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THE ROLE OF TOPICEUTICALS IN CANCER PAIN

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ABSTRACT

Purpose of review: Pain is one of the most common and feared symptoms associated with a new diagnosis of cancer and its subsequent treatment. Unfortunately, it remains undertreated in around one third of patients. It has been recently postulated that one mechanism for this could be failure to recognise neuropathic pain. One attractive option in both the case of neuropathic pain and pain associated with intolerable side effects of prescribed opioids is the use of 'topiceuticals', as a means of targeted pain relief with potentially fewer side effects. This review summarises the evidence base for the various topiceuticals available for the treatment of localised neuropathic pain.

Recent findings: The recent evidence base for established treatments such as capsaicin and lignocaine is examined. A variety of novel and previously used therapies are considered.

Summary: The use of topiceuticals in localised neuropathic pain associated with malignancy remain a valuable option with many advantages over systemic treatments. In addition to anecdotal reports of efficacy, there is a growing body of evidence to consider the early use of topical lignocaine and capsaicin in this context. The authors' have proposed a guideline including the use of topiceuticals to aid in the management of neuropathic pain

KEYWORDS

Topiceuticals, cancer, pain, topical, therapy

INTRODUCTION

Pain is one of the most common and feared symptoms associated with a new diagnosis of cancer and its subsequent treatment[1]. Unfortunately, some 30 years since the advent of the World Health Organisation's palliative pain ladder, it remains undertreated in around one

third of patients [2,3]. Whilst for many an approach using the analgesic ladder will alleviate symptoms, there are many for whom strong opioids fail to control pain. It has been recently postulated that one mechanism for this could be failure to recognise neuropathic pain and targeting treatment towards it [4]. Sources of neuropathic pain in this population include chemotherapy induced peripheral neuropathy and chronic post-surgical pain (which includes scar hypersensitivity) from curative and palliative surgeries. For a significant number of patients, pain may be ameliorated with strong opioid analgesics, but this may be at the expense of intolerable side effects. Options available to the Palliative and Pain Physicians in such scenarios include invasive interventions such as intra-thecal drug delivery (ITDD), cordotomy and coeliac plexus block. Such an approach requires input from a multidisciplinary team in a specialist centre[5]. One attractive option in both the case of neuropathic pain and pain associated with intolerable side effects of prescribed opioids is the use of 'topiceuticals', as a means of providing targeted pain relief with potentially fewer side effects.

BACKGROUND

The use of topical remedies is not a new concept. In prehistoric times, humans recognised that local flora and fauna could be applied to wounds and passed this knowledge down through the generations[6]. In the context of this article, topical, from the greek *topikos* (of a place) refers to the local application of a medication to the tissues to achieve high concentrations and thus effect at the target site. This is in contrast to transdermal therapy which aims to achieve steady systemic absorption of a medication, typically through the application of an adhesive patch to the skin. Commonly used topiceuticals include Non-Steroidal Anti-Inflammatory Drugs (NSAIDS), the Lidocaine 5% plaster (Versatis®), Capsaicin cream 0.025% and 0.075% and the Capsaicin 8% patch (Qutenza®).

WHEN TO USE TOPICEUTICALS?

The multi-factorial nature of the pain experience associated with malignancy and the plethora of sources that pain can present from, are beyond the scope of this text. There are, however, several scenarios where adjuvant analgesics may be useful. These include bone pain (bisphosphonates, radiopharmaceuticals), bowel obstruction (anticholinergic drugs, somatostatin analogues), cerebral oedema (dexamethasone), and neuropathic pain (anticonvulsants, antidepressants) [7]. It is also in the case of the latter where topiceuticals can be a useful adjunct.

In a systematic review of over 13,000 cancer patients the prevalence of neuropathic pain was estimated to be between 19 and 39% [4]. A rational approach to the treatment of neuropathic pain is described in the most recent NICE guidelines[8]. This details a stepwise approach using systemic treatments such as anticonvulsants and antidepressants. However, it has recently been noted that just over half of cancer patients with neuropathic pain will have a consistent and circumscribed area of maximum pain[9]. It is this 'localised neuropathic pain' (LNP) that forms the basis for using topiceuticals in cancer-related pain.

WHY USE A TOPICAL TREATMENT?

The need for further strategies such as topical treatment is borne out of the difficult nature of treating neuropathic pain. Even amongst the commonly used and most effective systemic analgesics such as the tricyclic antidepressants and gabapentinoids, the number-needed to treat (NNT) to achieve a 50% pain reduction varies from three to seven or greater [10]. These medications are not without side effects which limit their use.

Topiceuticals have a theoretical pharmacokinetic and pharmacodynamic advantage because they result in low systemic drug absorption, thus potentially less side effects and reduced drug-drug interactions. This property also infers a safer profile for use in patients with liver and renal dysfunction. There is generally no requirement or delay in therapy to titrate the dose for the available formulations and similarly no dose reduction for patients with co-morbid disease. It is arguably simpler to apply a topical treatment in comparison to medications, which often require dose titration and re-adjustment. The dosing schedule can also be significantly less frequent than oral medication, *e.g.* once daily for lidocaine plasters or even three monthly for the capsaicin 8% patch, Qutenza[®]. Furthermore this offers a route of treatment in those with an inability to swallow or absorb systemic medications. Another benefit perhaps less commonly considered in the context of malignancy, but more pertinent to persistent non-malignant pain, is that topical treatments are generally not likely to be associated with misuse or abuse.

A simple screening tool has been devised to aid in the initiation of topical treatment for localised neuropathic pain[table 1]. A numerical score of '4' based on history, examination and size of the affected area suggests a diagnosis of LNP and consideration can be given to the various agents available described below.

NSAIDS

Non-steroidal anti-inflammatory drugs are among the most prevalent topical agents, being readily available in 'over the counter' preparations without a prescription in the United Kingdom. They exert their action via inhibition of prostaglandin synthesis in a mechanism involving the opening of adenosine triphosphate sensitive potassium channels [12,13]. This inflammatory property explains their demonstrated efficacy in randomised controlled trials

for treating conditions characterised by somatic nociceptive pain such as tendonitis [14] and acute soft tissue injuries [15]. It is perhaps unsurprising that there is a paucity of evidence for their use in neuropathic pain. A small numbered double-blind crossover placebo-controlled study demonstrated that aspirin was significantly better than placebo for treating both acute and post-herpetic neuralgia, whereas diclofenac was not[16]. In the authors' experience NSAIDS are not generally considered successful in the treatment of localised neuropathic pain and there is not a significant body of evidence to support their use in this context.

LIDOCAINE

Local anaesthetics exert their action through the preferential blockade of active sodium channels present in the neuronal cell membrane[17]. Recently the role of various sodium channel subtypes has been characterised and described with a postulated mechanism involving neuronal excitability and lowering of the action potential threshold to explain spontaneous pain and the peripheral and central sensitisation seen in chronic neuropathic pain states [18]. The commonly used topical local anaesthetic preparations include the 5% lidocaine Versatis™ plaster, the eutectic mixture of local anaesthetics (EMLA); containing 2.5% prilocaine/2.5% lidocaine), and the Synera™ tetracaine 70mg/lidocaine 70mg patch. The bulk of the evidence for the lidocaine patches comes from short duration trials in the context of post-herpetic neuralgia (PHN). A double blind placebo-plaster controlled trial of 265 patients found the lidocaine plaster to be a safe treatment associated with benefits in pain, allodynia, sleep and quality of life [19]. Another retrospective study of the lidocaine 5% plaster comprising a cohort of 467 patients with peripheral neuropathic pain from a variety of causes, demonstrated that pain intensity was reduced by 50% in 45.5% of patients, and reduced by 30% in 82.2% of patients [20]. Side effects observed in the latter included

erythema (n=19), pruritis (n=11), burns (n=12) and oedema (n=4) representing a relatively good safety profile. In a retrospective audit of 97 patients within a comprehensive cancer centre, lidocaine plasters were found to be particularly efficacious in patients with allodynia [21]. Although a substantial evidence base for the use of lidocaine plasters in LNP secondary to cancer or treatment complications of cancer is lacking, it is the authors' experience that it is a safe and efficacious treatment in those with positive sensory signs. It is a useful second line treatment but can be considered first line in the elderly and frail.

CAPSAICIN

Capsaicin, an active ingredient of chilli peppers from the genus *capsaicum*, is a colourless odourless, volatile, hydrophobic compound. It was first isolated in 1816 by Christian Friedrich Bucholz and subsequently first synthesised in 1930 by Ernst Spath and Stephen Darling [22,23]. Capsaicin activates the transient receptor potential vanilloid 1 (TRPV1) ligand-gated channels of the peripheral Ad and C nociceptors. This causes depolarisation and the propagation of action potentials resulting in transmission of pain to the spinal cord with the resultant initial burning sensation experienced by patients [24]. After continued treatment, the TRPV1 containing nerves are "defunctionalised", a term used to describe the epidermal nerve fibre degeneration that is seen on nerve biopsy in the area of application [25]. In clinical terms, this means that initiation of treatment is associated with a burning sensation for a number of days, followed by analgesia. It is available as 0.025% and 0.075% creams for application four times daily to the affected area, and as a one hour application of the 8% patch which, in the United Kingdom, is applied in the hospital setting so the patient can be supervised and monitored appropriately. Clinical trials involving 10% and 20% applications are currently in progress [26,27]. The 0.025-0.75% cream and 8% patch are approved for the

treatment of peripheral neuropathic pain in the UK as 2nd line agents or in those who cannot tolerate systemic treatments, although the NICE guidelines comment that outside of post-herpetic neuralgia and painful diabetic neuropathy the use is off-label and at the prescriber's discretion [28,29].

A review of the recent literature by the authors did not yield a significant body of evidence for the use of capsaicin specifically in cancer-related pain, however there is a growing body of evidence in other localised neuropathic conditions suggesting a putative role.

In the recent multi-centre randomised 'ELEVATE' trial involving 568 patients [30], the Capsaicin 8% patch was shown to be non-inferior to pregabalin in patients with painful non-diabetic neuropathy. The withdrawal rate from the capsaicin group (6 of 282 patients) was low and attributed to patient choice (n=4) and perceived lack of effect (n=2). The systemic adverse event rate was 0-1% in the capsaicin group and 2.5-18.4% in the pregabalin group. Local adverse events were greater in the capsaicin group comprising pain on application (24% vs 0%), erythema (21% vs 0.4%, and a burning sensation (16% vs 0.4%). However, only patients in the pregabalin group (n=24, 8.5%) withdrew because of treatment- emergent adverse effects. The primary endpoint of 30% pain intensity reduction was reached by 55.7% in the capsaicin group and 54.5% in the pregabalin group. The time of onset to pain reduction was faster (7.5 days vs 36 days) and the treatment satisfaction was higher in the capsaicin group. The study was limited by its duration (8 weeks), the fact that a significant proportion of patients with LNP have already trialled gabapentinoids and the exclusion of patients with HIV neuropathy post radiotherapy neuropathy. That said, it was the first head to head study comparing these two readily available treatments and provided novel and clinically relevant

information. The cost over a two year period for the two treatments has been considered relatively similar at £1,197 and £1,207 for capsaicin and pregabalin respectively[31].

The interval between 8% patch applications is determined by the individual patient's response to treatment. Interim results from an ongoing phase IV, prospective, multicentre, non-interventional 'ASCEND' study of routine practice using capsaicin patch in 296 patients demonstrated a median time to re-treatment of 5.5 months [32]. The capsaicin 8% patch can be considered a safe, relatively effective treatment in localised neuropathic pain. Despite the common local effects of erythema and burning discomfort on application, the rate of treatment discontinuation is low.

OPIOIDS

There are many transdermal opioid preparations available. Considering in isolation 'topical' opioid treatments as defined above, the evidence is conflicting. In a case series examining the use of topical morphine for arthritic pain, it was found to be an effective treatment. However, systemic absorption was evident from urinary analysis, thus negating both the advantages and claim of being a true topical treatment[33]. The concerns of systemic absorption and the resultant long-term side effects such as immunosuppression and impaired endocrine function are perhaps less significant in the palliative setting where a role for topical opioids may exist. It has been used in this context for painful mucositis but there is no substantial evidence for topical opioids in LNP[34].

MENTHOL

A recent proof of concept study looked at the potential of menthol as a clinically useful analgesic in patients with chemotherapy induced peripheral neuropathy(CIPN) and scar

related pain[35]. This was on the basis of basic science findings that activation of the TRPM8 ion channel by topical agents produced significant analgesia[36]. The small numbered study found that 82% of subjects had an improvement in brief pain inventory (BPI) scores [35]. Improvements in mood ($P = 0.0004$), catastrophising ($P = 0.001$), walking ability ($P = 0.008$) and sensation ($P < 0.01$) were also observed. These results require to be validated on a larger scale but these limitations notwithstanding, menthol can be considered a safe inexpensive readily available treatment with potential efficacy in this patient group.

OTHER TOPICAL ADJUNCTS

A number of other drugs and drug combinations have been trialled for localised neuropathic pain. Clonidine has been used for sympathetically mediated peripheral neuropathy[37]. A small trial of topical amitriptyline 1%, an amitriptyline 1%/ketamine 0.5% combination, and placebo did not demonstrate a significant difference at 48hrs during the blinded phase of the study [38]. Interestingly no systemic absorption, as judged by serum sampling, was observed. In the subsequent open-label phase, combination therapy was significantly effective at 7 days. In a small number of patients with refractory radiation associated LNP, an amitriptyline-ketamine-lidocaine combination cream was found to be safe and effective [39]. Ketamine has been used in topical preparations with concentrations of 2% with systemic absorption in less than 10% of subjects [40]. Beyond case reports involving mucositis, it has not been used extensively in the cancer setting [41]. Topical gabapentin has been used in a study of 51 patients with vulvodynia to good effect but has not been extensively investigated in large number trials for LNP [42].

Other treatments that have been trialled in small number studies include; dimethyl sulphoxide (DMSO), palmitoylethanolamide (PEA), and essential oxygen oil [43-45]. Although

arguably not a topical treatment *per se*, intradermal botox has been recently shown in a randomised double-blinded controlled trial to have a sustained effect over 24 weeks when used in peripheral neuropathic pain[46]. In the palliative setting, radioactive strontium paste has been used to control pain from bony metastases[47].

CONCLUSION

The treatment of neuropathic pain remains a difficult entity despite advances in our understanding of the pathophysiology and the increasing availability of novel treatments. The best systemic treatments are still only effective for 1 in 3 patients[10] and associated with intolerable side effects that limit their use in many. The use of topiceuticals in localised neuropathic pain associated with malignancy remain a valuable option with many advantages over systemic treatments as outlined above. In addition to anecdotal reports of efficacy, there is a growing body of evidence to consider the early use of topical lidocaine and capsaicin in this context. The authors' have proposed a guideline including the use of topiceuticals to aid in the management of neuropathic pain (figure 1). The potential of other topical treatments such as opioids, ketamine, amitriptyline and gabapentinoids has yet to be established but small numbered trials have shown promising results.

KEY POINTS

- Simple scoring systems are available to aid in the diagnosis of localised neuropathic pain
- Topiceuticals should be considered in a diagnosis of LNP, particularly in the frail and elderly population
- Capsaicin and lidocaine patches are relatively safe and effective treatments for neuropathic pain

- The role of other topiceuticals has yet to be fully evaluated but small numbered trials have shown promise

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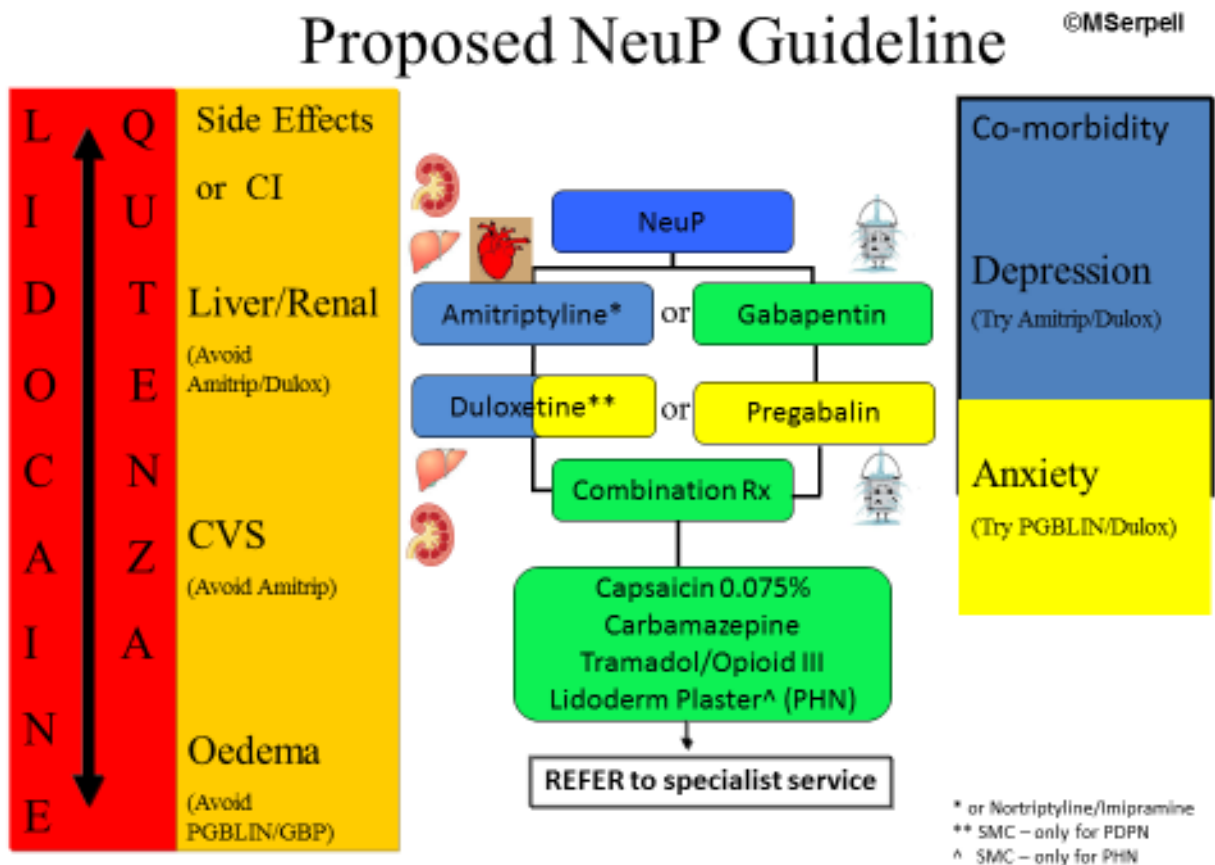
FIGURES AND TABLES

Table 1: A simple scoring tool for localised neuropathic pain (reproduced from [11])

Does the patient's history suggest a relevant nerve lesion or disease?	YES/NO
Is the pain distribution neuroanatomically plausible?	YES/NO
Does the neurological examination reveal any negative or positive sensory sign in the area of the presumably lesioned nerve?	YES/NO
Is the most painful area circumscribed and smaller than an A4 paper?	YES/NO

3 Yes = probable neuropathic pain; 4 Yes = at least probable localised neuropathic pain

Figure 1



Legend. SMC = Scottish Medicines Consortium PDPN = Painful Diabetic Peripheral Neuropathy

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