Royal College of Obstetricians & Gynaecologists

Therapies Targeting the Nervous System for Chronic Pelvic Pain Relief

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1. Background

Chronic pelvic pain (CPP) is defined by the Royal College of Obstetricians and Gynaecologists as 'intermittent or constant pain in the lower abdomen or pelvis of a woman of at least 6 months in duration, not occurring exclusively with menstruation or intercourse and not associated with pregnancy'.[1] Women with CPP may experience constant or cyclical pain, which can be unprovoked or associated with specific activities including urination (dysuria), bowel opening (dyschezia) or sexual intercourse (dyspareunia). CPP is associated with a significant reduction in quality of life and psychological distress is frequently seen in these women. Over one million women in the UK suffer with CPP[2] yet it is a condition that is frequently difficult to treat, with many patients not achieving adequate analgesia even after many years.[3] While CPP is known to occur in association with a number of gynaecological pathologies, including endometriosis, adenomyosis, chronic pelvic inflammatory disease and pelvic organ prolapse, in many cases an underlying pathology cannot be identified (chronic pelvic pain syndrome [CPPS]).[4] Moreover, even where a cause is found, such as endometriosis, the painful symptoms experienced may be disproportionate to the extent of disease identified or persist after optimal treatment.[5]

The experience of pain necessitates the involvement of the central nervous system (CNS) and there is increasing evidence that pain, no matter where it is perceived to originate from, can be both generated and perpetuated by the CNS itself.[6] Furthermore, chronic pain is associated with long-lasting changes both to the structure and function of the CNS which are relatively similar no matter the underlying pain condition.[6] There is now good evidence that such alterations in the CNS occur in a wide variety of gynaecological conditions associated with CPP, including endometriosis, vulvodynia, interstitial cystitis/bladder pain syndrome (IC/BPS)* and dysmenorrhoea.[7] Moreover, CNS dysfunction can also be responsible for many of the symptoms associated with CPP, including altered regulation of organ function leading to urinary frequency/retention and diarrhoea/constipation, and endocrine dysfunction, particularly alterations in the activity of the hypothalamic–pituitary–adrenal axis, potentially resulting in increased rates of infections and autoimmune conditions.

Women with CPP frequently present to gynaecologists, of whom the majority will focus their assessment and treatments on the pelvis. This paper will therefore review the available treatments for CPP that target the nervous system rather than the pelvis. Although many of these treatments are already, or are becoming, commonplace in chronic pain clinics, they are unfamiliar to the majority of gynaecologists. It will not specifically consider the treatment of CPP associated with cancer or of isolated dysmenorrhoea or dyspareunia as they do not fall within the RCOG definition of CPP.[1] However, much of the discussion is still relevant to these conditions since other organisations, such as the International Association for the Study of Pain (IASP) and the European Association of Urology (EAU), do include the latter two within their definitions[4,8] and dysmenorrhoea, in particular, has been associated with significant central changes.[7]

While it would be appropriate for some of the therapeutic options described in this paper to be initiated by a gynaecologist, it should be remembered that once pain has become chronic it is likely to be multifactorial. In all but the most responsive of patients, the outcome is likely to be best if management is by a multidisciplinary team potentially including those with expertise in hormonal, medical, invasive/surgical and psychological therapeutic modalities. Although more invasive therapies should be reserved for patients who are refractory to standard treatment of any identified pathology or where no such

* The International Association for the Study of Pain (IASP) no longer recommends the use of the term interstitial cystitis (IC), having replaced it with the more correct bladder pain syndrome (BPS). However, as gynaecologists still use IC, we have used the two terms together (IC/BPS) throughout this document.

pathology can be identified, other options (e.g. antidepressants, anticonvulsants, local stimulation [transcutaneous electrical nerve stimulation, TENS]) can be commenced whenever a patient presents with CPP and continued while further investigation and/or treatment is carried out. Such a strategy, if successful in at least partly alleviating pain, would be expected to improve quality of life and may help to prevent the development of long-lasting central changes.

2. Medical treatments

2.1 Antidepressant and anticonvulsant medication

Antidepressant and anticonvulsant drugs have been a mainstay of the management of chronic pain, particularly neuropathic pain, for many years,[9–13] although the mechanisms of action are not completely understood. It appears that antidepressants act by altering activity within pain inhibitory systems via modulation of serotonin, noradrenaline, dopamine and acetylcholine and potentially by direct anti-inflammatory, opioidergic or *N*-methyl-D-aspartate (NMDA) antagonistic effects.[14] What is known is that their analgesic activity is independent of their antidepressant activity and often occurs at lower doses than would be required to produce an antidepressant effect. Anticonvulsant drugs also appear to act through a combination of mechanisms, including inhibition of voltage-gated sodium and calcium channels and interactions with the γ-aminobutyric acid (GABA) system.[14] Given that women with CPP frequently report feeling that their doctors thought their pain was psychological, these points can be useful in counselling women prior to commencing an antidepressant or anticonvulsant medication.

In general, both classes of drugs are well tolerated with relatively minor adverse effects (drowsiness and nausea most commonly), although specific adverse effects vary between drugs. The wide variety of drugs available means that head-to-head comparisons of efficacy and adverse effect profiles have frequently not been undertaken and it is therefore difficult to recommend any particular drug over another. The varying mechanisms of action mean that if one drug is not successful another may well be, as may combination therapy if only partial efficacy is achieved. Similarly, if the adverse effect profile of a specific drug is not acceptable, there is likely to be an alternative that may suit the patient better. It is worth remembering that a dose–response curve likely exists for both classes of drugs[14] and therefore doses should be gradually increased if no initial response is observed. However, if no response is seen with adequate doses or if adverse effects are not tolerated then the drug should be tapered and withdrawn.

While a number of papers report the use of these drugs in CPP, few good quality trials of these drugs for this indication have been undertaken.

2.1.1 Evidence for the use of antidepressants in CPP

A systematic review of the evidence available for the use of antidepressants in chronic urological pain was undertaken in 2009.[15] Although focusing on urological pain conditions in both male and female patients (interstitial cystitis, chronic prostatitis), this review also included studies where patients only had a diagnosis of CPP. Vulval pain syndromes, however, were not covered. They identified ten studies meeting the authors' criteria, assessing the effectiveness of amitriptyline, sertraline, nortriptyline, duloxetine and citalopram. While the main conclusion was that 'the use of antidepressants in the management of chronic urological pelvic pain is not supported by an adequate number of well designed randomized controlled trials', it was acknowledged that for amitriptyline and sertraline, at least, there was some evidence of benefit. Moreover, the drugs investigated were well tolerated and generally safe, including the more long-term use of amitriptyline.

2.1.2 Evidence for the use of anticonvulsants in CPP

Even less evidence is available to support the use of anticonvulsant medication in CPP. Sator-Katzenschlager and colleagues compared the effectiveness and tolerability of amitriptyline with gabapentin and the

two drugs combined.[16] This study had no placebo arm and was relatively small (n = 20 for each drug alone and n = 16 for the combination); however, it did conclude that the drugs were both well tolerated and that gabapentin alone or in combination appeared to be more effective than amitriptyline alone, particularly for long-lasting relief of pain. We are aware that a pilot randomised controlled trial of gabapentin versus placebo is currently underway.[17] A second study investigated the role of lamotrigine in CPP.[18] The interpretation of the results of this study is difficult due to the relatively small cohort of patients recruited into the three subcategories of CPP: diffuse abdominal (n = 7), neuropathic (n = 7) and vulvodynia (n = 17). Although there appeared to be some efficacy in all three groups of women, only those with vulvodynia had a significant reduction in their pain ratings after 8 weeks of treatment (although the neuropathic group approached significance and was a markedly smaller sample). A further study investigated gabapentin specifically in the treatment of vulvodynia.[19] In this study, 17 patients with vulvodynia were treated with gabapentin, with 14 (82%) reporting partial or complete relief of pain. While this study was not well controlled, it did include women who had failed treatment with other pharmacological options including amitriptyline.

2.2 Botulinum toxin

The use of botulinum toxin (onabotulinumtoxin A or Botox®, Allergan, Marlow, Bucks, UK) injections to relieve CPP is increasing although studies presenting the evidence of benefit are thus far poor. As well as affecting muscles directly, it is thought that botulinum toxin has effects on the central nervous system, which are important although not yet fully understood. Two small observational studies in a review appear to indicate some benefit from botulinum toxin injections to structures in the pelvic floor without significant adverse effects in vulvodynia, but these groups were uncontrolled and have selection bias.[20] The story is similar for the use of intravesical botulinum toxin injections for IC/BPS, except that because detrusor function is affected, significant numbers of patients in these small studies required intermittent self-catheterisation.[20,21]

There is a small single centre randomised controlled trial on the use of botulinum toxin in women who had greater than 2 years of pelvic pain and 'objective evidence of pelvic floor myalgia', as demonstrated by the presence of contracted pelvic muscles on palpation and elevated vaginal manometry pressures.[21] The treatment group (n = 30) had the puborectalis and pubococcygeus muscles injected with botulinum toxin while the control group (n = 30) had these muscles injected with saline. Pain scores were reduced in both groups but were not statistically significant. Compared to baseline, the women in the botulinum toxin arm had a significant reduction in dyspareunia and nonmenstrual pelvic pain and their pelvic floor pressures were reduced. Two patients who were treated with botulinum toxin into the puborectalis and pubococcygeus muscles had urinary stress incontinence and one of these was also incontinent of faeces intermittently for 4 months. Trials of botulinum toxin in women with overactive bladder suggest that it is a well-tolerated treatment with the potential to significantly improve quality of life in these women[20] and thus further investigation of the use of botulinum toxin in vulvodynia and CPP is justified. Furthermore, dry needling (the use of either acupuncture or hypodermic needles to disrupt trigger points/stimulate muscle without injection of either active or placebo [inactive] fluid)[22] also appears worthy of further research given the greater than expected effect seen in the control group after saline injection described above.[21]

2.3 Other

Three other pharmacological treatments targeting the nervous system have been investigated for the relief of CPP.

Of particular note, melatonin was found to significantly reduce daily pain, menstrual pain, dyschezia and dysuria in a cohort of 40 women with CPP and laparoscopically confirmed endometriosis.[23,24] However, this finding may not be generally applicable to women with CPP where no endometriosis is present.

Lofexidine hydrochloride, an α_2-adrenoceptor agonist that acts both via a direct antinociceptive action and to prevent vasospasm in the utero-ovarian bed, was investigated in a cohort of women with CPP and no obvious pathology on laparoscopy.[25] While this study did not find a significant difference compared to placebo, the numbers investigated were relatively small (19 lofexidine: 20 placebo) and it was only powered to detect a substantial effect.

Dexamfetamine sulfate, a sympathomimetic amine, has also been reported as a successful treatment for CPP, but only in association with coexisting idiopathic orthostatic oedema which is extremely rare.[26,27] Further randomised controlled trials are therefore required before this treatment can be recommended for CPP in general.

3. Non-invasive nonpharmacological treatments

External application of both electrical and magnetic stimulation can be used to alter neurophysiology locally (at the site of pain) or centrally (brain or spinal cord), potentially producing analgesia. Additionally, electrical stimulation can be performed directly on the peripheral nerves, spinal cord or brain and will be discussed in section 4.

3.1 Local stimulation

3.1.1 Electrical

Transcutaneous electrical nerve stimulation (TENS) is a familiar form of analgesia used during labour. The exact mechanism by which it exerts an analgesic effect is not known. It had long been assumed to work via the 'gate-control' theory, whereby activity in large diameter Aβ fibres inhibits activity in smaller fibres (Aδ and C: those transmitting pain) from the same segments. However, electrical stimulation of small fibres alone can also produce segmental and extrasegmental inhibition leading to analgesia.[14] Furthermore, the use of low-frequency electrical stimulation increases the release of endogenous opioids, thereby further reducing pain in both acute and chronic situations.[28] It has been shown to be effective in reducing pain in men with CPPS/prostatitis[29,30] but has not been evaluated in women with CPP specifically. In view of the location of pain in women with CPP, intravaginal electrical stimulation (IVES) has been proposed as an alternative strategy. Preliminary data suggested that IVES is associated with a significant reduction in pain and dyspareunia, with the reduction in pain being maintained at 7 months' follow-up.[31] More recently, IVES for CPP was assessed in a placebo- (sham stimulation) controlled randomised trial.[32] This confirmed that active stimulation was superior to sham, with a significant reduction in pain intensity at the end of the 5-week course of treatment. However, there was no long-term follow-up in this study.

3.1.2 Magnetic

A number of mechanisms have been proposed by which magnetism may influence pain, including: i) selective attenuation of neuronal depolarisation by altering membrane resting potential; ii) increasing blood flow (potentially accelerating tissue healing and removing noxious mediators); iii) altering ion binding kinetics and therefore modulating release of cytokines and other inflammatory mediators.[33] While there is some evidence of benefit in osteoarthritis sufferers (although potentially related to accelerated tissue healing rather than a direct analgesic effect),[34] only three small studies have been undertaken in women with CPP. The first of these used pulsed electromagnetic fields at the area of the pain in 20 women with acute or chronic pelvic pain.[35] All nine women with CPP showed a good improvement in pain intensity after treatment, although it should be noted that four of these women were being treated for an acute event on the background of CPP (ovarian cyst rupture or urinary tract infection). The second study attempted to use placebo magnets in a randomised double-blind study of static magnetic field therapy;[33] however, by the end of the study all of those wearing active magnets were aware which treatment group they were in. At the end of the 4-week treatment period, although there

was not a significantly greater decrease in pain scores in the treatment group, these women did report significantly less pain disability than those in the placebo group (measured with the pain disability index, a self-report measure that assesses pain-related disability in seven domains including home, work, social and sexual activities). The final study reported stimulating both the site of pain and the sacral spinal cord with repetitive magnetic stimulation (rMS) in 48 patients with CPPS.[36] Pain remission was reported in 67% of patients and a placebo-controlled trial is currently being undertaken.

3.2 Transcranial stimulation

Non-invasive methods of brain stimulation can be electrical (transcranial direct current stimulation [tDCS] and cranial electrotherapy stimulation [CES]) or magnetic (repetitive transcranial magnetic stimulation [rTMS]). They aim to modulate pain by a direct effect on brain activity. There are good experimental data suggesting that these techniques can both produce an immediate alteration in neurotransmitter concentrations, including the major inhibitory neurotransmitter GABA, and induce long-term synaptic changes. In the context of chronic pain, it is thought that analgesia is produced secondary to a reduction of activity in brain networks involved in the processing of pain and the facilitation of descending pain inhibitory mechanisms.[37] Although clinical studies undertaken across chronic pain conditions do in general support an analgesic effect of rTMS and tDCS, the pain relief obtained is not sufficient to be considered clinically meaningful.[37] Only one study has specifically addressed the effectiveness of such techniques in CPP.[38] Fenton and colleagues compared tDCS to sham tDCS in seven women with CPP refractory to treatment. They did identify a modest reduction in pain after active treatment, but the sample size was too small to draw any meaningful conclusions without further studies.

4. Surgical/invasive treatments

4.1 Nerve blocks

Only two small case series have looked at the benefit of hypogastric blocks and found limited benefit. Other papers discuss injection techniques and practical management without evidence[39,40] or describe multimodal treatments at one centre that included various nerve blocks.[41]

4.2 Neurectomy/nerve ablation

Interruption of the Lee–Frankenhauser sensory nerve plexuses by laparoscopic uterosacral nerve ablation (LUNA) was widely practised to alleviate pelvic pain until the publication of the largest trial of LUNA and a meta-analysis of all LUNA trials in 2009 and 2010 respectively.[42,43] The meta-analysis[43] reinforced the conclusions drawn from the trial[42] that the LUNA procedure is not effective in alleviating pain. Indeed, there is some evidence that women who have the LUNA procedure may suffer from more pain in the short term than those who do not.

Presacral neurectomy (PSN) involves the total transection of the presacral nerves lying within the boundaries of the interiliac triangle (a procedure that can be performed laparoscopically). Data on the efficacy of the procedure in the alleviation of pelvic pain are limited and conflicting.[44–48] However, the largest and most recent randomised controlled trial suggests that PSN may be effective for the treatment of severe dysmenorrhoea caused by endometriosis.[47] Laparoscopic PSN demands very significant surgical skills and expertise from the surgeon and is open to vascular and lymphatic complications because of the vicinity of the great vessels and lymphatic channels. An alternative is laparoscopic presacral neurolysis that involves the injection of a neurolytic solution (e.g. phenol) to chemically destroy the microscopic neural architecture of the presacral nerves. There is evidence from one study[49] to suggest that this technique can be considered in the treatment of pelvic pain, either as a single treatment or as an adjunctive procedure. However, without more data supporting a favourable balance of both efficacy and safety, neither presacral neurectomy nor neurolysis can be recommended.

4.3 Neuromodulation

The role of neuromodulation in the management of chronic pelvic pain syndromes is yet to be fully determined. Its role in overactive bladder and faecal incontinence, however, is much better established. While there is growing evidence of efficacy in pelvic pain from small case series or pilot studies, more properly controlled research is required. At present, it is generally agreed that neuromodulation should only be considered by specialists in pelvic pain management within the context of a broader pain management plan. Techniques available include peripheral nerve stimulation (e.g. posterior tibial nerve stimulation, sacral nerve/root stimulation and pudendal nerve stimulation) and spinal cord stimulation.

Intermittent percutaneous tibial nerve stimulation (PTNS) is a minimally invasive treatment option which has been shown to significantly decrease accompanying pain complaints in patients with lower urinary tract dysfunction, such as urge incontinence or urgency and/or frequency. In a study by van Balken et al.,[50] 33 patients with CPP were assessed after PTNS therapy. The visual analogue scale (VAS) score was seen to subjectively improve in 42% of all patients, with seven patients (21%) reporting a mean VAS score of less than 3 after 12 weeks of treatment. In all patients, both quality of life and total pain intensity score were significantly improved. The results of this study are mirrored by those carried out by Kim et al.,[51] Aggamy et al.[52] and Gokyildiz et al.[53] Thus PTNS may have a place in the treatment of patients with CPP who have already tried many other therapies and are left with no further options. However, all authors make the point that long-term follow-up studies are required.

Sacral neuromodulation (SNM) or sacral neurostimulation (SNS) was first introduced as a possible therapy in CPPS in 1999 by Feler and co-workers, but there still remains a paucity of literature. The difference between the two terminologies lies in the fact that SNS focuses on the stimulation of the nerve being the main driver of the positive response, whereas several authors believe that neurostimulation may be the start of the response but the maintenance of the long-term effect is due to the modulatory impact on the neural system. Essentially, both the sacral nerve and sacral root are stimulated initially, and modulated eventually, as the placement of the electrode lead often covers both sites. Thus, for the purposes of this document, sacral neuromodulation will be considered to be the therapeutic entity and it is assumed both components of the sacral neural system are being modulated.

Case studies, as reported by Lavano and co-workers in 2006,[54] showed that in five out of seven patients SNM reduced pain scores significantly. Similar reports are found throughout the literature but the data sets remain small. One of the largest groups studied included 78 patients treated from 1994 to 2008. Permanent SNM implantation was performed in patients who showed at least 50% improvement in their symptoms with a temporary peripheral nerve evaluation test. Median follow-up was 61.5 (SD ± 27.7) months and good long-term success was seen in 72% of the patients. Implants had to be removed in 28%, with the most frequent reason for device removal being poor outcome (54% of the failed patients). The revision rate in this study was 50%,[55] which is much higher than that seen in the general SNM literature for bladder and bowel dysfunction. In another observational, retrospective, case–controlled review, 34 female patients underwent permanent device implants. The mean pre-/postoperative VAS pain scores were 6.5 ± 2.9/2.4 ± 1.1 ($P < 0.01$). These positive results were sustained over a mean follow-up period of 86 ± 9.8 months. The reoperation rate was 25%.[56] Thus, SNM has a role but it is not without a significant complication rate.

Pudendal neurostimulation (PNS) in refractory CPPS is thought to have a better outcome in patients in whom other therapeutic options have failed.[57] In a prospective, single-blind, cross-over trial of PNS and SNM for patients with BPS (n = 22), PNS gave an overall 59% improvement in symptoms, whereas SNM gave an overall 44% improvement ($P = 0.05$). Most patients who tested both a sacral and pudendal electrode chose PNS as the better site for their pain relief. It would appear that neuromodulation options are well tolerated and over 90% of patients treated with neuromodulation stated that they would undergo implantation again.[58] PNS may also have a role in pudendal neuralgia, which is really a peripheral nerve

injury and as such should respond to neuromodulation by implanted pulse generators. However, it is important that the stimulation is perceived in the same site as the perceived pain.

Spinal cord stimulation (SCS) is considered an important treatment option for certain forms of chronic neuropathic pain that are otherwise resistant to treatment.[14] Its role in CPPS remains uncertain. SCS may be effective for thoracolumbar afferents. However, it is difficult to obtain appropriate stimulation from SCS for the sacral nerves, including pudendal, thus limiting the use of this therapy in chronic pelvic pain management. Nevertheless, where a specific visceral cause has been determined, such as in endometriosis, there is a possibility that it does have some impact. In a small (n = 6) study by Kapural et al.,[59] SCS was used to treat visceral pelvic pain after a successful test period with hypogastric blocks or neurolytic hypogastric blocks. Over an average follow-up period of 30.6 months, the mean pain VAS score decreased from 8 to 3, with a concomitant reduction in opiate use from 22.5 mg to 6.6 mg of morphine sulfate. The pain disability index also improved, thus suggesting that SCS may have a role in visceral pain management, which deserves further investigation.

Quite clearly neuromodulatory therapies are complex and patient selection is therefore key to their success. These patients are vulnerable, have often failed to respond to other treatment modalities and are psychologically frail. Thus, if neuromodulation is being considered then it should only be undertaken in specialised centres and in centres that can provide multidisciplinary care.

4.4 Deep brain stimulation

For chronic pain refractory to all other treatment options, deep brain stimulation (DBS) can be undertaken by a neurosurgeon. As with the non-invasive methods of brain stimulation, the aim is to enhance activity in pain inhibitory systems and stimulation is usually performed on one or more of the thalamus, periventricular grey and periaqueductal grey. More superficially, the motor cortex can also be stimulated (MCS).[60] Meta-analyses (albeit of mainly case series) suggest that DBS has a long-term success rate of 46%,[61,62] while MCS success rates vary, dependent on the indication, between 40% and 75%.[60] Surprisingly, both procedures have a relatively low complication rate with infection being the biggest risk. DBS is associated with a risk of intracranial haemorrhage (up to 4%); a complication that does not occur with MCS, however.[60] No studies have specifically assessed the efficacy of MCS or DBS in CPP in women.

5. Opinion

When assessing and planning treatment for women with CPP, it is important to consider the key role that the CNS plays in the experience of pain. Treatments targeting the CNS can be initiated alone while a patient is under investigation, or prescribed alone or combined with hormonal therapies and/or surgery if pelvic pathology is suspected or identified.

While there are few data supporting the efficacy of these treatments in CPP specifically, there is good evidence to suggest that the underlying pain mechanisms and central changes associated with chronic pain are similar no matter where the pain is perceived to originate from and it is therefore reasonable to consider these treatment options for all women with CPP.

Medical options such as antidepressant and anticonvulsant drugs are well tolerated and could therefore be started by a gynaecologist or primary care physician. Other more novel or invasive therapies are likely to require referral to a pain management team. However, it is important that gynaecologists are aware that such options exist so that referral can be considered for patients who are refractory to standard treatments prior to performing radical or fertility-removing surgery.

While little is known about the extent to which central changes can be reversed, prompt treatment of pain symptoms may prevent or at least minimise the development of long-term changes associated with chronic pain.

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Dr Vincent's department holds patents relating to obstetrics and gynaecology, but none related to pain or centrally acting analgesics.

Dr Curran: none declared.

Dr Elneil works as a consultant to Medtronic: company for sacral neuromodulation. She is Chair of the Board of Trustees of FORWARD UK (FGM) and a member of the National Institute for Health and Care Excellence (NICE) Interventional Procedures Advisory Committee.

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