment and management (**Berry & Dahl 2000**). In the past decade, numerous legislative initiatives made their way through Congress, and most recently, bills supporting improvements in pain care in Department of Veterans Affairs and Department of Defense healthcare facilities were signed into law. In 1998, the Veterans Health Administration, the largest integrated healthcare system in the United States, launched its National Pain Management Strategy, which has helped to build capacity for pain care and pain relevant research for veterans (**Kerns et al. 2006**).

In the past half century, an integrative and multidimensional biopsychosocial theoretical framework has largely replaced more restrictive unidimensional and biomedical models as the predominant contemporary model of pain (**Gatchel et al. 2007**). The biopsychosocial model of pain builds on **Melzack & Wall's (1965)** groundbreaking “gate control theory of pain” that described pain as a central nervous system phenomenon in which ascending, sensory neural inputs from the periphery were hypothesized to be modulated by downward motivational-affective and cognitive-evaluative influences. More recently, Melzack and others extended this earlier view and described a “neuromatrix theory of pain” that highlights a more complex, widely distributed, and characteristic neural signature in the brain (**Melzack 2005**). The original articulation of the gate control theory and more recent elaborations of the biopsychosocial model have been associated with a virtual explosion of scientific investigation that cuts across the basic sciences, translational research, and specifically relevant to the current review, a broad array of clinical psychological research.

A large, broad, and growing empirical literature continues to inform increasingly sophisticated understanding of key psychological and behavioral factors that reliably influence the perpetuation, if not the development, of pain and pain-related disability. Early work focused on the identification of personality factors hypothesized to be causally related to the development of chronic pain, such as a predisposition toward denying emotional and/or interpersonal distress, a somatic focus of attention, or displaying features associated with a “depression-prone” personality such as pessimism (**Blumer & Heilbronn 1982**, **Gentry et al. 1974**). A major focus of both laboratory analogue and clinical research is on articulating both the affective properties of the experience of pain and the central role that emotions play in determining pain severity, quality, and impact. Perhaps not surprisingly, the role of negative emotions, especially anxiety, depression, and anger, has served as the primary focus of investigation (**Fernandez & Kerns 2008**). **Fordyce's (1976)** operant behavioral model has served an important heuristic role that continues to yield important discoveries and a sophisticated understanding of the social learning context. The model continues to inform research that has identified the role of social contingencies (e.g., expressions of sympathy from family members and friends, disability payments, and prescription medications) for overt expressions of pain, termed “pain behaviors” (e.g., verbal and paraverbal expressions of pain, visits to doctors, and avoidance of work-related activities and social responsibilities). The cognitive-behavioral perspective of **Turk et al. (1983)** remains a dominant model in the field and continues to encourage research that has led to the identification of cognitive and other psychological factors that appear to be strongly and reliably positively associated with pain severity and disability. Among factors that have the strongest empirical support are such constructs as pain catastrophizing (**Turner & Aaron 2001**), fear avoidance (**Vlaeyen & Linton 2000**), low self-efficacy and lack of perceived control (**Arnstein et al. 1999**, **Litt 1988**), and passive pain coping (**McCracken & Eccleston 2003**).

Significant advances have continued on the clinical front as well. Pain continues to be viewed as a private, covert, and subjective experience, so perhaps it is not surprising that clinical psychologists continue to play central roles in the development of psychometrically sound and sophisticated measures of pain and the broader multidimensional experience of chronic pain. In the clinical setting, psychological measures of pain severity or intensity, pain-related disability or interference, and emotional impact have taken their place as the most widely employed measures of pain treatment effectiveness. Psychological measures are widely recommended to be used in the context of a comprehensive pain assessment in order to better characterize, if not explain, an individual's experience of pain and to inform treatment decision-making and planning. These measures are also employed for determining an individual's appropriateness for specialized pain interventions such as implantable pain medication delivery systems and neural modulation therapies. Over the past ten years, an important consensus process, called the Initiative for Methods, Measurement, and Pain Assessment in Clinical Trials (which includes pain experts from academia,

industry, government agencies, and patient advocacy groups), has endorsed several psychological measures of core domains for use in pain clinical trials (**Dworkin et al. 2005**). Most recently, the National Institutes of Health has launched a broadly conceived and novel initiative called Patient-Reported Outcome Measurement Information System, which blends classical test theory and modern measurement theory methods, including item response theory and computer adaptive testing, for the efficient assessment of core constructs related to chronic disease. The majority of the proposed measures use items from existing psychological instruments, such as one of the first published measures designed to assess pain behavior frequency (**Revecki et al. 2009**).

Most experts in the field of pain management appreciate the importance of a comprehensive, multidimensional, multimodal, and interdisciplinary approach to management of chronic pain. In this context, psychological and behavioral interventions are widely accepted as important, if not critical, components of effective pain care. As early as the late 1960s, data began to emerge that supported the effectiveness of psychological interventions for persistent pain, either in the context of interdisciplinary pain programs or in isolation of other interventions. Research has documented the benefits of various psychological interventions for a broad array of common pain conditions such as headache, low back, and arthritis, among many others. A growing number of systematic and meta-analytic reviews document the efficacy, effectiveness, and even cost-effectiveness of psychological interventions (**Hoffman et al. 2007**). One particularly influential meta-analysis of the cost-effectiveness of interdisciplinary pain care that included psychological interventions, published by Flor and her colleagues, documented the benefits of such programs on pain and functioning, including return to work (**Flor et al. 1992**). Clinical investigators have specified roles for psychologists and other mental health professionals in interdisciplinary pain rehabilitation programs (**Townsend et al. 2006**). A recent line of investigation has begun to focus on identification of predictors of change during pain treatment, the process of change, and the potential to improve outcomes through a process of matching individual characteristics with different treatments (**Asenlof et al. 2005**). Particularly exciting are reports on the cost-effectiveness of population-based dissemination of psychological interventions for persistent pain (**Kroenke et al. 2010, Lamb et al. 2010**).

The primary purpose of this article is to provide a focused and critical review of the broad domain of psychological interventions for chronic pain. Using a framework offered by our group in a recently published meta-analysis of psychological interventions for chronic low back pain (**Hoffman et al. 2007**), four categories of psychological interventions are considered: self-regulatory, behavioral, cognitive-behavioral, and acceptance and commitment therapies. Future directions, including the need to address pain treatment disparities, age-related differences in pain care, and the innovative use of technologies to promote

access to psychological interventions for chronic pain management, are also discussed.

Biofeedback

Biofeedback is a systematic methodology through which individuals are provided with real-time feedback about a variety of physiological processes, with the goal of developing an awareness of when these processes change so that the individual can learn to voluntarily exert control over the bodily reactions associated with these processes. In the context of pain management, the physiological targets are typically factors that are directly associated with pain exacerbations or those related to emotional responses to the pain. Biofeedback plays a prominent role in the treatment of headache pain. Recent meta-analyses have demonstrated empirical support for a variety of biofeedback methods for chronic headache, including blood volume pulse feedback, electromyographic feedback, temperature feedback, galvanic skin response, and encephalography feedback. Among the outcomes assessed in these trials were frequency of headache, self-efficacy for self-management of headache, anxiety, depression, and use of analgesic medication. On average, effect sizes in these meta-analyses were medium to large, and clinical effects were shown to persist for approximately 15–17 months post treatment for both migraine and tension-type headaches in adults, adolescents, and children (**Nestoriuc et al. 2008, Nestoriuc & Martin 2007**).

Relaxation Training

Relaxation training is an adjuvant method that is often used in the context of biofeedback training and also as a component part of other treatment regimens (e.g., cognitive behavioral therapy). Relaxation training focuses on the identification of states of tension within the mind and body, followed by the application of systematic methods such as diaphragmatic breathing (deep breathing), progressive muscle relaxation, or visualization to reduce tension and to alter the perception of associated physical pain. Pain produces both physiological and emotional stresses, which collectively feed into a cycle that results in increased pain perception and ongoing alteration of the physiology of the body in ways that only exacerbate pain (muscle tension or spasm, constriction of blood vessels). Relaxation training focuses on educating individuals about the relationship between emotional and physiological stresses and seeks to empower individuals by teaching them systematic self-control methods for altering physical states (e.g., muscle tension) and psychological states (e.g., stress). The use of relaxation training for the management of chronic pain has been shown to be effective through studies on a variety of conditions, including migraine pain (**Kaushik et al. 2005**), musculoskeletal pain (**Middaugh et al. 1991**), and low back pain (**McCauley et al. 1983, Strong et al. 1989**).

Hypnotherapy

Another self-regulatory approach that psychologists utilize in the management of chronic pain is hypnotherapy. Closely related to relaxation training, hypnotherapy involves an altered state of awareness that is guided by suggestive statements made by the hypnotherapist that are designed to focus participants' attention in such a way that they come to change their own subjective experience of pain. As with relaxation training, participants are taught methods for reconnecting with this state of hypnotic relaxation at any time by using behavioral cues, such as deep breathing. Although the methods used to deliver hypnotherapy for chronic pain vary widely (**Jensen & Patterson 2006**), defining guidelines for the practice of hypnotherapy have been published by the American Psychological Association's Society of Psychological Hypnosis (Division 30) (**Green et al. 2005**). However, despite the variations in methodology utilized, a growing body of literature provides empirical support for the use of hypnotherapy for pain management. A recent meta-analysis of 13 controlled trials of hypnotherapy for a variety of chronic pain conditions, including cancer pain, low back pain, arthritis, pain from sickle cell disease, temporomandibular pain, fibromyalgia, and mixed pain conditions, found good empirical support for the use of this methodology. These findings were based on comparisons to either control conditions or other baseline interventions such as education and physical therapy (**Elkins et al. 2007**). These authors do highlight the relatively low number of controlled studies that have been conducted on hypnotherapy, but these reported findings are promising.

Mindfulness

One final and closely related self-regulatory approach for chronic pain management is mindfulness meditation. Rooted in the principles of Theravada Buddhism, mindfulness meditation is based on increasing intentional self-regulation of attention to what is happening in the moment. One of the pioneers in the field of mindfulness meditation is Jon Kabat-Zinn, who has developed mindfulness-based stress-reduction programs that have been effectively utilized in the treatment of chronic refractory pain. Similar in many ways to the previously described methods of relaxation training and hypnotherapy, the goals of mindfulness meditation include the attainment of both relaxation and greater focus of attention. However, mindfulness meditation emphasizes the attainment of stress reduction through increased focus on phenomenon that are occurring in the moment, without the natural tendency to interpret such events or form associations between events and our thoughts about them. Instead, the focus is on fully experiencing the phenomenon in rare form in the moment, without reference to the past or future. In using this approach for pain management, one of the goals is to separate the sensation of pain from the thoughts that often occur in response to such sensations. These thoughts are typically rooted in the past and project to the future, thus triggering emotional responses that are based on associations. By focusing only on the phenomenon of pain, as if one is a detached observer, an individual can learn to separate the experience of pain from these thoughts. In so doing, the individual can begin to accept the pain as it is without the cognitive and emotional connections that are typically alarming to the patient and that serve to

make the experience of pain worse. The early works of Kabat-Zinn in applying the mindfulness meditation approach to chronic pain management demonstrated the effectiveness of this approach in reducing current pain intensity, improving body image, increasing physical activity, and improving mood and anxiety (**Kabat-Zinn 1982, Kabat-Zinn et al. 1985**). A more recent meta-analysis found that mindfulness-based stress reduction was an effective intervention for helping individuals to cope with a variety of health conditions, including chronic pain (**Grossman et al. 2004**).

BEHAVIORAL APPROACHES

The use of behavioral methods in the treatment of chronic pain is based largely on the operant conditioning model of learning that was delineated by B.F. Skinner. The underlying premise of this model is that behaviors that are reinforced tend to increase in frequency, whereas behaviors that are punished or not reinforced tend to decrease in frequency. In the context of chronic pain, the behaviors that are targeted through behavioral strategies are often referred to as pain behaviors, which can include response patterns such as excessive verbalization of pain (grunting, sighing), frequent discussion about pain, facial expressions, guarded movements, or restriction of movement. These behaviors are commonly reinforced through social contingencies, such as responses from other people. These responses can include expressions of sympathy, relieving the individual of responsibility for even basic activities of daily living (solicitousness), or verbal reinforcement of the individual's pain symptoms. The reinforcement provided by such responses serves to increase the pain behaviors and thus contribute to what has been referred to as the disuse syndrome. The disuse syndrome is marked by excessive pain behaviors that are in the service of decreasing physical activity, which leads to physical deconditioning and increased risk for the development of worsening pain and other medical comorbidities (e.g., obesity) (**Verbunt et al. 2003**).

COGNITIVE-BEHAVIORAL THERAPY

CBT is an empirically supported psychotherapeutic treatment that aims to help individuals resolve their problems concerning maladaptive emotions, behaviors, and cognitions through a goal-oriented, systematic procedure. Originally developed to better address the treatment needs of individuals with depression and anxiety disorders, over time CBT has been effectively applied as a treatment for a host of psychophysical disorders (e.g., insomnia, posttraumatic stress disorder, bulimia nervosa, and chronic fatigue syndrome), including chronic pain (see **Morley et al. 1999** for review). The development of CBT for pain management is steeped in the cognitive behavioral model of pain management, which has been developing over the past four decades. **Fordyce (1976)** pioneered the behavioral model of multidisciplinary pain management. During this time, CBT primarily focused on operant conditioning: overt motor and physiologic self-management techniques such as reinforcement for participation in functional activities,

progressive relaxation, and self-hypnosis. An individual's behavioral responses to pain were modified according to the consequences of the environment in which the behavior occurred: Behavior that is reinforced increases, and behavior that is ignored decreases. Over time, CBT evolved to include more cognitive interventions, such as the identification of negative automatic thoughts and replacement of these maladaptive thoughts with adaptive, beneficial ones (Turk et al. 1983). The cognitive aspects of CBT have been reviewed and found to contain critical aspects of treatment that not only reduce pain and increase functional ability, but also stabilize mood and decrease disability (Kerns et al. 1986). Most recently, CBT has been subsumed by the biopsychosocial conceptualization of pain management (Turk & Monarch 1996). The hallmark of the biopsychosocial model of pain and its management is the notion that pain is a complex experience that is influenced not only by its underlying pathophysiology, but also by an individual's cognitions, affect, behavior, and sociocultural status.

ACCEPTANCE AND COMMITMENT THERAPY

Acceptance and commitment therapy (ACT) (Hayes et al. 1999) is an acceptance- and mindfulness-based psychotherapeutic intervention that can be applied to many clinical disorders, including chronic pain. ACT is based on relational frame theory, a comprehensive theory of language and cognition that is framed as an offshoot of behavior analysis (Hayes et al. 2001). ACT differs from traditional CBT in that rather than trying to teach people to better control their thoughts, feelings, sensations, memories and other private events, ACT emphasizes observing thoughts and feelings as they are, without trying to change them, and behaving in ways consistent with valued goals and life directions. The core conception of ACT is that psychological suffering is usually caused by the interface between human language and cognition and the control of human behavior by direct experience. Psychological inflexibility is argued to emerge from experiential avoidance, cognitive entanglement, attachment of a conceptualized self, loss of contact with the present, and the resulting failure to take needed behavioral steps in accordance with core values. Therefore, one of the primary goals of ACT is to promote psychological flexibility, which means contacting the present moment fully as a conscious human being, and based upon what the situation affords, changing or persisting in behavior in the service of chosen values. ACT has shown promising results in several recent studies examining the benefits of ACT for people suffering with chronic pain (Dahl & Lundgren 2006, McCracken et al. 2004, Robinson et al. 2004).

The basic premise of ACT as applied to chronic pain is that while pain indeed hurts, it is an individual's struggle with pain that causes suffering (Dahl & Lundgren 2006). The pain sensation itself is an adaptive reflex serving the function of alerting us to danger, tissue damage, or the threat of such damage. The noxious sensation of pain is critical for our survival. Likewise, the same applies to emotional pain, such as the sadness and despair often experienced after the death

of a loved one or the loss of a relationship. It is natural and necessary to experience such pain in the bereavement process in order to heal and move on with life. In the case of chronic pain, causal and maintaining factors may be unclear, and efforts to reduce or eliminate the pain may be unsuccessful. For these reasons, continuing attempts to control pain may be maladaptive, especially if they cause unwanted side effects or prevent participation in valued activities, such as those involving work, family, or community (**McCracken et al. 2004**).

When patients find their pain unacceptable, they are likely to attempt to avoid it at all costs and seek readily available interventions to reduce or eliminate it. These efforts may not be in their best interest if the consequences include no reductions in pain and many missed opportunities for more satisfying and productive functioning. From this conceptualization came much of the research examining the acceptance of pain, the rationale being that some patients may achieve better overall adjustment to chronic pain if they reduce their avoidance and other attempts to control pain, accept it, and direct their efforts toward goals they can achieve. As a result, several studies have now shown that greater acceptance of pain is associated with reports of lower pain intensity, less pain-related anxiety and avoidance, less depression, less physical and psychosocial disability, greater physical and social ability, and better work status (**McCracken 1998, McCracken & Velleman 2010, McCracken & Zhao-O'Brien 2010, Vowles & McCracken 2008**). Also, acceptance of pain was found to be a significant predictor of adjustment on several measures of patient function, independent of perceived pain intensity (**McCracken 1998**).

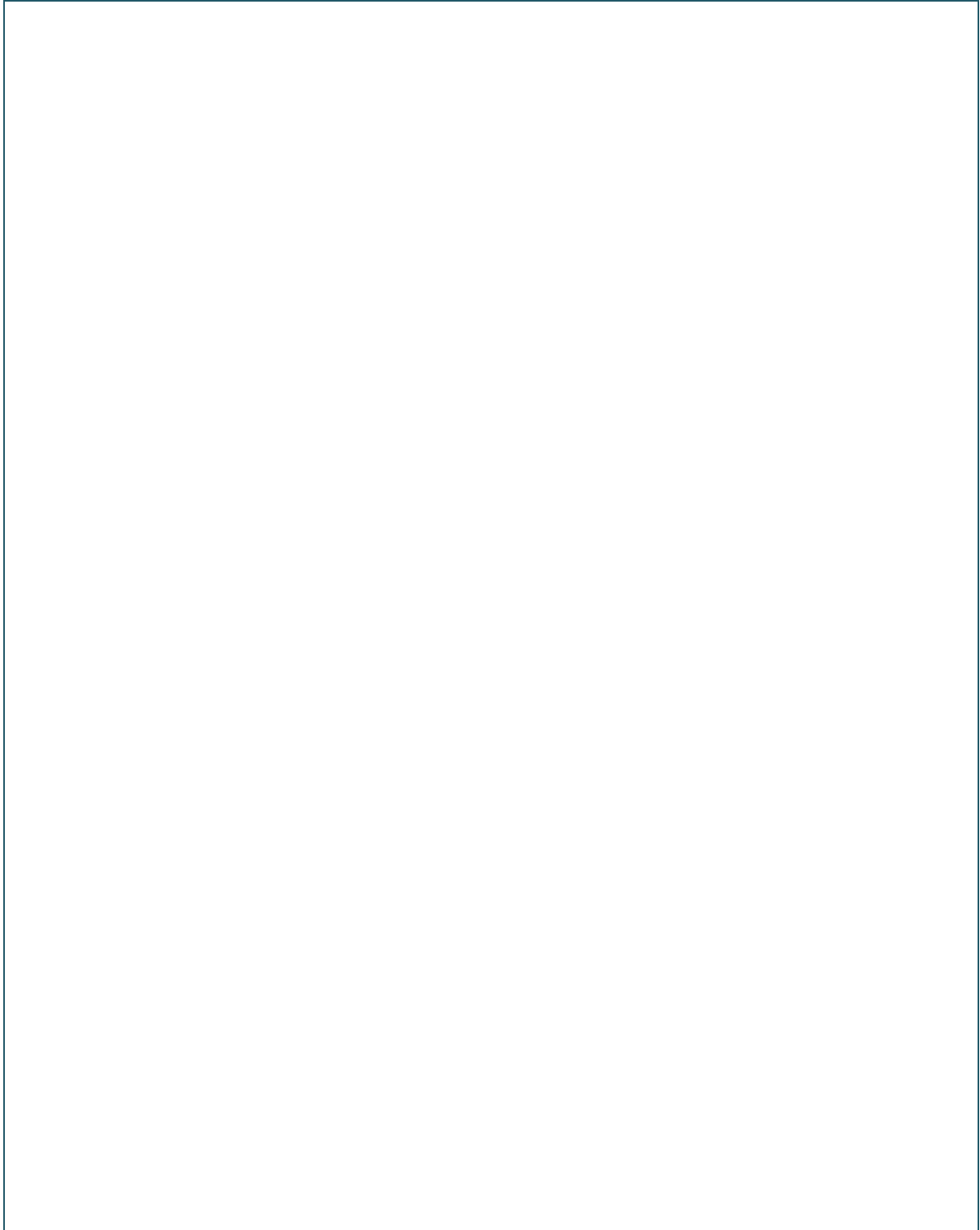
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Acceptance and commitment therapy (ACT) (**Hayes et al. 1999**) is an acceptance- and mindfulness-based psychotherapeutic intervention that can be applied to many clinical disorders, including chronic pain. ACT is based on relational frame theory, a comprehensive theory of language and cognition that is framed as an offshoot of behavior analysis (**Hayes et al. 2001**). ACT differs from traditional CBT in that rather than trying to teach people to better control their thoughts, feelings, sensations, memories and other private events, ACT emphasizes observing thoughts and feelings as they are, without trying to change them, and behaving in ways consistent with valued goals and life directions. The core conception of ACT is that psychological suffering is usually caused by the interface between human language and cognition and the control of human behavior by direct experience. Psychological inflexibility is argued to emerge from experiential avoidance, cognitive entanglement, attachment of a conceptualized self, loss of contact with the present, and the resulting failure to take needed behavioral steps in accordance with core values. Therefore, one of the primary goals of ACT is to

promote psychological flexibility, which means contacting the present moment fully as a conscious human being, and based upon what the situation affords, changing or persisting in behavior in the service of chosen values. ACT has shown promising results in several recent studies examining the benefits of ACT for people suffering with chronic pain (**Dahl & Lundgren 2006, McCracken et al. 2004, Robinson et al. 2004**).

The basic premise of ACT as applied to chronic pain is that while pain indeed hurts, it is an individual's struggle with pain that causes suffering (**Dahl & Lundgren 2006**). The pain sensation itself is an adaptive reflex serving the function of alerting us to danger, tissue damage, or the threat of such damage. The noxious sensation of pain is critical for our survival. Likewise, the same applies to emotional pain, such as the sadness and despair often experienced after the death of a loved one or the loss of a relationship. It is natural and necessary to experience such pain in the bereavement process in order to heal and move on with life. In the case of chronic pain, causal and maintaining factors may be unclear, and efforts to reduce or eliminate the pain may be unsuccessful. For these reasons, continuing attempts to control pain may be maladaptive, especially if they cause unwanted side effects or prevent participation in valued activities, such as those involving work, family, or community (**McCracken et al. 2004**).

When patients find their pain unacceptable, they are likely to attempt to avoid it at all costs and seek readily available interventions to reduce or eliminate it. These efforts may not be in their best interest if the consequences include no reductions in pain and many missed opportunities for more satisfying and productive functioning. From this conceptualization came much of the research examining the acceptance of pain, the rationale being that some patients may achieve better overall adjustment to chronic pain if they reduce their avoidance and other attempts to control pain, accept it, and direct their efforts toward goals they can achieve. As a result, several studies have now shown that greater acceptance of pain is associated with reports of lower pain intensity, less pain-related anxiety and avoidance, less depression, less physical and psychosocial disability, greater physical and social ability, and better work status (**McCracken 1998, McCracken & Velleman 2010, McCracken & Zhao-O'Brien 2010, Vowles & McCracken 2008**). Also, acceptance of pain was found to be a significant predictor of adjustment on several measures of patient function, independent of perceived pain intensity (**McCracken 1998**).



Attachments

Agenda (pdf)	Modern approaches to the diagnosis and treatment of pain
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Attendance sheet (pdf)	Anex 4-HEPMP-attendance list Slatina (pdf)
Photos (jpg)	Title(s)
Quality control (pdf)	Title Accreditation by The Ministry of Health and Social Welfare; Event evaluation list- Anex 6 HEPMP Output test
Deliverable (pdf)	Website of the Faculty of Medicine of the University of Banja Luka; Website of the Institute for Rehabilitation „Dr Miroslav Zotović“ Website of the Association of Psychiatrists of the Republic of Srpska Website of the
Presentations (pdf)	<i>Klinički pristup dijagnostici, patofiziologiji i liječenju neuropatske bol</i> prim.dr Mira Fingler, počasna predsjednica HUBKB, Hrvatska
	<i>Opioidi u terapiji bola</i> Prof.dr Darko Golić, UKC RS
	<i>Adjuvantni analgetici u terapiji neuropatskog bola</i> Mr pharm. Gordana Ljubojević, ZFMR „Dr Miroslav Zotović“
	<i>Bol u starijih osoba –poseban izazov u rehabilitaciji</i> Prof.dr Snežana Tomašević Todorović, Klinika za medicinsku rehabilitaciju, Novi Sad, Srbija
	<i>Diskusija</i>
	<i>Intervencijsko liječenje hronične boli</i> Doc.dr Ivan Radoš, Zavod za liječenje boli Kliničkog bolničkog centra, Osijek, Hrvatska
	<i>Stimulacija kičmene moždine u tretmanu hroničnog bola</i> Prof.dr Tatjana Bućma, ZFMR „Dr Miroslav Zotović“ mr sc. dr Ostoja Savić, UKC RS
	<i>Rana iskustva i rezultati SCS sistema u tretmanu hronične boli</i> dr Tatjana Boškić, ZFMR „Dr Miroslav Zotović“
<i>Biopsihosocijalna procjena i tretman bola</i> dipl.psiholog Lena Topić Arambašić, soc.radnik Ana Grubišić ZFMR „Dr Miroslav Zotović“	
Other personal remarks	

There was great interest in the seminar, because pain therapy is multidisciplinary, but insufficiently represented in education. The conclusion of the seminar is that due to the broad topic, lectures will be organized that will be intended for narrow specialties.

Organisation details

Invitation sent to	Clinical Center Banjaluka Institute for Rehabilitation „Dr Miroslav Zotović“
Date of event material release	11.05.2019.
Date of participants list's finalisation	11.05.2019.
Date of agenda finalisation	30.06.2020.
Number of participants (according to the participants list)	30
Comments	

Problems encountered during the event preparation phase

Please add your comments, if any:

Strengths and limitations of the event (please include comments received)

Strengths of the event and contributions or activities by participants	Participants learned that different pain states, as well as diseases associated with pain syndrome, are recognized, assessed for the intensity of pain, and determined by the intensity of the type of therapy. They were also introduced to the side effects of analgesic therapy. They are aware of the biggest mistakes that doctors make in their offices when treating pain.
Suggestions for the improvement	In the next seminar, we intend to dedicate separate lectures to psychiatric treatment and pain, pain after polytrauma, and pain in the elderly population.
Any further comments	

Evaluation details

Results of evaluation of the general organisation of the event

Description
The participants highly rated the choice of educational topics, the content of the education program, the method used, the duration and organization of the education.
Table(s)/Figure(s)

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Results of evaluation of general working communication

Description
Table(s)/Figure(s)

Results of evaluation of overall success of the event

Description
Table(s)/Figure(s)

Please indicate your suggestions for further event's improvement:

Location, date

Slatina,11.05.2019.

Signature

