Chronic Pain: Management Strategies That Work

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This course will describe and assess the evidence supporting commonly used strategies of chronic pain management using an evidence based medicine approach.

Background

The perception of pain is a complex interaction that involves sensory, psychological, and environmental factors. Thus, patient selection for various treatment options depends heavily on a rigorous multidisciplinary assessment of the foregoing factors and careful weighing of the relative contributions of the factors in these three major areas.

A consideration of the potential for methods to reduce pain is of obvious importance to the patient, as is the likely persistence of such pain relieving effects over time. Of equal importance should be a consideration of the likely contribution to the restoration of physical and mental function; it is very likely that more than one measure will be required to meet these objectives (1).

It is important to emphasize that there has been a major "sea change" in the conceptual framework on which consideration of the options for treatment of chronic pain is made. It is no longer appropriate to consider a "hard wired" system with a pure "stimulus response" relationship. Recent expansion of knowledge concerning peripheral and central sensitization has raised awareness of the plasticity of the nervous system, along with the multidimensional aspects of chronic pain. Thus it is crucial to consider the patient's pain in the context of a bio-psycho-social model of pain. The use of temporary or permanent neural blockade techniques, neuroablative surgery, neurostimulation or other treatment methods based on the Descartes model of pain has a high chance that the patient will not only fail to achieve the desired end point but also has a significant chance of adverse outcome (1–3). This presentation will consider the use of various strategies in chronic pain, however applications in a cancer pain or acute pain setting will not be considered.

Evidence Based Medicine and Chronic Pain

As is the case in many areas of medicine, and particularly with interventional medicine, objective documentation of outcome has been lacking. However, we now live in an era of "evidence based medicine" (EBM) and this means that we should identify the "level" of evidence for each treatment, using the randomized prospective controlled study as the "gold standard." An example of levels of evidence is given in Table 1 and this approach will be used in the remainder of this presentation.

Recently, there has been a call for some moderation of the EBM approach by also testing under "normal clinical conditions", the results of treatments that were highly rated on the EBM scale. This is not to say that the EBM data should not first be obtained in controlled studies. However sometimes patient populations in studies may differ from those that present in the clinic. A worldwide initiative in EBM is the Cochrane Collaboration, which aims to identify controlled studies (RCTs) relevant to various fields of medicine, and to encourage groups to carry out systematic analyses. In the pain field there are major foci in Boston, Massachusetts (Dr. Dan Carr et al.), Oxford, UK (Dr. Andrew Moore, Henry McQuay et al.) and Hamilton, Canada (Dr. Alex Jaddad et al.). It is important to acknowledge that the non-availability of RCTs does not preclude the use of an EBM approach that can be defined as follows:

"Evidence-based health care is the conscientious use of current best evidence in making decisions about the care of individual patients or the delivery of health services. Current best evidence is up-to-date information from relevant, valid research about the effects of different forms of health care, the potential for harm from exposure to particular agents, the accuracy of diagnostic tests, and the predictive power of prognostic factors" (4).

The International Association for the Study of Pain (IASP) has sponsored a Special Interest Group (SIG) on EBM and chronic pain (SIG website: http://www.jr2.ox.ac.uk/bandolier/painres/srprg.html).

Table 1. Levels of Evidence Ratings

Level 1
Evidence obtained from systematic review of relevant randomized controlled trials (with meta-analysis where possible
Level II
Evidence obtained from one or more well-designed randomized controlled trials
Level III
Evidence obtained from well-designed non-randomized controlled trials; OR from well-designed cohort or case-control analytical studies, preferably multicenter or conducted at different times
Level IV
The opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees.

A different, but partly related, approach to evaluating current practice and its scientific basis is to carry out a "citation analysis" of the literature for pain management. This indicates publications that may be important but does not evaluate the level of evidence (5).

Neural Blockade and Chronic Pain

Diagnostic nerve blocks may be valuable in delineating the pain problem and in deciding on subsequent treatment. However, the results of such blocks must be viewed in light of all information gained at assessment. Performance and interpretation of such blocks is more complex than previously acknowledged (2).

Neural blockade may also be used to facilitate rehabilitation via various intraarticular techniques of injection (Table 2) (6–14). It should be noted that corticosteroids are used in these studies either alone or in combination with local anesthetic. Overall, the evidence is weak other than for short-term benefit.

With respect to the shoulder joint, despite the widespread use of intraarticular steroids for shoulder pain, the evidence for efficacy is weak. However, this may reflect a failure of many studies to identify clearly subgroups that may benefit, poor study design, different treatment comparisons, and different outcome measures (15).

With respect to the lumbar and cervical zygapophyseal joints, level II evidence now indicates a lack of effective sustained outcome for intraarticular steroid injection for neck and low back pain. This is despite short-term pain relief obtained in some patients. On the other hand, the more precise technique of diagnostic medial branch block followed by radiofrequency lesioning (Table 3) (16–21) appears to have strong evidence of long term efficacy for lumbar and cervical and weak evidence for thoracic facet related pain (16) (level III) (17) (level II) (22) (level IV) (18) (level II) (19) (level IV) (20) (level IV).

Epidural Corticosteroid Injection

Although epidural corticosteroid injections are frequently utilized with the aim of reducing edema and inflammation around the nerve root, the efficacy and indication for this treatment continues to be debated. Many studies have significant design flaws and systematic reviews have also presented varying conclusions. A systematic review of 12 randomized controlled trials found six studies reporting a positive effect for epidural steroid; the other six studies had negative results. If pain relief was achieved, it was only maintained in the short term, and there was no indication that epidural steroids were effective in the management of back pain without sciatica (23). A further metaanalysis of 11 trials comprised 907 patients with sciatica and clinical evidence of nerve root irritation or compression; epidural injections varied in different studies with respect to the site of injection (lumbar or caudal), and also with respect to the steroid injected (methyl prednisolone, triamcinolone, or hydrocortisone). A positive effect was seen for the treatment group with an odds ratio for short term relief of 2.61, but reduced efficacy in the long term (odds ratio, 1.87) (24) (level I). The data were subsequently analyzed in terms of number needed to treat (NNT). For short-term relief, the NNT for >75% relief was 6 and for >50% relief NNT was 3. For long-term relief (12 weeks to 1 yr) the NNT increased to 13 for >50% pain relief (i.e., only one in thirteen patients had sustained relief) (25) (level I). In a randomized double-blinded trial (26)(level II), up to three epidural injections of methylprednisolone acetate (80 mg) were administered to patients with sciatica attributable to a herniated nucleus pulposus. A significantly greater reduction in leg pain (assessed by visual-analog pain scale) was recorded in the methylprednisolone group, with an associated improvement in sensory deficits and reduced need for analgesics. However, the difference in pain score was not maintained at three months and there was no difference in functional level (assessed by Oswestry score) or the need for subsequent surgery in these patients. Therefore, current data indicate short-term relief of leg pain, but minimal effects on back pain and function after epidural corticosteroid injection for herniated intervertebral discs (15).

Recently, Abram (27) reviewed the use of epidural steroids for lumbosacral radiculopathy. He alluded to substantial differences in opinion and practice concerning the techniques of epidural steroid injection (e.g., caudal, lumbar, thoracic, cervical epidural, extraforaminal, transforaminal). He opined that pain associated with radiculopathy was the principal indication, particularly if there is an association with disk herniation, a dermatomal pattern of sensory loss, and positive sciatic stretch signs. Previous back surgery and long duration of symptoms seem to predict a

Table 2. Intraarticular Corticosteroid Injection

Site	Injection	Outcome	Evidence/Reference
Interventions for painful shoulder	Glucocorticoid injections (also analyzed nonsteroidal antiinflammatory drugs and physiotherapy)	Subacromial glucocorticosteroid injection superior to placebo in improving range of abduction in rotator cuff tendinitis (methodological quality of trials poor)	Systemic review of RCTs—level I (Green et al. 1998) (6)
Steroid injections for shoulder disorders		No conclusive evidence about which patients and at which time during the course of shoulder disorders most benefit was obtained from steroid injections	Systematic review of RCTs—level I (Vander Heyden et al. 1996) (7)
Local corticosteroid injection for treatment of rotator cuff tendinitis		"Seem to be effective" and greater efficacy than NSAIDs for pain long-term efficacy, deleterious effects and optimal timing and technique for injection unable to be determined from current studies	Review: no pooling of data, no evaluation of effect size—level IV (Goupille 1996) (8)
Lumbar zygapophyseal joints	Methylprednisolone vs saline (patients responsive to local anaesthetic facet joint injection) injection site confirmed with arthrography	No difference in outcome measures at 1 or 3 months (pain, functional status and back flexion assessed)	Randomized placebo controlled—level II (Carette et al. 1991) (9)
Cervical zygapophyseal joints	Bupivacaine vs betamethasone (patients with positive response to medial branch block of cervical zygapophyseal joints) injection site confirmed with arthrography	Less than 50% reported relief greater than one week and less than 20% relief for one month irrespective of treatment group-median time to return of 50% of preinjection pain: 3 days in steroid group and 3.5 days in bupivacaine group	Double-blind controlled randomized—level II (Barnsley et al. 1994) (10)
Medial epicondylitis	Local anaesthetic +/− methylprednisolone	Steroid group less pain at 6 wk but no difference at 3 months or 1 yr	Double-blind prospective randomized study—level II (Stahl 1997) (11)
Hip: osteoarthritis and rheumatoid arthritis and ankylosing spondylitis	Methylprednisolone and lidocaine injection under xray control	Reduction in pain at 2 and 12 wk, return to baseline by 26 wk; greatest improvement for pain at night; hips with atrophic pattern on radiograph had least benefit, associated increase range of internal rotation but no functional change	No placebo group, only evaluation of underlying Xrays blinded—level II (Plant et al. 1997) (12)
Knee rheumatoid arthritis	Hydrocortisone succinate (HC) vs triamcinolone acetonide (TA) vs triamcinolone hexacetonide (TH)	Little effect with HC; 18% pain-free at 12 wk after TH and 9% after TA; higher proportion maintained analgesia at 12 wk after TH	Single blind randomized—level III (Blyth et al. 1994) (13)
Knee osteoarthritis	Methylprednisolone vs placebo	Short term relief of pain at 3 wk—no predictors of response—15% decrease in pain score defined "response"	Double-blind placebo controlled crossover—level II (Jones 1996) (14)

NSAID = nonsteroidal antiinflammatory drug; RCTs = randomized controlled trials.

Table 3. Radiofrequency Lesions of Medial Branches

Site and Procedure	Outcome	Evidence/Reference
Cervical medial branch RF lesions	Prolonged relief of "mechanical neck pain (mean 227 days)	RCT, RF vs Placebo—level II (Lord et al. 1996) (17)
	Resolution of psychological distress	RCT—Level II (Wallis et al. 1997) (18)
	Prolonged relief after repeat RF	Level IV (McDonald et al. 1999) (19)
Lumbar medial branch RF lesions	Prolonged relief of "mechanical" low back pain: 45% RF patients 50% pain relief at 3.2-yr follow up	Longitudinal case series with "blinded" observer—Level III (North et al. 1994) (16)
	Prolonged pain relief	Level IV (Tzaan and Tasker 2000) (20)
	60% patients obtained 90% relief at 1 yr	Prospective audit—level IV (Dreyfuss et al. 2000) (21)

RF = radiofrequency.

lower success rate (level IV). Spinal stenosis also seems to be associated with a low, but not absent, success rate (Level IV). He also opined that the needle must be placed at a level close to the affected nerve root. This concept is also cited by those favoring transforaminal injection. However, in the presence of nerve root compression, this technique carries a risk of needle trauma to the nerve root and definitive data for risks/benefits are not available.

Sympathetic Plexus Blockade

Because the sympathetic ganglia are separated from somatic nerves (except in the thoracic region), it is possible to achieve selective blockade of sympathetic fibers without effects on sensory and motor function. Details of techniques for sympathetic blockade are found elsewhere (28). Sympathetic blockade has potential diagnostic and therapeutic effects in patients with chronic pain by the following:

1. Blockade of afferent visceral nociceptive fibers that may reduce or eliminate visceral pain,
2. Blockade of sympathetic efferent fibers that may interrupt the interaction between nociception and the sympathetic nervous system in sympathetically maintained pain states associated with Complex Regional Pain Syndromes,
3. Producing vasodilatation that may provide relief of ischemic pain, and facilitate the healing of chronic ulceration in inoperable peripheral vascular disease, and
4. Relief of ischemic pain by mechanism 2) above.

Diagnostic Sympathetic Blockade

Sympathetically maintained pain is pain that is maintained by sympathetic efferent innervation or neurochemical or circulating catecholamine action (29,30). Pain relieved by a specific sympatholytic procedure (pharmacological or sympathetic nerve blockade) may be considered sympathetically maintained pain, although the duration of pain relief will only be temporary in some cases (30) and the degree of sympathetic dysfunction may not correlate with the degree of analgesia or response after sympathetic blockade. The use of sympathetic blocks as diagnostic procedures is associated with the problems of all local anesthetic diagnostic blocks (see above).

Therapeutic Sympathetic Blockade

Sympathetic blockade has also been used in a variety of chronic pain states but there are few placebo-controlled trials (see Table 4) (31–34).

Complex Regional Pain Syndrome

Local anesthetic sympathetic blocks are commonly used in the management of Complex Regional Pain Syndromes (28). Early sympathetic blockade is advocated in the adult literature to reverse the autonomic changes (changes in blood flow, temperature, sweating, and edema) associated with Complex Regional Pain Syndromes and to provide analgesia, but controlled trials have not been conducted. In a review of seven studies including over 500 patients, 46% of patients had satisfactory pain relief of prolonged duration after local anesthetic stellate ganglion or lumbar sympathetic blocks (34) (level IV). However, the studies used different diagnostic criteria, methods, and techniques. Comparison of a control group not receiving lumbar sympathetic blocks with a prospective group who did receive blocks showed an increase in the percentage of patients improving from 41% to 65% (33) (level IV) but this was a nonrandomized, unblinded study with a retrospective control group.

Postherpetic Neuralgia. Sympathetic blocks have been reported to relieve pain in the early acute phase of herpes zoster infection (28). However, recent reviews found no clear evidence for sympathetic blocks in the subsequent prevention of postherpetic neuralgia

Table 4. Sympathetic Plexus Blockade

Indication	Agent	Result	Evidence (Reference)
Peripheral occlusive vascular disease: rest pain and ulceration	Neurolytic lumbar sympathetic block 100% alcohol; 6% phenol in water; 10% phenol in contrast medium	—Pain relief: complete 49% patients; partial 31% patients; non 20 patients mean duration of effect 5.9 +/− 0.6 mths pain relief correlated with onset and duration of sympathetic block —Healing of skin ulcers in 70% of patients with ulceration —Severe (> 1 wk) L_1 neuralgia; 26% after 100% alcohol; 14% after 6% phenol in water; 7.5% after 10% phenol in contrast and injection under continuous imaging	Case series of 386 patients: objective assessment of sympathetic function by cobalt blue sweat test; skin blood flow changes (skin temperature and occlusion plethysmography—level IV (Cousins et al. 1979) (31)
Prevention of postherpetic neuralgia	Repeated local anesthetic blocks	—Relief of pain in acute phase —No clear evidence for prevention of postherpetic neuralgia	Review of case series; conflicting retrospective reports; no adequate placebo controlled trials (Ali 1995) (32)
CRPS	Local anesthetic lumbar sympathetic blocks	—Retrospective "no block" control group: 41% showed improvement —Prospective block group: 65% showed improvement	Case series: not randomized, not blinded—level IV (Wang 1985) (33)
CRPS	Local anesthetic sympathetic block (lumbar or stellate ganglion)	—Review of 7 studies of >500 patients —46% patients had satisfactory pain relief of prolonged duration	Level III: studies with differing methods, techniques, and criteria (Kozin 1992) (34)

>CRPS = complex regional pain syndrome.

(32,35). Opinion remains divided on this issue, as results of retrospective reports are conflicting, and there are no adequate prospective placebo-controlled trials.

Neurolytic celiac plexus block has been used for chronic abdominal pain such as chronic pancreatitis, but there is no controlled data to support any long-term benefit for such patients.

Neurolytic blockade of the superior hypogastric plexus has been utilized for control of pelvic pain, and blockade of the ganglion impar (which is located at the level of the sacrococcygeal junction) has been utilized to control perineal pain; however, no controlled data are available (36).

Peripheral Vascular Disease

Lumbar sympathetic ganglion blockade with local anesthetic and neurolytic agents has been utilized in patients with occlusive peripheral vascular disease affecting the lower limbs (28). Reduction in rest pain in 80% of patients and healing of skin ulceration in 70% of patients have been shown to occur in conjunction with objective evidence of sympathetic blockade (decreased plantar sweating and vasoconstrictor ice response, increased skin blood flow, and temperature). The mean duration of effect was 5.9 ± 0.6 months (31) (level IV). The new option of spinal dorsal column stimulation is discussed below.

Neurolytic Intrathecal Blockade

The indications for various intrathecal neurolytic procedures are greatly diminished by the improved use of oral analgesic regimens and the broad scope of spinal opioid and nonopioid drug delivery (see below). Although valuable in some situations, neurolytic spinal techniques have suffered from a lack of efficacy data, short duration of analgesia, and significant complications. A more detailed description of these techniques and their outcome is given elsewhere (36). Such techniques are rarely if ever appropriate for patients with noncancer pain who have a normal life expectancy.

Epidural Analgesia and Ischemic Heart Disease

High thoracic epidural anesthesia has the potential to reduce myocardial oxygen demand by reduction in sympathetic efferent activity and to improve myocardial oxygen supply via improved endocardial to epicardial blood flow and increased luminal diameter of stenotic arteries in some patients (37).

Because of the beneficial physiological changes, and as cardiac pain is mediated via sympathetic afferent fibers, thoracic epidural anesthesia has a potential role in the management of refractory angina. A randomized controlled comparison of thoracic epidural anesthesia with bupivacaine and conventional medical therapy in severe refractory angina showed a significant reduction in the incidence (22% vs 61%) and severity of myocardial ischemia in the thoracic epidural anesthesia group (38) (level II). The thoracic epidural anesthesia group had a reduced number of ischemic episodes, reduced ischemic episode duration, and a reduced area under the ST-time curve (as assessed by Holter monitor). The risks and benefits of thoracic epidural anesthesia during acute episodes of severe angina continue to be debated. Long term treatment of anginal pain has been reported in which patients self inject bupivacaine via a tunneled thoracic epidural catheter if their pain is unresponsive to sublingual nitrates (37) (level IV). An important alternative is the use of dorsal column spinal cord stimulation (see below).

Epidural Analgesia: Prevention of Development of Chronic Pain States

A correlation has been found between the severity of acute postoperative pain and the development of chronic pain after thoracotomy (39) (level III)(40) (level II) and mastectomy (41) (level III). The relative contributions of preoperative pain, intraoperative trauma, and postoperative injury and inflammation to the development of long-term pain remains to be determined (42), and large prospective trials are required to determine if improved control of perioperative pain reduces the development of chronic pain in high-risk groups.

Phantom Pain after Amputation

Phantom limb pain develops in up to 70% of patients after amputation (43). Many factors are likely to be involved in the transition from acute postoperative pain to long-term pain, but as a high proportion of patients have pain resulting from vascular insufficiency before surgery this may contribute to a preoperative state of central sensitization and an increased risk of chronic pain. This hypothesis is supported by an early trial showing a reduction in the incidence of phantom limb pain after amputation by pretreatment with epidural local anesthetic and opioid (bupivacaine and morphine) for 72 h before amputation (44) (level II). Since that time, a variety of regional analgesic techniques have been used to investigate the effect of perioperative analgesia on the incidence of phantom limb pain with positive results for epidural techniques (45,46) and negative results for peripheral nerve sheath techniques (47,48).

The presence of intense preamputation pain has been found to significantly increase the incidence of stump pain and phantom pain after one week and the incidence of phantom pain after three months (49). However, in a recent randomized trial, perioperative epidural blockade started a median of 18 h before the amputation and continued into the postoperative period did not reduce the incidence of phantom or stump pain when compared with a control group receiving preoperative epidural saline and oral or IM opioids (50) (level II). However, both groups received epidural bupivacaine and morphine in the postoperative period for a median duration of 166 h. Currently available agents may not be sufficiently specific and potent, and blockade may have inadequate duration, to prevent development and persistence of central sensitization.

Efficacy of Long Term Spinal Opioids

Data on the long-term efficacy of spinal opioids is emerging but interpretation of different studies is difficult because of variation in inclusion criteria, outcome parameters, and duration of follow-up. Adequate diagnostic testing with temporary catheters should be performed before implantation. Frequently pain relief alone is assessed but is not reported in a uniform manner (e.g., proportion of patients achieving "good" or "excellent" relief, or overall degree of pain relief across all patients). Particularly in patients with chronic noncancer pain, improvement in functional capabilities should be considered, in addition to analgesic response. Independent assessment of outcome is ideal and a reduction in side effects or improved efficacy over systemic treatments without an increase in complications needs to be confirmed (51,52). As with the use of oral opioids for chronic noncancer pain (53) the use of spinal opioids should be part of a multimodal and interdisciplinary pain management plan. Comparative data of epidural, subarachnoid, and intracerebroventricular opioids in patients with cancer pain suggest similar efficacy, with 58% to 75% of patients achieving excellent pain relief (54) (level I). In a retrospective survey (55) (level IV) of patients receiving intrathecal morphine for cancer and noncancer pain, the mean percent relief was 61%; whereas study of 18 patients with intrathecal opioids for failed back surgery syndrome or arachnoiditis reported only four patients to have objective evidence of benefit at 2 yr follow-up (56). Clinical trials of opioids as single agents for neuraxial delivery in chronic pain have questioned whether this technique offers advantages over systemic infusion (57) (level II). Combinations of opioids and nonopioid analgesics and occasionally local anesthetics may be more effective for the control of neuropathic or incident pain; controlled studies of "combination" spinal analgesia with respect

to pain relief and functional capabilities are awaited. There is currently widespread use of multiple agents intrathecally, often in combination. Unfortunately, data are lacking concerning the efficacy and lack of neurotoxicity of such combinations.

Nonopioid Spinal Analgesic Agents

Knowledge of physiology and pathophysiology of nociceptive processing in the spinal cord is increasing, and resulting in future potential for pharmacological manipulation (Table 5) (58–101). Nonopioid receptor systems are being modulated with the aim of improving analgesia (particularly in patients with neuropathic pain), and reducing side effects. Analgesic efficacy, as well as systemic and local toxicity, of potential spinal analgesics must be carefully evaluated before clinical use. As pain presents as an event with several pharmacologically and functionally distinct components, analgesia may be improved in the future by the use of a combination of analgesic agents acting at different receptor sites. It is possible that a combination of drugs that act by different mechanisms will produce an effect that is substantially greater than that anticipated from the addition of their individual effects (i.e., a synergistic interaction) (58).

Recently, a "within-patient" randomized prospective placebo-controlled study examined the efficacy of intra morphine and clonidine, alone and in combination, for treatment of neuropathic post-spinal cord injury pain. A morphine-clonidine combination, but neither drug alone, was significantly superior to placebo in relieving spinal cord injury pain (59) (level II), This appears to be the first controlled study of spinal "combination therapy" for neuropathic pain.

Systemic Opioid and Nonopioid Drugs

Surprisingly the evidence for efficacy of systemic opioid and nonopioid drugs is still far from conclusive, except for the use of some specific agents in particular chronic pain conditions.

With respect to opioids, patients with ongoing nociception would appear to be logical candidates. This is supported by a controlled study in patients with osteoarthritis receiving oxycodone (102) (level II) with improvement in pain and function. However, in some studies, although pain may be improved, mental and physical function is not (53). Thus further controlled studies are urgently needed to define patient categories that are appropriate for opioid use (103).

With respect to nonopioid drugs, the evidence (level II studies) for use in chronic pain has been evaluated by the Oxford group for anticonvulsants (proven efficacy of carbamazepine for trigeminal neuralgia, NNT 2.6; of anticonvulsants for diabetic neuropathy, NNT 2.5), tricyclic antidepressants (proven efficacy for diabetic neuropathy, NNT 3; for postherpetic neuralgia, NNT 2.3; for atypical facial pain, NNT 2.8) and systemic local anesthetics (evidence for efficacy of lidocaine in neuropathic pains of various types, with lower level evidence for efficacy of mexiletine) (15).

More recently, the new anticonvulsant gabapentin has been reported to have efficacy for postherpetic neuralgia and diabetic neuropathy (104) (level II) (105).

Novel sodium channel agents show great promise but are only in early stages of development (106). Other novel drugs are also in a developmental stage, e.g., NMDA antagonists (although there is evidence for ketamine infusion in neuropathic pain), Lamotrigine, Vigabatrin, Adenosine (107). Cyclooxygenase-2 drugs have been studied in the setting of rheumatoid arthritis and osteoarthritis, with evidence for efficacy and fewer side effects compared to traditional nonsteroidal antiinflammatory drugs (108).

Spinal Dorsal Column Stimulation

This is a large subject in its own right and an excellent summary of the current status of evidence for treatment of various chronic pain syndromes has been provided by Myerson and Linderoth (109). In brief, the best indication for dorsal column stimulation (DCS) appears to be neuropathic pain of various types including complex regional pain syndromes. Unfortunately, most data is limited to longitudinal case series and follow-up data (110). However, many publications also deal with "failed back surgery syndrome" (111). It is clear that an adequate trial of stimulation with independent "blinded" observation of pain relief and change in function is vital in deciding on the use of this modality because controlled studies are not available to point to any one group of conditions as being "indications" for DCS (109).

However, two conditions stand out as potentially excellent and neglected applications, namely pain because of peripheral vascular disease (PVD) and angina. The results for peripheral vascular disease are better than for neuropathic pain conditions, with about 67% of patients trialled having successful outcome (112). Angina pectoris has also been treated with DCS, with a success rate of about 80% (113). A randomized prospective study comparing DCS and coronary artery bypass grafting found similar results for both treatments (114) (level III). Stimulation of brain areas remains experimental but motor cortex stimulation appears promising (109).

Ablative Neurosurgery

This extensive area was reviewed recently by Loeser (115). Such techniques have greatly declined with availability of less invasive methods. Virtually no controlled data are available and most procedures are

Table 5. Nonopioid Spinal Analgesic Agents

Drug	Mechanism	Efficacy	Side effect	Toxicity	Clinical use
Clonidine	Alpha-2 agonist: inhibitory effects pre and post synaptic on primary afferent projections onto second order neurons in spinal dorsal horn	Synergistic with opioids (Ossipov et al. 1990) (60); Plummer 1992) (61)Analgesia independent of opioid (Glynn 1988) (62) Efficacy in SCI pain (RCT-Siddall et al. 2000) (59)	Sedation, hypotension, bradycardia	Safety in animal and human studies (Gordh 1986) (63)	Case reports: -neuropathic cancer pain (Eisenach 1995a) (64) -SCI (Siddall 1994) (65) -CRPS/epidural (Rauck 1993) (66)
Dexmedetomidine	Alpha-2 agonist (3.5 × lipophilicity of clonidine)	Kinetic studies in sheep—maximum antinociception 20–30 mins after intrathecal injection (Eisenach 1994) (67)	? Similar to clonidine	Unclear	? No human studies
Neostigmine	Acetylcholinesterase inhibitor, cholinergic agonist, dose-dependent antinociception; activation of cholinergic muscarinic receptors is a mechanism of endogenous analgesia	Analgesia in human volunteers (Hood 1995b) (68) increase BP & HR as action at pregnaglionic symp neurons (seen in animal but not human study); enhances analgesia from systemic opioid in human volunteers (Hood 1997) (69)	Nausea and vomiting (N&V), lower limb motor weakness, urinary retention; postoperative single dose assoc with N&V (Hood 1995b) (68)	No toxicity in sheep, rats or dogs (Hood 1995a (70), Yaksh 1995 (71))	Phase 1 study in humans (Hood 1995b) (68)? combine with alpha-2 agonist to counteract hypotension (Williams 1993) (72) and improve analgesia (Naguib 1994) (73)
Midazolam	GABA-A agonist	Animal studies (Goodchild 1987) (74)	? Sedation	Toxicity not fully elucidated -? toxic (Malinovsky 1991) (75), ? not toxic (Bahar 1998) (76)	Case reports in cancer pain (Aguilar 1994) (77); Barnes 1994) (78)
Baclofen	GABA-B agonist-presynaptic on afferent neurones inhibits calcium influx and suppresses release of excitatory transmitters	Inhibition of monosynaptic and polysynaptic spinal motor reflexes (Azouvi 1993) (79); analgesia in animal studies (Yaksh 1981) (80)	Sedation, hypotonia and respiratory weakness if excess dose	No toxicity in animal studies (Sabbe 1993) (81); no toxicity seen in long term follow up human studies (Coffey 1993) (82)	Spasticity (Coffey 1993) (82); no human data on analgesic effects (Carr 1998) (83)
SNX 111	Synthetic omega-conopeptide (analogue of omega-conotoxin from cone shells): blocks N-type voltage sensitive calcium channel presynaptically to reduce transmitter release	Antinociception in rat model, no development of tolerance (Malmberg 1994, 1995) (84,85)	Nausea, light headedness, headache, constipation, confusion	Unpublished (Yaksh 1996) (86)	Unblinded trials in cancer patients; neuropathic pain case report (Brose 1997) (87)
Dextromethorphan	NMDA receptor antagonist activity	Subarachnoid has analgesic action in rat (Dickenson 1991) (88) not formulated for intrathecal use			No spinal administration trials in humans
Ketamine	NMDA receptor antagonist	Animal models (see Carr and Cousins 1998) (83)	? Psychotomimetic side effects with rostral spread; reduced side-effects with s-ketamine after IV use but no data on spinal use	? Preservative free preparation not toxic (Borgbjerg 1994 (89); Malinovsky 1991) (75)	Case reports only
CPP	NMDA Antagonist	Case report; reduced area of pain sensation? "reduced wind-up phenomenon"	Psychotomimetic effects 4 hrs after injection	Incomplete toxicology; no change in spinal cord blood flow in one rat model (Kristensen 1994) (90)	Human case report (Kristensen 1992) (91)
Somatostatin	Somatostatinergic pain inhibiting pathways	Initial analgesia in patients unrelieved by high dose opioid; required escalating doses (Mollenholt 1994) (92)		Potential neurotoxicity: reduces spinal cord BF; augments postsynaptic effects of flutamate; morphological changes in cord (Yaksh 1994) (93)	Case report in 6 cancer pain patients (Mollenholt 1994) (92)
Octreotide	Stable analogue of somatostatin	Pain (unrelieved by oral opioid) reduced and opioid requirement reduced		No documented clinical neurotoxicity—in use for >5 yr for opioid resistant chronic pain (Paice 1996) (94)	Case report in cancer pain (Penn 1992) (95); non-cancer pain (Paice 1996) (94)
R-PIA	Adenosine A_1 agonist	Animal efficacy (Yaksh & Malmberg 1994) (58) Reduced allodynia in one uncontrolled case report (Karlsten 1995) (96)		Animal safety (Yaksh 1996) (86)	Single dose human case (Karlsten 1995) (96)
Calcitonin	CNS mechanism of antinociception unclear		Nausea and vomiting	Spinal toxicity in animal studies (Eisenach 1988) (97)	No current role; case report in cancer pain (Blanchard 1990) (98)
Amytriptyline	Bind to NMDA receptor; monoamine uptake inhibitor, augments action of NA and 5HT	Reverses hyperalgesia in rats by NMDA mechanism (Eisenach 1995b) (99); potentiates IV morphine antinociception in rats (Eisenach 1995c) (100)	Dose-dependent sedation (Cerda 1997) (101)	Toxicity not fully evaluated; possible toxicity in animal model; but no changes in spinal cord BF (Cerda 1997) (101)	

BP = blood pressure; HR = heart rate; SCI = spinal cord injury; CRPs = complex regional pain syndrome; BF = blood flow.

supported only by longitudinal case series. Destructive procedures are rarely, if ever, indicated for chronic noncancer pain. However two procedures stand out as exceptions: radiofrequency lesioning of the trigeminal ganglion for tic douloureux and dorsal root entry zone lesions for brachial plexus avulsion (115).

Cognitive Behavioral Programs

Cognitive behavorial therapy is currently probably the best-documented effective treatment for patients with chronic pain. This should be qualified to point out that pain relief is rarely achieved but indices of mental and physical function show statistically significant improvement. Recently a systematic review of cognitive behavorial therapy identified 25 trials suitable for metaanalysis. The analysis concluded that cognitive behavorial therapy was efficacious in improving mental and physical function of patients with chronic pain (116).

Other Approaches

Recent evidence of neuroplastic cerebral cortical changes after amputation has pointed to new strategies for phantom limb pain. Use of a myoelectric prosthesis decreases phantom limb pain and also decreases associated cortical reorganization (117).

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