REVIEW

Acute and chronic pain: where we are and where we have to go

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ABSTRACT

In recent years, increasing attention has been focused on the treatment of acute and chronic pain with a considerable number of publications about it. Nevertheless all the attention focused on it, the evidence of pain treatments is still unfolding, and occasionally conflicting. Hence it is still necessary that we point out our research efforts in trying to obtain a better understand of pathophysiology of pain and of real efficacy and safety of acute and chronic pain treatments. Our goal with this review is to summarize the latest research trends and the most advanced therapeutic standards for pain syndromes described in the literature, the discussion will be divided in four main topics, as these topics were treated during the SIMPAR (Study In Multidisciplinary PAin Research) meeting, held on December 2010 in Pavia: pathophysiology of pain, acute postoperative pain, opioids and pain, and chronic pain (Failed Back Surgery Syndrome). In the chapter of pathophysiology of pain we analyzed how to obtain a more personalized treatment through the study of the genetic and neurophysiological characteristics of patients and how to select the right local anesthetic according to anatomic and metabolizing patterns of patients. In acute postoperative pain we focalized our attention on the evidence supporting the use of continuous peripheral nerve blocks in the treatment of postoperative pain and in the prevention of chronic persistent post-operative pain, with a special attention in preventing side effects of regional anesthesia. We also reviewed the current evidence about the use of new very interesting modality to control postoperative pain after laparoscopy: pre-emptive nebulization of local anesthetic in abdominal cavity. As opioids are currently widely used to control chronic oncologic and non-oncologic pain, in this review we analyzed the level of evidence for their use, how to manage them better and psychological factors that can affect their success and/or determine addiction. Finally, we summarized the current evidence about Failed Back Surgery Syndrome focalizing our attention both in diagnosing it correctly and treating this syndrome with specific knowledge of the anatomic space that we have to approach and applying the possible treatments depending on pain pathophysiology and patient characteristics. In conclusion, it is important to try to personalize even better the therapy of patients with acute and chronic pain through a more accurate knowledge of anatomy, pathophysiology of pain, pharmacokinetic of pain drugs and of new device/therapies available. *(Minerva Anestesiol 2012;77:222-35)*

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In recent years, increasing attention has been focused on the treatment of acute and chronic pain. In Pubmed, from January 2010 to January 2011, we found more than 32000 articles have "pain" as a keyword. In limiting the search parameters to studies on humans, we found 14892 articles including 2,288 reviews and 30 practice guidelines. Despite this considerable number of articles and consequent improvements in creating more reliable animal models,[1, 2] understanding the pathophysiology of pain,[3] and evaluation of new drugs, pain continues to be a major

health and social problem. In fact, in five European countries, approximately 49 million people reported pain and 11.2 million reported severe pain with a consistent correlation between severity of pain and impairment of health-related quality of life, increased healthcare resource utilization,[5] and decreased labor force participation.[6]

For all these reasons, it continues to there be a growing need to update our knowledge and understand this complex phenomenon. In this review, we analyze and summarize the four main topics that were discussed during the last international meeting on acute and chronic pain (SIMPAR: Study in Multidisciplinary Pain Research), which was held in Pavia, Italy, on 3rd-4th of December, 2010: pathophysiology of pain, acute postoperative pain, opioids and pain, and chronic pain. We reviewed the topics analyzing and comparing them also with the literature published in the period between November 2010-June 2011.

Pathophysiology of pain

Pain is defined as "an unpleasant sensory and emotional experience of actual or potential tissue damage or an experience expressed in such terms".[7] During the last 13th World Congress on Pain in Montreal (Canada) the delegates adopted a Declaration that Access to Pain Management is a Fundamental Human Right.[8]

Pain is classified into three different types:[3, 9] inflammatory, neuropathic and dysfunctional pain. Although this kind of classification schematizes and facilitates our clinical approach to treating pain, there is a large interindividual variability in the response of analgesics when administered to patients. However, in recent years, predicting the response of patients to analgesics is possible with improved genetic and neurophysiological characterizations of patients and better understanding of the pharmacokinetic properties of the medications administered, such as local anesthetics during epidural infusion.

Genetic predictability of pain response: how we can predict pain

In the last decade, genetic studies of pain have been undertaken to determine if it is possible to explain interindividual variability in pain perception, response to analgesic drugs, and risk of developing chronic pain syndromes.[10] Lacroix-Fralish [11] established a Pain Genes Database, in which over 300 candidate genes were published based on research in animal models. Furthermore, there is good evidence that, in some "pain syndromes" such as migraine,[12] spinal pain,[13] lower back pain, neck pain in females [14] and fibromyalgia [15, 16] a heritable risk can be identified.

Currently, among genes correlated with pain perception, catechol-O-methyltransferase (*COMT*) gene is the best studied and associated with perception of pain in both acute and chronic pain states as well as the risk of developing chronic pain after an injury.[17-23] Considering that *COMT* metabolizes catecholamine and enkephalins modulating the neurotransmission of pain, patients homozygous for the rare allele met158 complain more consistently of pain following noxious stimulation [24, 25] and that these individuals have a *COMT* enzyme activity 11 times lower [26] than heterozygotes or homozygotes for the more common allele 158 (val/val).

Another well-studied gene is the opioid receptor μ1 (*OPRM1*) that exhibits a polymorphism [27] and is related not only to pain sensitivity,[28-31] but also to opioid consumption and development of side effects.[32] Furthermore, there is some preliminary evidence that significant synergistic effects exist in patients who possess both *COMT* and *OPRM1* polymorphisms with respect to a predisposition to experiencing pain.[33]

Furthermore, recent studies [34] have demonstrated that the expression of the opioid receptors can be modified by virally mediated gene transfer in afferent neurons. In particular, an increased expression is associated with the administration of a lower dose of peripheral opioids to produce adequate analgesia. Accordingly, this strategy may be used in treating neuropathic pain to avoid the dose-limiting and central nervous system-mediated side effects such as sedation and addiction.

Another promising field of research about genetics and pain is related to voltage-gated channels.[35] These ion channels could be implicated in the perception of pain, response to a new class

of specific analgesic drugs, and defining the potential risk of a patient developing chronic pain. The candidate genes are *SCN9A* for sodium channels,[36, 37] *CNA1B* [38] for calcium channels, and *KCNQ2* [39, 40] and KCNQ339 for potassium channels.

Finally, another issue involving genetics and pain concerns enzymes metabolizing drugs [41] such as cytochrome CYP450 enzymes (CYP), these liver enzymes are important for the activation or inactivation of opioids and several other drugs used in pain therapy (such as anticonvulsants and tricyclic antidepressants), and UGT2B7, which metabolizes morphine to morphine-3-glucoronide (inactive metabolite with possible neutoxicity) and morphine-6-glucoronide (active metabolite). Detecting genetic variants of these genes could assist in predicting if a drug could be toxic or if a patient could be responsive to a specific treatment.[22] For example, concerning the metabolizing enzymes, approximately 70 CYP2D6 allelic variants (the number is still growing) give rise to substantial interindividual variability in the metabolism of the substrates, and create four phenotypic classes: extensive metabolizers (EMs), intermediate metabolizers (IMs), poor metabolizers (PMs), and ultra-rapid metabolizers (UMS). EMs metabolize substrates at an average rate; IMs metabolize substrates at a slower rate; PMs have a defective metabolism (with an increased risk of adverse effects due to drug accumulation or lack of efficacy because certain drugs are activated by metabolic reactions, such as codeine); and finally, UMs metabolize the substrates more quickly (with an increased risk of adverse effects due to active metabolite accumulation or lack of efficacy because other drugs are metabolized to an inactive compounds).[42]

Acute pain and neurological evaluation: can we predict pain? [43]

Another great research challenge in order to predict how a patient will respond to a specific noxious stimulus (for example, postoperative pain) is to investigate a possible correlation between specific preoperative neurological markers [44] with pain in the postoperative period. Tools such as quantitative sensory testing (QST), which allows evaluation of patient responses to peripheral noxious stimuli (mechanical, thermal, or electrical stimuli),[43, 45] have been useful. In a review by Werner,[43] it was reported that preoperative QST was significantly related to postoperative pain [46, 47] (predicting 4-54% of the variance of postoperative pain complained of by patients) or to medication consumption in the postoperative period.[48] In elective cesarean sections, preoperative QST evaluation could help to predict postoperative pain intensity,[49] even though all these results are widely influenced by several factors (psychological variables, type of surgery, type of anesthesia, etc.) that can confound the real predictive value of this tool.[50]

There have also been studies that investigated whether preoperative QST assessment can predict the development of persistent postoperative pain (PPP) in certain specific surgical settings, such as herniotomy, thoracotomy, or breast cancer surgery. They also helped us to improve our knowledge of pathophysiology of postoperative pain. For example, Werner underlined how, in PPP after herniotomy, the combination of spontaneous or evoked pain, cutaneous sensory loss, and increased pain threshold is suggestive of a neuropathic component.[42] Repetitive pin-prick or brush stimulation significantly increased pain intensity in 51% of PPP patients compared with 15% of pain-free individuals.[51]

More rational surgical procedure-specific approach trials are needed before these results can be incorporated into clinical practice, but the results are promising in developing the tools that can predict the risk of a patient not only complaining of postoperative pain but also developing PPP.

Epidural pharmacokinetics of local anesthetics

Although epidural anesthesia is widely accepted, considerable variability is still reported in the efficacy of blocks performed due to the anatomical properties of the epidural space [53] and to the different pharmacokinetic profiles of local anesthetics injected.[52] Therefore, in order to improve the efficacy of treatment of postoperative pain, these problems must be understood in order

to choose the right drug for the right patient. When we inject local anesthetics into the epidural space, the distribution of epidural fat must be considered [53, 54] (epidural fat increases in the cranio-caudal direction and is reduced as the age of the patient increases) because the bioavailability of these agents may be reduced. Furthermore, during the diffusion of the medication through the spinal meninges (pia and dura mater), based on its lipophilicity, the capillary vessels between these layers may increase the clearance of the drug. This message is very important because we have to give more attention in using epidural blocks in patients who can have alterations of epidural fat (as in the elderly).

As local anesthetics are relatively lipophilic drugs, the absorption rate into the systemic circulation is correlated both to the amount of epidural fat and to local blood flow (generally at least 95% of the drug passes to the systemic circulation through epidural fat and epidural veins [55]). Currently, with stable-isotope methods, it is possible to evaluate the absorption profile of all local anesthetics administered epidurally.[56-58] The absorption profile has also been confirmed for continuous epidural administration with a plateau of total plasma concentration after the first 24-48 hours.[59, 60] The distribution and elimination of local anesthetics can vary owing to patient-related and enantiomero-selective factors: the total plasma clearance of local anesthetics is age-related for ropivacaine[58,60] (with a reduction of elimination with increasing age), but not for levobupivacaine[57]. Furthermore, the reduction of epidural fat, sclerosis and calcification of intervertebral foramina with increasing age can explain the increase of the epidural longitudinal spread of lipophilic local anesthetics.[61, 62] On the basis of these data, Olofsen *et al*.[63] also developed a population pharmacokinetic/pharmacodynamic model that could predict the absorption profiles and disposition of levobupivacaine or ropivacaine after single-shot epidural administration. Hence, in order to improve the success of postoperative analgesia, the importance of the choice of the best local anesthetics on the basis of characteristics of the patient has become evident. For example, in elderly people we have to choose the drug that could not present variations in its clearance and pharmacokinetic properties and to use lower flow in order to reduce the possible spread of the drug.

Acute postoperative pain

Acute postoperative pain continues to be a major problem [64] despite the safety of the drugs [65] used in perioperative settings and the guidelines available.[66, 67] for correct management of postoperative pain. Hence, it is very important to focus attention on all the multimodal techniques that can permit us to control pain in order to achieve improved outcome. While there are still significant differences across Italian hospitals (university *vs*. non-university hospitals and among geographic locations) with respect to the use of standardized protocols/guidelines and the use of regional anesthesia and patient-controlled modalities, there has been significant improvement in adopting European standards.[68-71] Other topics debated in the literature include the safety of regional anesthesia,[72] the role of continuous peripheral nerve blocks in the management of postoperative pain,[73] and new modalities of administration of local anesthetics for the management of postoperative pain, such as nebulization during laparoscopic surgery [74] and continuous wound infusion.[75]

Complications of regional anesthesia

Complications of peripheral nerve blocks are fortunately rare, but can be devastating for patients. The actual incidence of neurologic dysfunction resulting from complications associated with neuraxial blockade, although rare, is unknown.[76] The majority of neurological adverse events administration results in temporary sensory symptoms while long-term or permanent motor and sensory problems are very rare. Distinguishing between factors associated with serious neurologic complications, such as cauda equina syndrome, and transient symptoms when making recommendations for the clinical management of patients is important.[72] Finally, infection and hemorrhagic complications, particularly with neuraxial blocks, can also cause neurological adverse events.[77, 78]

A prospective survey recently evaluated the incidence and characteristics of serious complications related to regional anesthesia and concluded that needle trauma and local anesthetic neurotoxicity were the etiologies of most neurologic complications.[79]

Direct needle- or catheter-induced trauma rarely resulted in permanent or severe neurologic injury (as those caused by meningitis or abscesses).

A retrospective study of 4767 cases of spinal anesthesia noted the presence of paresthesias during needle placement in 6.3% of patients.[80] However, there is a lower frequency of persistent paresthesia/radiculopathy following epidural techniques.[76, 79]

Regarding peripheral nerve blocks, the potential added risk of neurologic complications resulting from placement of a plexus or peripheral nerve catheter (PNC) remains still undefined.[81] In a recent prospective study involving 1416 patients with continuous catheters, 12 patients (0.84%) experienced serious adverse events and three (0.21%) patients had neurologic complications (paralysis and neurological deficit) attributed to the continuous peripheral nerve block.[82]

Regarding side effects related to anticoagulant drugs, more active thromboprophylaxis with potent antihemostatic drugs has increased the risk of bleeding into the spinal canal. European and American guidelines for minimizing these risks of serious complications from spinal bleeding in patients who benefit from neuraxial blocks vary in their recommendations for safe clinical practice.[83, 84]

Neurologic complications after neuraxial anesthesia or peripheral nerve block may also be a direct result of local anesthetic toxicity. Although the local anesthetics currently used have a high safety profile, prolonged exposure, high dose, or high concentrations of local anesthetics at the spinal roots may result in permanent neurologic deficits.[85] The American Society of Regional Anesthesia recommendations have recently been published for the prevention, diagnosis, and treatment of local anesthetic systemic toxicity (LAST).[86]

Hence, it is important to highlight that simply understanding the etiologies of these complications and the implementation of protocols that try to minimize their occurrence will promote the safe practice of regional anesthesia. Prevention of complications, along with early diagnosis and treatment, is important in the management of regional anesthetic risk[87]. Finally, it is important always to use the best technique related not only to patients but how I can also manage that specific patient in postoperative period (What kind of postoperative care I can do, what kind of surveillance I have, and so on).

Continuous peripheral nerve blocks in the management of postoperative pain

Continuous peripheral nerve blocks (CPNB) for postoperative pain management have been administered for more than 25 years, providing specific analgesia for a variety of surgeries.[87] The advantages of regional techniques include site-specific anesthesia and decreased postoperative opioid use.[88, 89] Placement methods for perineural catheters vary with the nerve localization technique employed, such as electrical nerve stimulation *versus* ultrasound guidance, and the specific type of equipment involved. CPNB procedures should be performed with standard noninvasive hemodynamic monitoring, an available oxygen source,[90] and intravenous sedation to ensure patient safety and comfort.[73] The use of a stimulating catheter may increase perineural catheter placement accuracy and provide other clinical benefits if it is used for electrical stimulation alone.[91] There has been increasing interest in the use of ultrasound guidance alone for regional anesthesia,[92] requiring the understanding of two major concepts: first, target nerve imaging, and second, needle guidance. The options for needle guidance (out-of-plane *versus* in-plane) are distinguished by the location of needle insertion relative to the ultrasound transducer.

Randomized clinical trials have compared ultrasound-guided CPNB with non-stimulating perineural catheter insertion to stimulating perineural catheter insertion. Shorter procedural duration, higher catheter insertion success rates for ultrasound-guided placements, and/or a reduction in analgesic efficacy have yet to be definitively demonstrated.[93, 94] Furthermore,

electrical stimulation and US guidance can be combined for perineural catheter insertion.[93] This combined technique has yet to be compared to either technique alone, so the benefits, if any, remain unknown.

Because of increased safety, the blocks for pain control are frequently administered at home. Recently, multiple studies evaluating regional anesthesia and analgesia in the outpatient setting have supported its safety, efficacy, and application. The findings suggest that regional anesthesia in the ambulatory setting offers many benefits to patients with an acceptable risk–benefit profile. Perineural catheters are being used at home by adults and children with a favorable risk–benefit ratio and high patient satisfaction.[95] However, there are many unanswered questions remaining, particularly regarding the long-term outcome, that require additional prospective research.[73]

Finally, it is important to underline that some studies showed that continuous perineural use of high concentration of local anesthetic could represent an effective and safe treatment of phantom limb pain.[96, 97]

Nebulization of local anesthetic during laparoscopic surgery

Pain after visceral surgery is thought to be multifactorial in origin.[74, 98] The widespread popularity of minimally invasive techniques, including single-port laparoscopy and transluminal endoscopic surgery, is due to lower perioperative morbidity, less postoperative pain, reduced postoperative infections, less scar formation, and shorter length of stay compared with open surgery. Although this technique has greatly reduced the need for analgesia, these advances in technique still result in visceral dissection and nociception after disruption of the peritoneum and resection of viscera.

Administration of intraperitoneal local anesthetic as a part of a multimodal approach to postoperative pain management has been studied and proved as effective through randomized controlled trials for more than 10 years,[98] even if these studies have provided conflicting results, probably due to differences in the instillation site, in the timing of administration and differences in local anesthetic dose and concentration.

With the reports of intraoperative hypothermia during laparoscopic surgery and the potential benefits of humidified carbon dioxide (CO_2) during insufflation, several humidifying devices have become commercially available. These humidification devices can also be used to administer local anesthetics intraperitoneally. During recent years, many randomized controlled trials have been undertaken to study the effects of local anesthetic instillation in the peritoneal cavity.[99] The results suggest that these techniques could be valid approaches to providing complete pain relief during surgery. Local anesthetic instillation in the peritoneum as part of a multimodal approach to pain management reduced pain intensity and morphine consumption after laparoscopic cholecystectomy. Intraperitoneal nebulization, a new technique of drug administration, has been reported to provide a more homogeneous spread of drugs.[100] Alkhamesi *et al.*[100] found that intraperitoneal nebulization of local anesthetic significantly reduced pain after laparoscopic surgery. Differences between the instillation and nebulization techniques include the duration of local anesthetic administration and the potential for systemic absorption. The pharmacokinetic profile of ropivacaine nebulization is similar to direct intraperitoneal instillation, but with a lower absorption rate.[74] Future studies should determine the optimal dose of local anesthetics and the effect of local anesthetic nebulization in different clinical settings.[74] They should also determine if local anesthetic nebulization throughout the surgical procedure would further improve postoperative pain relief and the influence perioperative outcomes. It is important to underline that this technique could not eliminate the pain of the wound that could be improved with wound infiltration with local anesthetics.

Opioids and chronic non-cancer-related pain

Opioids are a class of drugs that relieve pain by interacting with mu receptors located in the brain, spinal cord, and peripheral nerves. Although opioid use for the treatment of acute,

postoperative, and chronic cancer pain is well demonstrated, there is debate about whether opioids are the drug of choice for the treatment of chronic non-cancer pain.[101] In a retrospective study about long-term opioid therapy in patients with back pain, they succeeded in reducing persistent spinal pain intensity by approximately 50%, with only mild side effects, and without leading to any significant dose increase.[102] Efficacy was sustained from three months to three years. A meta-analysis of 15 randomized, placebo-controlled trials of World Health Organization (WHO) for step three opioids in the treatment of chronic non-cancer pain found a mean decrease in pain intensity of at least 30%.[103] Another meta-analysis of opioids for the treatment of central or peripheral neuropathic pain found that short-term trials produced contradictory results, while intermediate-term trials demonstrated opioid efficacy for neuropathic pain.[104] No long-term trials have been reported. It is mandatory to remember that the choice of the pharmacological treatment has to be related to the specific pathophysiology that generated pain more than the intensity of pain referred.[105] If we do not consider the specific mechanism, it could be possible to generate a "vicious cycle",[105] in which "doses are increased because of inadequate pain relief, but this increases side-effects so doses are reduced, pain relief is then inadequate, so doses are increased, and so on".[106]

Chronic pain of moderate to severe intensity is experienced by 19% of adult Europeans. Pain seriously affects the quality of their social and working lives; however, very few patients were managed by pain specialists and nearly half reported inadequate pain management.[107] In recent years, new drugs, such as tapentadol,[108] new combinations such as naloxone plus oxycodone,[109] and new devices [110, 111] for administration of opioids have appeared on the market. Nevertheless, opioids continue to be misused, abused, and diverted for non-medical use by patients.

However, physicians contribute to the ineffective use of opioids. These practices could be the manifestation of ethical and cultural factors that influence decisions about drug prescriptions. For example, legislative and healthcare system controls serve to restrict the use of opioids for long-term treatment of non-cancer pain conditions and produce poor treatment acceptance by patients. In 2010, a recent Italian law was approved to encourage the treatment of chronic pain by helping facilitate practitioners and patients in the establishment of improvements in the management and use of opioids.

Clearly, it is important to keep in mind that long-term treatment with opioids may be complicated by the development of tolerance, dependency, addiction, abnormal pain sensitivity, cognitive dysfunction, hormonal changes, and immune dysmodulation.[112, 113] The management of chronic pain with opioids necessitates a meticulous balance between the risks of opioid misuse or diversion and the benefits of adequate pain relief. Many authors have described a set of key recommendations for the safe and effective use of long-term opioid therapy.[114, 115] These recommendations are summarized in Table I. It is important to remember that in a recent article Von Korf *et al.*[116] showed that unexpectedly time-scheduled dosing opioids could determine more side effects and higher dosages than pain-contingent dosing opioids. Hence, as suggested by Ballantyne [117] in her editorial, it could be revaluated the use of pain-contingent dosing opioid except in patients with addiction risk or problems.

In order to further improve the effectiveness of these drugs, not only is an accurate evaluation of the type of pain experienced by patients necessary, but it is also important to try to individualize the treatment on the basis of their history and pharmacogenetic endowment.[118] In fact, the "pharmacokinetic and genetic characterization" of the patient could be useful not only in identifying *a priori* the population at risk of developing side effects or having greater susceptibility to opioid addiction but could also prevent side effects due to interaction between different drugs.

Finally, an important bias in the management of opioids for patients with chronic pain could also be due to the fact that many physicians prescribing pain medication have little training in the evaluation and management of addiction and/or aberrant drug-related behavior.[119] Furthermore,

Table I.—*Reccomendations suggested to practitioners for optimizing long-term opioid therapy.*[109, 110]

Sixteen Recommendations to Practitioners for Optimizing Long-Term Opioid Therapy
– Obtain a thorough history and perform a thorough physical examination to determine the etiology of pain.
– Establish a clear diagnosis and differential.
– Primary care providers should get a second opinion from a pain management specialist, a specialist in the involved organ system, or a specialist in the overall disease process before writing the first opioid prescription.
– Identify those at risk for substance abuse or refer to someone capable of making this determination before starting long-term opioid therapy.
– Document everything contemporaneously seen, felt, heard and considered about the patient from the first encounter onward.
– Obtain informed consent from the patient before opioid therapy is started, so there is no doubt about the treatment proposed or the outcome expected.
– Use a written opioid treatment agreement defining the expectations and obligations for the patient and the prescriber.
– Have the patient agree to use only one prescriber for opioid prescriptions and one pharmacy to obtain opioid medications.
– Administer pre- and post-intervention assessments of pain intensity and function (performance of activities of daily living).
– See the patient on a regular basis, evaluating the level of analgesia and activity, and emergence of adverse effects or aberrant behavior.
– Prescribe long-acting opioid analgesics on a time-contingent basis so that stable levels are achieved and reinforcement of pill taking is minimized.
– Consider "rational polypharmacy" using adjuvants with opioids and see opioid prescribing as part of some larger plan rather than the only plan.
– Determine the minimum dose necessary to maintain function and useful activities of daily living by potentially trying to decrease the dosage (25-35%).
– Order urine drug screens for patients of concern to establish that prescribed medications are recovered (to rule out significant diversion) and that potential use of illicit substances (drugs not prescribed) is considered.
– Periodically review the diagnosis and co-morbid conditions that contribute to the overall pain experience, including the development of addiction.
– Stay current with changing rules for opioid prescribing, obtain relevant education, and keep politically aware of developments.

the lack of standardized diagnostic criteria and definitions for problematic behaviors associated with medication use and formal substance use disorders across professional disciplines is another major problem[120]. However in the last years some abuse-deterrent opioid formulations have been introducted helping us in the prevention of addiction in selected patients.[121, 122]

In effect, pain cannot be adequately managed if complicated by substance use disorders and will likely worsen in this context. Therefore, it is mandatory to identify and manage opioid addiction during long-term opioid therapy of patients with chronic pain. Unfortunately, the utility of screening questionnaires and/or other attempts at predicting or detecting opioid-related substance use has yet to replace careful examination by an expert clinician. A comprehensive approach for the psychiatric evaluation of patients with chronic pain treated with opioids will optimize the chances for success of long-term opioid therapy.[120]

Chronic pain in Failed Back Surgery Syndrome (FBSS)

Lower back pain with or without lower extremity pain is the most common problem among chronic pain disorders with significant economic, societal, and health costs.[123-126]

The term FBSS is mainly used to describe patients who have ongoing chronic pain after surgery of the lumbar spine for degenerative disc disease. In general, the patients present with persistent spinal (lower back or cervical) pain that may or may not radiate into the limb(s). Also known as postlaminectomy syndrome, this umbrella term overlies a constellation of different symptoms and etiologies. A significant proportion of these patients experience some form of neuropathic pain, and the success rate of repeat back surgery declines in parallel with the number of reoperations. The most suitable interventions for patients suffering from FBSS and effectively managing their chronic spinal pain include: epidural injections, spinal cord stimulation (SCS), and intrathecal drug delivery.

FBSS from semiology and etiology to different therapeutic algorithms

One of the most important causes of FBSS is the suboptimal selection of candidates for spine surgery.[127-132] Other major causes of this difficult chronic pain syndrome are attributable to poor diagnostic evaluations with consequently inap-

propriate surgeries [133] and persistence of or even increased pain because of unresolved primary pathology or new operative pathology producing symptoms.[134, 135] Nevertheless, psychosocial factors or unrealistic expectations likely play a significant role in the pain and disability of patients with FBSS.[136] A comprehensive evaluation (patient history, physical examination, evaluation of the different contributions of neuropathic and nociceptive pain, and psychological evaluation) of patients suffering from FBSS and the recognition of possible "red flag" symptoms is crucial before deciding upon a particular therapeutic algorithm (pharmacological, interventional or rehabilitative program).

The suggested first-line option for patients suffering lower back pain with or without accompanying leg pain is a conservative program of therapy (pharmacological and rehabilitative). If this approach is insufficient, radiofrequency ablative treatment administered adjacent to the dorsal root ganglion may be considered.[137] In cases of persistent nociceptive pain, intrathecal drug administration should be considered, even if the evidence for its long-term relief of pain is still limited.[138, 139] For those patients who are suffering from refractory pain predominantly in the leg of a mainly neuropathic nature and who do not exhibit signs of a structural cause for pain, a trial with spinal cord stimulation is strongly recommended.[137]

SCS is currently indicated for FBSS patients with pain that predominantly involves the leg(s) for whom conservative treatments have failed, and who have no obvious indication for reoperation. The use of SCS in the treatment of axial lower back pain as the only or main complaint (>50% of the pain) is still being explored with some promising results.[134, 140] Electrical stimulation at the level of the spinal cord generates paresthesias in the corresponding dermatome. Multipolar, multichannel, and multiprogram techniques allow the stimulation to be optimally adapted to each patient's specific needs. The evidence for spinal cord stimulation in failed back surgery syndrome is strong for short-term relief and moderate for long-term relief.[141, 142]

Restricted to the (sub)acute form of failed back surgery syndrome, epidural corticosteroid administration remains an option. Access to the epidural space is available via caudal, interlaminar, and transforaminal approaches. The target is the dorsal root ganglion and sensory nerve roots within the dural sleeves compressed by the degenerated disc or foraminal stenosis. Ultrastructural anatomical elements may help explain the role of spinal nerve root cuffs and the structures that play a role in the spread of substances injected into the epidural space and in transforaminal blockade. Careful characterization of the anatomy of the target area for injection of medication guides the choice of the best approach for diagnostic and therapeutic blocks.

The characteristics of the intervertebral foramina (IVFs) such as their width, shape, and the structures passing through them, should be known before approaching this region. The amount of adipose tissue and its distribution, the quantity and course of blood vessels, and the location of cellular and fibrillar components of nerve root cuffs influence the permeability to injected drugs.

In the cervical region, dorsal and ventral nerve roots are found in the foramen's lower portion at or below the disk level while epidural fat and blood vessels can be identified in its superior aspect. The IVFs in the thoracic and lumbar region face laterally in contrast to those of the cervical spine which have an oblique anterolateral orientation.[143] The size of nerve root canals varies from the upper to lower lumbar segments. They become progressively longer from L1 to S1 as the dural root sleeves exit at a more oblique inferior angle.[144]

At the lumbar level, the spinal nerve is located in the upper third of the foramen. Here the nerve is accompanied by branches of the lumbar segmental artery, the superior segmental (pedicle) veins, which connect the external and internal vertebral venous plexuses, and by the sinuvertebral nerve.[145] Nerve root cuffs (lateral prolongations of dura mater, arachnoid lamina, and pia mater)[137] function as a barrier between the axons and somata in the dorsal root ganglion and injected drugs. The thickness of nerve root cuffs is formed by internal cellular and fibrillar components in the outer portion of the nerve root cuff.

In the translaminar approach of an epidural block, the administered solution will follow a path through the epidural fat (the real component of the epidural space) with a smaller proportion of the volume being dispersed to the lateral epidural fat next to the preganglionar dural cuff, and the remaining majority of the solution staying in the posterior epidural space. There will be little distribution to the anterior epidural space and into the intervertebral foramen.[128]

In the transforaminal approach, the medication is deposited in the intervertebral foraminal canal, next to the nerve root, and in the fat surrounding the nerve, even though the tip of the needle frequently remains extraforaminal, next to the nerve, but outside the foraminal canal. The latter approach has greater effectiveness, because we administrate drug closer to the preganglionar and ganglion areas where the fat tissue within the dural cuff could facilitate the redistribution inside the nerve root.[123]

Conclusions

With this review, we have summarized the topics discussed during the SIMPAR meeting that was held on December 4, 2010, in Pavia. In the last decade, pain therapy has greatly improved in terms of both understanding pathophysiology and anatomy and developing new drugs and devices that can help clinicians in correctly managing acute and chronic pain. Despite these improvements, there is still a lack of a strong evidence for efficacy in improving the long-term outcome for both acute and chronic pain. In order to "resolve" this problem, all the research analyzed herein shows the need for further investigation into how we can personalize therapy as much as possible for a specific patient through an accurate diagnosis of the pain syndrome and through genetic and clinical evaluation of the patient. The next steps in research will attempt to identify how we can objectively measure pain, effectively incorporate placebo effects into therapy,[147] and standardize therapies by emphasizing long-term outcome including the reduction of social costs related to acute and chronic pain.

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