The goal of chronic pain management is always to reduce pain (not to eliminate the pain completely) and improve the person's ability to cope with the pain that remains.

Other aims include:

- Greater endurance
- Increased strength
- Improved flexibility
- Improved functioning at home
- Improved interaction with family and friends: reduced isolation
- Improved overall quality of life
- Return to employment if possible
- Optimised/Decreased medication use (reduced side effect profile)
- Fewer visits to doctors
- Fewer hospitalisations and emergency department visits
- Lower costs of maintaining pain care

There should be 3 major components to arachnoiditis treatment:

1. Management of symptoms

2. Prevention of secondary and tertiary problems

3. Minimisation of ongoing pathology (and avoidance of trigger factors for exacerbation)

SURVEY RESULTS:

In the Global survey, only 3% of respondents were not using medication regularly.

In the New Zealand survey, the figure was 20%. In the latter, 12% found no treatment effective, 24% were on drug therapy alone, 44% were on drugs and other treatments, 20% were only on non-pharmacological treatments.

Those on medication were on between 1 and 7 different drugs.

The predominant pain is as we have seen, neuropathic, so that regimes should be based on this.

Sindrup and Jensen ([1]) reported on treatment of polyneuropathy in 2000: they stated NNT's* for the various treatments as follows (based on placebo-controlled trials and calculated numbers needed to treat (NNT) to obtain one patient with more than 50% pain relief): *NNTs: low= more effective

tricyclic antidepressants: 2.6

selective serotonin reuptake inhibitors: 6.7

anticonvulsants sodium channel blockers: 2.5

anticonvulsant calcium channel blocker gabapentin: 4.1

tramadol (mixed opioid and monoaminergic drug): 3.4

dextromethorphan (NMDA-antagonist) 1.9

L-dopa: 3.4

Capsaicin: 5.9 (note: data are controversial owing to trial methodology)

Mexiletine: 38 (? biased because of a lack of dichotomous data in several positive trials)

The New Zealand survey ([2]) found:

In terms of the success of different types of treatment:

12% found that no treatment helped. 24% found relief solely from drug treatment, whilst 44% improved with drug and ?other treatment' (by contrast, of those using ?other treatment' but no drugs only 20% had relief.)

68% of the respondents were using drugs (58% narcotic; 15% anti-inflammatory; 11% anticonvulsant; 18% antidepressant; 17% muscle relaxant).

A variety of other measures were being used by the respondents to reduce their pain: rest, warmth, massage, TENS, acupuncture, relaxation/self hypnosis, frequent position changes etc.

Current treatment practice using a neuropathic pain ladder similar to the WHO pain ladder would suggest the following strategies:

NEUROPATHIC PAIN LADDER (after Nurmikko)(*another graph Doc*?)

Major sensory loss due to deafferentation may best be treated using lamotrigine or topiramate as they have multiple actions.

Devulder and Crombez ([3]), in writing about central pain, suggest that

"amitriptyline as an adrenergic reuptake inhibitor and the sodium channel blockers are the drugs of first-choice".

Advanced treatment might require a test procedure with lignocaine, propofol or ketamine.

Opiates

Of the well-established treatment regimes, opiates are frequently used. However, these may be ineffective in combating any central component of the pain.

Survey findings on opiate use: New Zealand survey: 58%, Global 56%, Long 71%

The issue of addiction and dependency concerns most practitioners and may lead to reluctance to prescribe. There will most certainly be physical dependence, and the problem of withdrawal symptoms if the opiate medication is discontinued.

Also, there is an element of tolerance that may develop in long-term use, with the need for increasing doses for effective pain relief. This is not a major problem in most patients.

Addiction - psychological dependence and abuse - is very unusual in chronic pain patients treated with an appropriate level of analgesia, as opposed to those who use opiate drugs for recreational purposes (see Side Effects).

Note that, unlike anti-inflammatory drugs (NSAIDs), opiates do not cause damage to organs.

It is best to start with short-acting morphine such as Oramorph, 4- hourly, until adequate analgesia is established. Breakthrough pain may require top-up doses.

Once control has been established, it is advisable to change to a slow release preparation such as MS Continus or Oramorph SR, which has a predictable duration of action for 8-12 hours, and can thus be given twice daily. Oxycodone is a new preparation now being prescribed.

One of the most important points that patients need to be made aware of is the need for ?round the clock' dosing rather than in response to pain (prn, as required). This approach achieves a much better pain relief, whilst minimising side effects.

Fluctuations in dose requirement may occur, and in this case, the slow-release preparation should be replaced with a shorter acting one for the period of increased dose requirement.

Patients also need to be aware that the initial side effects of nausea and sedation are transient and should subside within two weeks or so, as tolerance to these effects develops. The most persistent side effect is constipation (see below).

Occasionally opiates may induce a paradoxical hyperpathia, (increase in pain) which is resolved

by substitution with an alternative opiate medication. ([4])

Morphine medication is available in many preparations including:

Sevredol? IR; Oramorph IR;; Morcap ? SR 20mg/12hr. or 40mg/24hr. ; MXL? sustained release 30/60/90/120/150/200mg;

Oxycodone: Oxynorm ? (ONR start 5mg 4-6 hourly) Oxycontin (oxycodone SR)
IR= immediate release; SR= slow release

Other opiates include:

Methadone: which can be beneficial for neuropathic pain, but may have an unpredictable duration of action

Pethidine has unwanted central effects and is too short acting

Dextropropoxyphene: a weak agonist, possibly metabolised to a cardiotoxic metabolite. (but a recent paper ([5]) has described it as an NMDA antagonist: see below) available in Co-proxamol/ Distalgesic (32.5mg combined with 325mg paracetamol) or Doloxene (60mg)

Fentanyl: short-acting; lozenge form helpful for incident pain; patch helpful for background analgesia

Pentazocine (Fortral?)

Palfium? dextromoramide

Palladone ? hydromorphone

Remedeine? paracetamol + dihydrocodeine

Dihydrocodeine

There are also partial opiate agonists such as buprenorphine (Temgesic?) which has a maximum analgesic dose equivalent to moderate doses of narcotics, but tend to cause less dependency. It has been used sublingually for some time (200-400 microgrammes 6-8 hourly).

Recently a buprenorphine patch (Transtec?) has been licensed for use in chronic severe non-malignant pain. The patch can replace weak or strong opioids or be used in combination with other analgesic agents if required. The starting dose in opioid na?ve patients is 35 microgrammes/hr.; the patch is applied every 3 days.

In March 2003, an article was published in the prestigious New England Journal of Medicine ([6]
), which reported on a randomised study of the mu agonist levorphanol. 81 adults with refractory neuropathic pain received either high dose (0.75mg) or low dose (0.15mg) capsules of levorphanol increased as individuals' requirements necessitated up to a maximum of 21 capsules a day.

In the high dose study, 66% of the patients who completed the study had moderate or better pain relief. Drop-outs from the study were due to side effects.

In addition to pain relief, there were improvements in mood, function and sleep. The authors concluded that levorphanol is as effective as tricyclic antidepressants and gabapentin, but that there may be intolerable side effects.

In an accompanying editorial, Dr. Kathleen Foley of the Memorial Sloan-Kettering Cancer Center in New York noted that the study supports the concept of opioid responsiveness in neuropathic pain syndromes, although it fails to address longer term efficacy.

She suggested an individually-tailored approach bearing in mind the possibility of rotating various opioids to maximise analgesia and minimise adverse effects.

Note: special precautions need to be taken with some opiates in hypothyroidism, hepatic/renal impairment, raised intracranial pressure, biliary tract disease (gallbladder etc.), pancreatitis, prostatic hypertrophy (enlarged prostate> may lead to urinary retention).

Opiates tend to interact with other medication in particular CNS depressants, MAOI antidepressants, and some preparations may affect antihypertensives (blood pressure tablets), muscle relaxants, quinidine, erythromycin, cimetidine and ketoconazole.

ADRs: (adverse drug reactions) with opiates include: nausea, somnolence (usually subsides after 1-2 weeks) constipation, blurred vision, fluid retention, confusion, itching/skin flushing.

Fentanyl patch can also cause skin reaction, drop in blood pressure, hallucinations, hypoventilation (reduced breathing rate), bradycardia (slow pulse), sweating, euphoria, headache.

Treatment of breakthrough pain (see also below)

McQuay ([7]) describes incident pain, which may be brought on by activity, and is a major problem, as adequate background analgesia may be insufficient to control it.

There may also be another type of incident pain, which is intermittent, and can occur at rest, without obvious trigger factors. It is very difficult to control. Use of the fentanyl lozenge (Actiq ?) may be useful in this situation.

OTFC delivers fentanyl within a sweetened matrix that dissolves in the mouth. The fentanyl is absorbed rapidly through the buccal mucosa due to its high lipid solubility.

A recent Reuters Medical News bulletin (November 29, 2002), reports on a study of 100 patients with severe chronic non-malignant pain (duration at least 3 years), treated with oral transmucosal fentanyl citrate (OTFC).

More than half the patients suffered from degenerative spine disease, some had neuropathy, migraine etc. and all were being treated with both a long-acting opioid and a short-acting one for breakthrough pain.

Patient used OTFC for severe breakthrough pain, and were able to reduce or eliminate use of the short-acting opioid by replacing it with OTFC. Pain relief was reported within 10 minutes of using OTFC.

Almost 3 quarters reported relief lasting at least 2 hours and more than 1 quarter found it lasted more than 4 hours.

62% reported fewer days confined to house or bed,

50% required less opioid medication and experienced less depression and anxiety and 45% were sleeping better.

Side effects of constipation, itching and nausea were reduced as was headache. The study was published in the October issue of the American Journal of Pain.

Coluzzi et al. ([8]) compared the efficacy of OTFC with that of immediate release morphine (MSIR) and found that OTFC gave significantly better outcomes relating to pain intensity and relief.

Common side effects include somnolence, nausea, constipation and dizziness; a long-term safety study ([9]) in cancer patients, OTFC was not found to be associated with any additional side effects.

Cephalon UK has recently (9th.April 2003) recalled batches of Actiq that had been distributed in the UK, as a precautionary measure to avoid any risk of overdose of fentanyl in patients which in extreme cases could be fatal.

During testing they found that a very small number of the lozenges had an amount of fentanyl higher than it should be. Although the number of lozenges that seemed to be affected was very low, Cephalon felt it was important to recall the supplies in order to avoid any patients taking an affected lozenge. Anyone taking an affected lozenge might experience:

- Excessive sleepiness (hypersomnolence)
- Low/shallow breathing (hypoventilation)
- A slowing of your pulse/heart rate (bradycardia)
- Dizziness (hypotension)

Cephalon routinely issue the following warnings with their product in the USA:

Indicated only for the management of breakthrough cancer pain in patients with malignancies who are *already receiving and who have tolera*

Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, A

This product *must not*

Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 mcg trans

Patients and their caregivers must be instructed that ACTIQ contains a medicine in an amount which ca

While all units should be disposed of immediately after use, partially consumed units represent a special

ACTIQ is intended to be used only in the care of cancer patients and only by oncologists and pain specia

The most common side effects observed in ACTIQ clinical trials were somnolence, nausea, vomiting, an

Patients should be closely followed and the dosage level changed until the patient reaches a dose that p

Once a successful dose has been found, the patient should limit consumption to four or fewer units per d

New Developments:

Currently nasal preparations of morphine are in development. One formulation uses chitosan, in order to increase the time the preparation remains on the nasal mucosa, thereby increasing

bioavailability.

A small trial of 14 patients ([10]) demonstrated that it was effective with a rapid onset within 5 minutes. Intranasal fentanyl has been used in 12 cancer patients ([11]) and found to give relief within a few minutes, with 7 patients reporting reduced pain after 10 minutes.

Further trials are necessary.

Dale et al. ([12]) reviewed nasal administration of opioid drugs, including studies in volunteers using fentanyl, alfentanil, sufentanil, butorphanol, oxycodone and buprenorphine.

Fentanyl, pethidine and butorphanol have been studied for postoperative pain. Onset times range from 12 -22 minutes and times to peak effect from 24- 60 minutes, with considerable interindividual variation.

The authors concluded:

"Nasal administration of opioids has promising features, but is still in its infancy."

Combination preparations:

MorphiDex? is a combination drug developed by Algos. This drug combines the NMDA receptor antagonist dextromethorphan with morphine, thereby increasing the effectiveness of the narcotic without increasing side effects.

Preclinical and double-blind single-dose placebo-controlled studies demonstrated that

MorphiDex (MS: DM), a 1:1 ratio of morphine sulphate (MS) to dextromethorphan hydrobromide (DM), provides significantly greater analgesia than an equal dose of immediate release MS, with a faster onset, and a duration of 8 hours or more. ([13])

Equagesic? = ethoheptazine cit.; meprobamate 75mg, aspirin 250mg, for use short-term for musculoskeletal pain.

Tramadol (Tramal/Ultram/Zydol/Zamadol?) is a synthetic centrally acting analgesic, which is unrelated to opiates and carries less risk of dependence.

It is a weak noradrenaline inhibitor and serotonin inhibitor and has weak opioid effects. It is useful for moderate to severe pain and has few serious side effects.

Harati et al. ([14]) found in a double blind, controlled trial of 131 patients with painful diabetic neuropathy, that there was a significant reduction in pain intensity at week 6.

There was a 15% drop-out due to adverse events.

However, it should be used with caution in patients who are also taking CNS depressants. Tramake ? is tramadol in sachet form, to be taken 50-100mg every 4-6 hours.

Hummel et al ([15]) have suggested that tramadol (like dihydrocodeine which they also studied) may exert a stronger analgesic effect when administered in the evening, and they recommend taking this into account if the usual routine of prescription leads to either an increase of pain in the morning (due to insufficient analgesia) or unnecessary excessive dose in the evening.

A slow-release preparation is available and can be given twice a day. (Every 12 hours) and this may circumvent these problems. Indeed, as neuropathic pain is often worse at night, if there is a

greater analgesic effect in the evening, this may be beneficial when used for this purpose.

Anti-depressants

The clinical "bottom line" (Source: Bandolier [16]):

Anti-depressants are effective in reducing neuropathic pain. The overall NNT (number needed to treat) for at least 50% pain relief compared with placebo is 3 (2.4-4): 30% of patients will gain more than 50% relief, 30% will have minor adverse reactions and 4% will need to stop treatment because of major adverse reactions.

SSRIs may be less effective but carry a 50% reduction in major adverse effects.

NNH (number needed to harm) for minor adverse effects is 3.7 (2.9- 5.2) across various pain conditions. NNH for major adverse effects is 22, although they were lower for SSRIs than for tricyclic antidepressants.

Amitriptyline (Lentizol?), a Tricyclic Antidepressant (TCA), is viewed by many as the agent of choice, because experience with it has been most widely reported. Generally, it is used to treat neuropathic pain at doses much lower than those used to combat depression.

Beneficial effects on pain may begin after about ten days (compared with about three weeks for anti-depressant action). It produces anticholinergic side effects such as dry mouth, constipation, blurred vision and urinary retention.

Dry mouth and drowsiness are experienced by about a third of patients. Amitriptyline is popular among Central Pain patients, not only because it makes dysaesthetic burning on the skin more bearable, but also because it lessens the hyperpathic pain of bladder distension.

Clomipramine (Anafranil?) is a tricyclic antidepressant that also has SSRI properties.
SSRIs: This type of antidepressant is much less effective in the treatment of neuropathic pain. Some clinicians state that SSRIs are virtually useless, unless there is an element of depression as well as pain.

SSRIs like Prozac tend to be less effective in treating pain although they have fewer (paroxetine) or no (fluoxetine, sertraline, fluvoxamine) anticholinergic effects.

The commonest side-effect is gastrointestinal distress (nausea, vomiting, diarrhoea), occurring in 20-40% of patients. SSRIs may carry other unpleasant side effects especially initially when they may cause agitation, distress and disturbed sleep.

Sexual dysfunction of various types occurs in approximately 20-40% of patients on SSRIs (reports as high as 75% have resulted from direct interviews).

The double-blind, placebo-controlled, cross-over clinical trial by Max et al. ([17]) in 1992, on patients with painful diabetic neuropathy, published in the
New England Journal of Medicine,
compared the efficacy of a tertiary amine, amitriptyline, to that of a secondary amine, desipramine, and the selective serotonin reuptake inhibitor (SSRI), fluoxetine.

The doses were about 100 mg each for amitriptyline and desipramine, and 40 mg for fluoxetine.

It was found that while on amitriptyline, 74% of patients experienced moderate or significant pain relief compared to 61% while on desipramine and 48% while on fluoxetine.

Note that 41% of placebo-treated patients also had moderate or significant pain relief, which means that the SSRI barely outperformed placebo.

Seroxat: there has been considerable controversy of late over this SSRI drug (Paroxetine). Whilst it undoubtedly helps great numbers of depressed patients, there have been various reports about the adverse effects, including what has been described as ?mental turmoil' (daytime irritability, morose and even suicidal thoughts, bizarre nightmares) and uncharacteristically violent behaviour (towards the self and/or others).

These can occur on starting the drug, within a few doses. They could be attributable to the initial decrease in serotonin that the drug causes. In addition, people have had difficulty stopping the drug. Although the manufacturers and many doctors fail to recognise the problems, there is a well documented set of withdrawal symptoms, including unpleasant experiences such as electric shock type sensations.

Dual reuptake agents such as tricyclic antidepressants (TCAs), venlafaxine (at doses of 150 mg/day or higher), mirtazapine, and monoamine oxidase inhibitors appear to be more effective than selective serotonin reuptake inhibitors (SSRIs) alone in treating either pain or depression.

In one large meta-analysis, venlafaxine at daily doses of 150 mg or greater was associated with higher remission rates than SSRIs (45% vs. 35%, respectively).

Mattia et al. ([18]) reviewed new antidepressants for treatment of neuropathic pain.

They discussed three classified categories: Serotonin and Noradrenergic Reuptake Inhibitors (SNaRI), such as venlafaxine and nefazodone; Noradrenergic and Specific Serotoninergic Antidepressants (NaSSA), e.g. mirtazapine, and Noradrenaline Reuptake Inhibitors (NaRI), such as reboxetine.

They noted that Venlafaxine (SNaRI), the most investigated of these new drugs, has been shown to be effective in the treatment of different kinds of pain, and has a significantly better side-effects profile than TCAs.

In Israel, a recent study looked at the antinociceptive properties of venlafaxine and mirtazapine. ([19]) Venlafaxine is a drug which blocks the synaptosomal uptake of noradrenaline and

serotonin and, to a lesser degree, of dopamine and mirtazapine enhances noradrenergic and 5-HT1A-mediated serotonergic neurotransmission.

It was found that both drugs have an effect on opioid receptors.

The antinociceptive effect of venlafaxine is influenced by opioid receptor subtypes (mu-, kappa1- kappa3- and delta-opioid receptor subtypes) combined with the alpha2-adrenergic receptor, whereas the antinociceptive effect of mirtazapine mainly involves mu- and kappa3-opioid mechanisms.

The authors Schreiber, Bleich and Pick suggested

"This opioid profile of the two drugs may be one of the explanations to their efficacy in severe depression, unlike the SSRIs and other antidepressants which lack opioid activity."

The same could be said of their efficacy in treating pain. Schreiber et al. ([20]) concluded that the antinociceptive effect of mirtazapine is mainly influenced by the kappa(3)-opioid receptor subtype combined with both serotonergic and noradrenergic receptors.

The authors stated:

"These results suggest a potential use of mirtazapine in the management of some pain syndromes".

They did, however, point out:

"However, further research is needed in order to establish both the exact clinical

indications and the effective doses of mirtazapine when prescribed for pain."

Theobald et al. ([21]) conducted a pilot study on mirtazapine in cancer patients. They found trend level differences for pain, pain relief, and mood and on numeric rating scales measuring nausea, anxiety, insomnia, and appetite. The authors concluded

"This open-label pilot study suggests that mirtazapine may be effective for improving multiple symptoms, depression and quality of life in patients with advanced cancer".

Finnish authors, Tasmuth, Hartel and Kalso, ([22]) conducted a randomised controlled trial of venlafaxine for neuropathic pain following treatment of breast cancer. They found that the average pain relief (diary) and the maximum pain intensity (retrospective assessment by the computer program) were significantly lower with venlafaxine compared with placebo.

Poor responders had low venlafaxine concentrations whereas those with high venlafaxine concentrations had "excellent pain relief".

They concluded that higher doses could be used in order to improve pain relief.

A recent Danish study ([23]) showed that venlafaxine successfully reduced pain paroxysms, constant pain, and pressure-evoked pain in neuropathy (although, like other agents, was ineffective against touch-evoked pain).

The authors of the study concluded:

"Venlafaxine relieves pain in polyneuropathy and may be as effective as imipramine."

Briley ([24]) wrote favourably about agents such as venlafaxine, milnacipran and duloxetine, suggesting:

"these compounds may be effective in relieving pain both associated with, and independent of depression."

The Danish University Antidepressant Group found similar results when comparing citalopram and paroxetine with clomipramine.[15]

Note: Drug Interactions: Antidepressants such as TCAs are central nervous system depressants and may interact with other CNS depressants such as opiates (morphine etc.) or benzodiazepines and increase sedation and possibly respiratory depression.

Either SSRIs or TCAs, if given with tramadol may increase the risk of seizures. Paralytic ileus (gut motion stopped) may occur in patients taking TCAs in combination with anticholinergic drugs such as oxybutinin (used for bladder dysfunction).

Anticonvulsant drugs may lower the plasma concentration of antidepressants. TCAs may enhance the muscle relaxant effect of baclofen.

Antidepressants are also helpful in tackling urinary incontinence if the bladder muscle is hyperactive (detrusor instability). Conversely, if there is a tendency for the bladder not to empty efficiently or there is some degree of urinary retention these drugs are not suitable as they may exacerbate the problem or even cause full blown urinary retention, requiring catheterisation.

Buproprion (Wellbutrin): a study by researchers at the University of Arizona([25]) and funded partly by the manufacturers, has found that 71 percent of patients with neuropathic pain reported that their pain decreased on Bupropion, and only suffered mild side effects such as dry mouth, insomnia and headache.

The authors concluded:

"bupropion SR* (150-300 mg daily) was effective and well tolerated for the treatment of neuropathic pain." *SR=Slow release

Other neurotransmitters may be involved. Descending modulatory pathways mediated by serotonin, norepinephrine, and gamma amino butyric acid may be used to limit the intensity of pain signals arriving in the brain from the body via spinal pathways.

Disruptions in this pathway or in the limbic system (controlling mood) may have the ability to influence or even disrupt the other.

Although speculative, this may account for the numbers of patients developing depression in response to chronic pain or for depression acting as a "soil" for the development of chronic pain states in patients with known vulnerability to mood disorders.

Other theories of interaction have also been suggested. One such theory emphasizes dysregulations in the hypothalamic-pituitary-adrenal (HPA) axis and reductions in brain-derived neurotrophic factor (BDNF).

Changes in BDNF in depressed patients are the subject of current research. BDNF levels in the hippocampus are reduced by increased levels of endogenous glucocorticoids often seen in depressed patients.

BDNF appears to retard neuronal atrophy under stress, and a loss of such protection may inhibit accommodation and response to stress that involves both neuron preservation and neurogenesis.

Antidepressants may increase levels of BDNF as a key part of their mechanism of action.

Anticonvulsants

Anticonvulsants such as carbamazepine are particularly useful for the sharp, lancinating type of neuropathic pain.

Carbamazepine (Tegretol?) was the first of this class of drugs to be studied in clinical trials and has been longest in use for treatment of neuropathic pain.

Its use in treating trigeminal neuralgia has been established in clinical trials, but data for use in diabetic neuropathy is less convincing. 70 to 90% of patients with trigeminal neuralgia experience a good initial response to this drug. Indeed, experts in this field suggest that a failure to respond to CBZ suggests an incorrect diagnosis.

On a dose of 200mg twice a day, within 1-2 days the pain is significantly relieved.

Once autoinduction occurs, the dose may need to be increased to 600-1000mg daily.

There is a good correlation between efficacy and serum drug levels, the effective serum level range being 6-10mg/cc, usually achieved on daily doses of 400-1000mg.

However, at follow-up to there is about a 30 to 40% drop-out rate at 1 year, either because of the development of tolerance or because of the development of significant side effects.

Carbamazepine has significant side effects, including nausea/vomiting; diarrhoea; rash, pruritus (itching); fluid retention (low sodium); drowsiness, dizziness, blurred vision, lethargy, headache, tinnitus, paraesthesia (tingling), abnormal involuntary movements, leg cramps. Urinary frequency or occasionally acute urinary retention may occur.

It also has numerous drug interactions, including calcium channel blockers e.g. Nifedipine; Verapamil (may be used to treat high blood pressure); Digitoxin (for abnormal heart rhythm), corticosteroids, diuretics ("water tablets" for fluid retention) Danazol (hormone), oral contraceptives, Lithium, muscle relaxants, Theophylline (used to treat asthma), Thyroxine, Cimetidine (ulcer-healing) Fluoxetine (Prozac), Erythromycin (antibiotic).

Liver enzymes and haematological indices should be monitored.

Oxcarbazepine: is a keto-analog of carbamazepine can be given twice daily and there is no autoinduction. It has a low propensity for drug interactions and fewer side effects than CBZ, whilst being as effective for pain relief.

In epilepsy trials, it has been better tolerated than CBZ. Oxcarbazepine is new in the United States, but has been approved in more than 50 countries.

In trigeminal neuralgia, oxcarbazepine (OXC) has been tested in a number of clinical trials. Lindstrom ([26]) performed a comparative trial of OXC vs. CBZ in a cross-over design. OXC was titrated to 900-2100 mg/day vs. CBZ at 400-1200 mg/day.

The efficacy was assessed on an 11-point scale and the data showed comparable analgesic effect in 12 patients, better efficacy on OXC for 2 patients and better efficacy for CBZ in 1 patient.

The author concluded that OXC offers an alternative to CBZ for the treatment of trigeminal neuralgia. With regard to dosage, 1mg CBZ is equivalent to 1.5mg OXC.

Remillard ([27]) looked at use of OXC to treat trigeminal neuralgia refractory to CBZ treatment. 67% of the 15 patients were completely controlled on 900-1800mg/day and a further 20% were controlled with occasional exacerbations on doses of more than 2g a day.

Beydoun et al. presented findings of 3 double-blind randomised studies of OXC versus CBZ at the American Pain Society Meeting in 2002. In newly diagnosed trigeminal neuralgia, 48 patients on 750mg OXC or 500mg CBZ median dose and 2 studies of refractory trigeminal neuralgia (84 patients) at 1050-1200mg OXC daily and 700-900mg CBZ showed that OXC has a similar efficacy to CBZ but fewer side effects.

Carrazana et al. presented at the same meeting, findings from a study of the use of OXC in painful diabetic neuropathy. 50% of patients experienced a 50% of better improvement in VAS scores, and both primary and secondary variables on the Quality of Life questionnaire improved.

Neurontin (gabapentin) is useful for pain relief and muscle spasms. It has been demonstrated as helpful in diabetic neuropathy and post-herpetic neuralgia.

Recent studies have also shown that it is beneficial in post-amputation pain ([28]) and also in patients with spinal cord injury.

In the SCI study ([29]), there was a "significant decrease of "unpleasant feeling" and a trend toward a decrease in both the "pain intensity" and "burning sensation" at the fourth week of gabapentin treatment compared with those on the placebo."

A recent randomised, double-blind study in Glasgow ([30]) found that Gabapentin was effective in a range of conditions causing neuropathic pain, including features of allodynia and hyperalgesia.

A Finnish group published a paper in October 2002 ([31]), in which they looked at the use of anticonvulsants in central pain.

The authors concluded:

"Present suggestions for anticonvulsant treatment of CP are lamotrigine as the first choice, followed by gabapentin or carbamazepine/oxcarbazepine. These compounds are considered as effective as the antidepressant amitriptyline."

In November 2002, Hurley et al ([32]) reported on animal studies which showed that gabapentin (and pregabalin: see below) interact synergistically with the NSAID Naproxen to reduce hyperalgesia.

The authors suggest that low dose combinations may be effective for persistent inflammatory pain.

It is important to start at a low dose (300mg at night) and increase very gradually to reduce the impact of side effects, which include sleepiness and unsteady gait. Some people report weight gain and others experience clouded thinking abilities on this drug. Usually a dose of around 2400mg a day is helpful in combating nerve pain.

Note that Gabapentin interacts with antacid medication, but not other drugs (this is one of its advantages.)

ADRs listed in MIMMS include: somnolence, dizziness, ataxia, fatigue, tremor, nystagmus(flickering eyes), diplopia (double vision), dysarthria (difficulty talking), amnesia, joint pains, purpura (rash), GI upset, anxiety, weight gain, urinary tract infection and pharyngitis.

Other anticonvulsants include: Lamotrigine, which has been reported to be effective in relieving pain from trigeminal neuralgia refractory to other treatments, HIV neuropathy, and central post-stroke pain.

Zonisamide may be effective in controlling neuropathic pain symptoms. Other anticonvulsants, including lorazepam, valproate, topiramate, and tiagabine, have also been under investigation.

There are no double-blind trials of the other anticonvulsants. The data for phenytoin suggest that high dosages and high serum levels between 15-25 mg/cc facilitate a positive response in a proportion of patients; mostly it has been mostly used as an adjuvant to CBZ in patients with only a partial response to this drug.

With clonazepam, there have been 2 open-label series, of 25 and 19 patients, of which approximately two-thirds of the patients were reported to have a positive response. A single open-label series of 20 patients taking valproate showed that about half experienced a positive response.

Novel Anticonvulsant, Pregabalin is a second-generation anticonvulsant agent similar to gabapentin but about 6-fold more potent. In animal studies, pregabalin has been found to be effective in raising the pain threshold, reducing allodynia, increasing slow-wave non rapid eye movement(REM)sleep, relieving anxiety, modulating acute pain symptoms, and reducing colon-related pain.([33] ; [34] ; [35] ; [36] ; [37] ; [38]) However, it may also induce nocturnal myoclonus.([39])

An 8-week, multicentre, randomised, double-blind, placebo-controlled study by Crofford et al ([40])from the University of Michigan, Arbor and colleagues from several other institutions evaluated the efficacy and safety of pregabalin in patients with Fibromyalgia (FMS).

Patients treated with the highest dose, 450 mg/day, of pregabalin experienced significant improvement in the end point mean pain score compared with those receiving placebo, and were more likely to experience a 50% reduction in pain.

For patients receiving either 300 or 450 mg/day, other variables, such as the mean sleep quality, fatigue were improved significantly.

Patients in all treatment groups demonstrated significantly improved Sleep Index scores

In total, 9% of patients withdrew from the study because of adverse side effects (most

commonly dizziness and somnolence) and 8% because of poor efficacy.

The other newer anticonvulsant felbamate was tested in 3 patients with refractory trigeminal neuralgia who had a good response.

Unfortunately the drug is associated with significant idiosyncratic reactions including aplastic anaemia and fulminant hepatic failure, which renders it unlikely to be further developed as a treatment for neuropathic pain.

Topiramate has not been found to be statistically effective relative to placebo in three large randomised multi-centre trials, so there is no evidence-based data to support its use in neuropathic pain. It causes significant side effects including weight loss.

NMDA RECEPTOR ANTAGONISTS

Dextromethorphan: available OTC as a cough suppressant, it is a low-affinity NMDA receptor antagonist; it is rapidly metabolised to dextrorphan, which is an active metabolite that also has NMDA receptor activity.

Various studies have had mixed results, but Nelson's study([41]) of dextromethorphan in diabetic neuropathy and post-herpetic neuralgia (using an initial dose of 120mg per day increasing up to maximum dose of 960mg per day) found significant improvement in pain.

Ketamine:

This dissociative anaesthetic is an NMDA (N-methyl D-aspartate) receptor antagonist. NMDA is implicated in the centralisation of pain and sensitisation of the central nervous system via the "wind-up" mechanism.

It has been used as an anaesthetic for many years and only recently has its application as an analgesic been explored.

In 1994, studies([42]) found ketamine to be effective in treating post-herpetic neuralgia(PHN).

Mercadante et al ([43]) recommended a starting dose of 150 mg/day, which they stated would allow the dose of opiate medication to be significantly decreased. In one patient whose case they presented, the treatment was effective over a studied period of 13 months.

Various other authors have described ketamine's properties in combating centralised pain([44] [45]
) but there have been no large studies of its use in chronic pain.

Ketamine has been used long-term in a few small studies. Klepstad et al([46]) treated a patient with PHN using a combination of ketamine and dextromethorphan(another NMDA antagonist) administered via various routes, without serious side-effects for 4 years.

Intravenous ketamine:

"Ketamine is an adjuvant analgesic for the treatment of cancer-related pain when other agents either fail or are intolerable." ([47])

Ketamine ointment: a recent Japanese study([48]) looking at the effects of 0.25-1.5% ketamine ointment in patients with CRPS types I and II found that it

"appears to be beneficial for the patients with acute early dystrophic stage of CRPS I because of either its local anesthetic effect or NMDA receptor antagonist action.

Patients with chronic atrophic stage of CRPS I and CRPS II patients do not appear to respond to this treatment."

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