TRANSDERMAL® THERAPEUTICS

We've Got Pain Covered.

PAIN

A TRANSDERMAL THERAPEUTICS WHITE PAPER

Joseph Vaughan, M.D.

UT Southwestern Medical Center

Dallas, Texas

Joseph Vaughan, M.D.
UT Southwestern Medical Center, Dallas, Texas

1. PAIN

Often a discussion of pain begins with the provision of the most commonly cited definition of pain, that from the International Association for the Study of Pain: an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage ("IASP Taxonomy"). Perhaps the best definition may be that pain is a complex multidimensional, sensory-perceptual phenomenon that is difficult to define (Kerstman, 2013). There are factors influencing pain generation and affecting the behavior of those afflicted with chronic pain, further complicating the overall presentation of pain patients (Shankland, 2011), including the significant interrelationship with depression (Klauenberg, 2008).

Pain is associated with treble higher annual healthcare charges, a number of severe chronic medical conditions, and most likely has a higher incidence and prevalence than currently claimed, but both are hard to quantitate due to various problems in both defining and studying pain (Kerstman, 2013).

There are a number of comorbidities in patients with neuropathic pain, for example, which provide for the wide-ranging effects pain has on the individual patient who is suffering. These include a number of sympathetic considerations at the time of the onset of pain, for example, as well as the longer term associations (Schlereth, 2008). These include mood changes (about a third of pain patients endorse moderate to severe depression); anxiety (about a quarter of patients with neuropathic pain endorse); and alterations in sleep patterns, along with reduced employment status and social isolation. Further, pain is more likely to persist in those patients suffering from depression, and vice-versa (McMahon, p. 927).

Regardless of the complexity of the definition and associated problems, crucially we now know that pain perception occurs in the brain, but the precipitating injury is felt to occur in the periphery (McMahon, p. 864). The periphery continues to play a pivotal role in ongoing pain, which allows for the use of transdermal preparations safely and effectively in treating not only acute but also chronic pain.

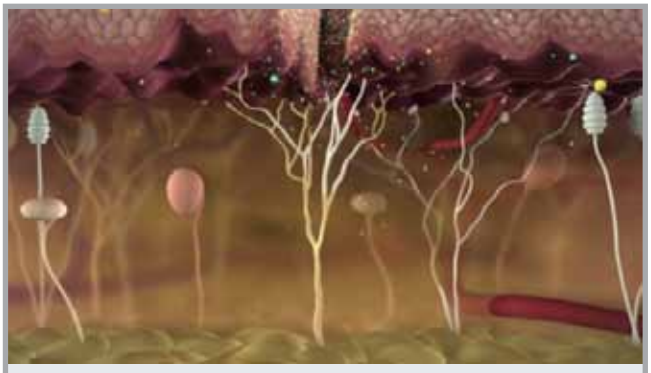
There are a number of ways to classify pain, and an exploration of these allows for a greater understanding of the lives of patients so suffering. Moller borrows from Merskey in providing the below nosological categories for pain:

- Physiological pain: caused by stimulation of pain receptors, also known as nociceptive pain
    - Somatic pain: involves skin, ligaments, joints, muscles, or by inflammatory issues; thus, associated with peripheral nerves and cranial nerves
    - Visceral pain: from internal organs, and often felt to have greater emotionality [and different—tends to produce a more sedentary, passive association whereas somatic pain is more often associated with an avoidance emotional and physical reaction], and may have more varied responses person-to-person; further, it is more commonly associated with nausea and autonomic nervous system (ANS) involvement (Moller, p. 90)
- Pathological pain: pain not caused by stimulating nociceptors

Moller posits that somatic pain may be protective, warning of trauma or disease, and discouraging tissue manipulation during healing; it may be acute or chronic. This pain can be modulated either in the periphery or in the CNS (peripheral and central sensitization both increase the sensation of pain), and via the CNS (for the reduction in pain sensitivity).

Somatic pain has two components temporally: an acute one, often described as sharp/stinging, and then a delayed sensation; this latter one often felt to be "aching" and/or "burning." The initial pain is associated with precise localization in the body for the source of the pain, whereas the second, more slowly appreciated aspect of pain is often poorly localized (Moller, pp. 45-51).

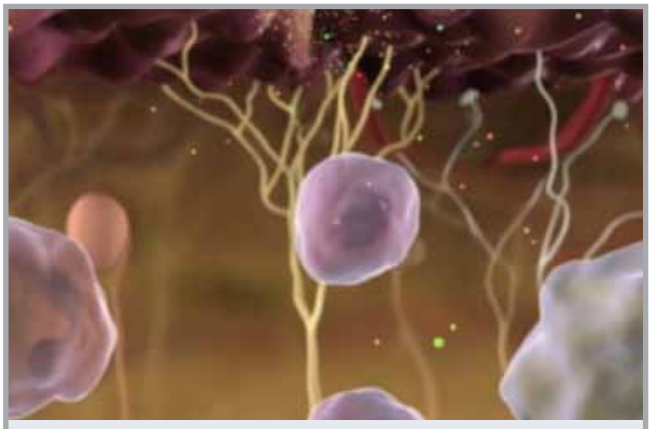
Clinically, two broad categories of pain are most important: nociceptive (generated by stimulating peripheral nociceptors in skin/joint/muscle) and neuropathic (from damage to the nervous system), with the fundamental difference being the absence of persistent stimulation of nociceptors in neuropathic pain (Kerstman, 2007).



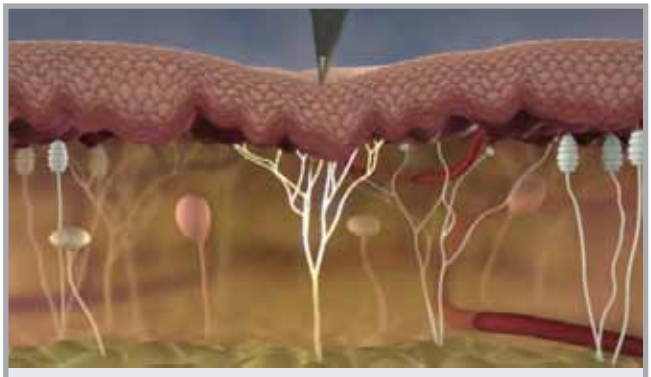
Local Tissue mediator releases immediately after injury, local tissue first releases prostaglandins and other chemical mediators which begin the process of nociceptor sensitization.

The initial pain sensation is mediated by myelinated, small diameter nerve fibers, α-δ fibers, whereas the secondary pain sensation is mediated by unmyelinated fibers, C-fibers (Moller, p. 59), though

not all C-fibers carry nociceptive information, as some of them convey light (pleasant) touch (Moller, p. 56). Whereas compressing a peripheral nerve may produce numbness with the preservation of pain due to preferential effects on myelinated fibers, local anesthetics work reciprocally: they affect C-fibers preferentially so they prevent the sensation of pain (the delayed, secondary pain), but preserve the sharp phase of pain and the sensation of touch (Moller, p. 56).

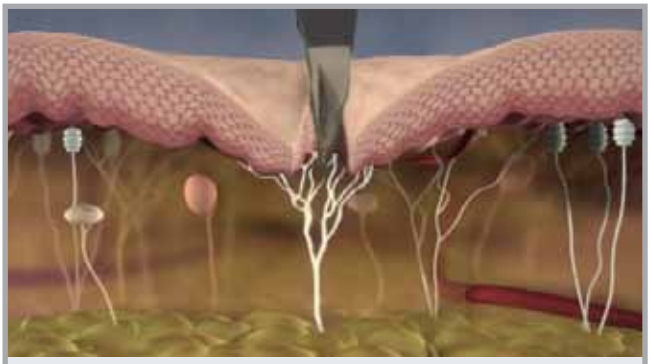


White Blood Cells are drawn to the area of injury. Mast cells, macrophages, neutrophils and other cells are drawn to the area of acute injury and inflammation.



"Primed" Nociceptor
With the Nociceptor fully "primed" and sensitized, a very small stimulus now elicits the sensation of severe pain.

There are three phases of change which occur in the periphery after tissue damage, a common cause of pain: immediate, later, and long-term events. There are overlapping chemical changes which occur during these phases which are important for the sensation of pain and development of peripheral sensitization. Potentially even during the immediate phase there may be changes in the spinal cord and/or brain which, if continued, can result in central sensitization. Strictly, both peripheral sensitization and central sensitization develop during the long-term phase after tissue damage. (Moller, p. 54).



Normal Nociceptor
Nociceptor triggered by painful stimulus and fires.

Nociceptors are classified as being:

- Chemoreceptors
- Thermoreceptors
  - Heat
  - Cold
- Mechanoreceptors (Moller, p. 54)

Nociceptor
Key pain sensory neurons sit below the subcutaneous tissue surrounded by sensors for pressure, heat and cold.

With pathology, pain can also be transmitted by touch receptors when they are overstimulated (Moller, p. 55).

After the peripheral nociceptor detects a painful stimulus, this signal is carried to the trigeminal nucleus in the brainstem (via cranial nerves V, IX, and X), for face and head sensations, and the dorsal horn of the spinal cord for pain below the neck, over the α-δ/C-fibers. α-δ fibers terminate on lamina I of the dorsal horn of the SC, and C-fibers on lamina II, with those laminae collectively known as the substantia gelatinosa (Moller, p. 58).

The dorsal horn is where the central processes of these axons terminate (with the cell bodies residing in the dorsal root ganglia), and it provides the first place in which the pain signals can be formally processed. There is an array of anatomical connections with interneurons here, and this is the first place in which more rostral control (e.g., inhibitory influences from the brain) can be felt on the perception of pain (Moller, p. 59).

Afferent Pain Pathway
Nerve impulse from peripheral pain sensor travels through the dorsal horn to the central nervous system.

From this area of first synapses in the dorsal horn of the spinal cord, the pain signals then ascend in at least three pathways, the best-known of which is the spinothalamic tract, to reach a number of sites in the cerebral hemispheres (Moller, p. 60). The thalamus cannot be excluded in its having an important role in pain perception (Moller, p. 72). Similarly, a number of rostral, subcortical and cortical sites project in a caudal fashion to influence the perception of pain (Moller, pp. 76-77).

Sensitization by chemical substances, inflammation, and neuropathic symptoms, consequently, may result from peripheral or central processes. The "sensitized nociceptor" results in hypersensibility from a reduction in the firing threshold of peripheral nociceptors. However, the "sensitized nociceptor" hypothesis does not explain "tactile allodynia," i.e., pain evoked by light touch. This results from central sensitization, as it is not simply just the amplification of pain, but central sensitization changes the response from perceiving light touch to actually feeling pain. The specific precipitating event appears to be less important than the effects of the induced pathology:

- Axonophathy and/or
- Segmental dysmyelination or demyelination (McMahon, p. 863)

The pathology then produces abnormal electrogenesis in electrically hyperexcitable neurons (McMahon, p. 864). Pathophysiological electrical discharges can emerge no matter how axons are injured (McMahon, p. 866). Temperature (generally heat), metabolic stressors, and a number of chemical factors can then cause firing of these damaged axons and result in the perception of pain (McMahon, p. 870).

Pain perception occurs in the brain, but the precipitating injury occurs in the periphery. As we shall see, the central changes involved in neuropathic pain are mostly triggered and maintained by abnormal input from the periphery. Thus, controlling the peripheral processes can also prevent or reverse the central ones.

There is little solid evidence currently that spinal cord sensitization can become "centralized" and independent of this peripheral drive, presumably from the requirement of neurotransmitter release to begin central sensitization (McMahon, p. 872).

The broadest, then, summary of neuropathic pain generation is: peripheral nerve damage resulting in inflammation and increased, abnormal firing of peripheral nerves which is combined with a decrease in the inhibition of pain from the CNS where there is altered processing of the pain signals (Kerstman, 2013).

There is general consensus today that both peripheral and central nervous system processes play a role in appreciating neuropathic pain. The CNS changes, however, are driven largely by changes in the PNS. Thus, controlling pathophysiological change in the periphery is likely to have greater therapeutic impact than approaches that target CNS processes. PNS processes also tend to be more accessible to therapeutic intervention (McMahon, p. 862).

In addition to evoking acute nociceptive pain, burns, abrasions, chemical irritations, and infections often cause more prolonged pain, both spontaneous and evoked by stimuli. Pain in response to weak, normally innocuous stimuli is "allodynia;" exaggerated pain in response to stimuli expected to be (moderately) painful is "hyperalgesia" (Jensen, 2014). In the case of allodynia, at least, tenderness in the "sensitized" tissue ("pain") no longer corresponds to the stimulus (which is non-noxious). This type of pain is usually called inflammatory pain since it is typically accompanied by an immune response and mediated by pro-inflammatory molecules (McMahon, p. 862).

Further, of growing interest is that there are many shared anatomical and chemical pathways for pain and headache (Burstein, 2000; Burstein, 2003; Yarnitsky, 2003; Landy, 2004; Silberstein, 2004; Edvinsson, 2005; Olesen, 2009; Edelmayer, 2009; Galletti, 2009; Burstein, 2010; d'Andrea, 2010; Burstein, 2011; Noseda, 2011; Burstein, 2012).

2. PERIPHERAL SENSITIZATION

Pain begets pain.

Indeed, early postoperative pain, for which topical preparations are being considered as helpful options (McCleane, 2010), was the only significant predictor of persistent pain in a group of patients undergoing thoracotomies (Katz, 1996). Thus, treating pain early and effectively would seem a laudable goal for its own sake, as well as to hopefully, then, prevent the development of chronic pain.

As summarized below, save for genetic or "central" pain syndromes, the periphery is whence pain generally arises (Stein, 2009), as is

a pathophysiological explanation of migraine (Borsook, 2012). There are great similarities between migraine and pain in the roles of their peripheral and central mechanisms (Burstein, 2000; Burstein, 2003; Yarnitsky, 2003; Landy, 2004; Silberstein, 2004; Edvinsson, 2005; Olesen, 2009; Edelmayer, 2009; Galletti, 2009; Burstein, 2010; d'Andrea, 2010; Burstein, 2011; Noseda, 2011; Burstein, 2012). Many of the treatments for both pain and headache are directed at the periphery (Richards, 2013), most especially for pain and topically applied medications, though central effects from transdermally used agents which have sparing absorption and low serum levels may be important as well.

There is a role, as well, for dorsal root ganglion neurons in pain, which may factor into the development, and perhaps maintenance, of central sensitization (Noguchi, 2004), given their unique anatomical localization and their physiology.

However, the focus on treating pain in the periphery is largely centered on the inflammatory milieu, which is highly complex, and on ion-channel blockade, as these two pathways are intimately involved in producing and perpetuating pain and many of our currently available drugs are felt to work in at least one of those routes.

A peripheral injury or the application of a noxious stimulus (equivalent in their ability to start the peripheral processes leading to pain) to the periphery activates a number of chemical mediators which directly stimulate nociceptors, but it also causes the release of substance P. This is a key early feature which has both local effects (cutaneous blood vessel dilatation and resultant cutaneous erythema, pain production) and magnifying effects (SP, a chemoattractant for leukocytes, releases histamine from mast cells). Substance P also causes synaptic hyperexcitability, which removes the magnesium ion's block of the NMDA receptor, and thus glutamate is allowed to activate the post-synaptic neurons in the spinal cord for the peripheral nociceptors.

In addition to substance P and histamine there are a number of other chemical mediators in the periphery, some of which are currently targets for pain therapy. This results from the injury and/or the magnification beginning with SP's release, including: bradykinin, the eicosanoids (prostaglandins, leukotrienes, and thromboxanes), serotonin, noradrenaline, adenosine, protons, free radicals, cytokines (interleukins and TNFα, especially), neurotrophins, nitric oxide, vasoactive intestinal peptide (VIP), and calcitonin gene-related peptide (CGRP).

These chemical mediators then stimulate nociceptors, which open cationic channels in their neuronal membranes. This allows for activation of voltage-gated sodium channels and thus the production of action potentials in the sensory axons.

The painful stimulus, as the NMDA receptor has now been unblocked and, is thus transmitted via the α-δ and C-fibers to the dorsal horn of the spinal cord where there are synapses with wide-dynamic range (WDR) neurons. These WDR neurons, located in the dorsal horn, are able to integrate the input from the various stimuli from the peripheral nociceptors and non-nociceptive stimuli. If the stimulus in the periphery is persistent, there are changes which occur in the spinal cord which can then both activate the peripheral nociceptors and increase nociceptor activation. This leads to an excessive amplification of a peripheral stimulus, which can then lead to the perception of light touch (an innocuous stimulus usually) as being a painful stimulus—the clinical symptom of cutaneous allodynia. The plasticity of the spinal cord which can lead to peripheral sensitization is felt intimately related to NMDA receptor activation (Melzack, 2001a; Melzack, 2001b; Melzack, 2005; Meeus, 2007; Basbaum, 2009; Latremoliere, 2009; Cheng, 2010; Kuner, 2010; Staud, 2010; De Felice, Pain, 2011; Woolf, 2011; Moayedi, 2013).

3. CENTRAL SENSITIZATION

The interactions between the peripheral processes initiating and, at least for a time, perpetuating pain and the central responses to persistent pain are quite complicated and summarized succinctly below (Yoshimura, 2004; Zhuo 2004; Campbell, 2006; Devor, 2006; Vranken, 2009; Vranken, 2012; shorter summary and diagrammatic representation in Gangadharan, 2013), and not just limited to the periphery's driving the pain but include possibly a more dynamic role for central effects in generating neuropathic pain (Wang, 2013) and for descending central influences, also seen in headache (Moulton, 2008). This has been specifically addressed for musculoskeletal problems (Winkelstein, 2004), for which manual therapists are alerted (Nijs, 2010).

Essentially, peripheral sensitization, if not reversed, can lead to central sensitization. There is evidence for sodium channel activation in the periphery driving central changes (Amir, 2006). Similar to the production of cutaneous allodynia via peripheral sensitization, hyperalgesia results from central sensitization. Once it is established, the appreciation of a degree of pain which exceeds the amount applied in the stimulus, essentially, an increased sensitivity to a painful stimulus (hyperalgesia) results. Central sensitization can also produce cutaneous allodynia.

Fundamentally, central sensitization is the abnormal and intense enhancement of pain by central nervous system mechanisms. It, like peripheral sensitization, reflects the plasticity of the nervous system, though in this case the plasticity of the CNS.

There are several physiological underpinnings required to develop central sensitization.

The first is wind-up, which is the progressive build-up of the amplitude of the response of dorsal horn neurons (WDR neurons) during the stimuli to C-fibers. This results from the summation of these slow synaptic potentials. It removes the magnesium blockade of NMDA receptors, and thus there is an increase in each progressive action potential due to the increased sensitivity to glutamate for the dorsal horn neurons.

Secondly is the facilitation of synaptic responses which results from both peripheral sensitization, hinging largely on the neurogenic inflammation, as well as structural changes (e.g., an increase in nerve fiber density in the periphery). This provides for greater nociceptive input to the spinal cord.

Lastly are two issues originating rostral to the dorsal horn neurons. The first is depressed inhibition of neuronal firing, and the second is an increase in facilitatory responses. Each of these originates from at least as rostral at a brainstem level if not even higher. Thus, there is a complicated loss of central inhibition for central sensitization's perpetuation of pain, which may be amenable to GABAergic agonism (Zeilhofer, 2012).

Further, given these shared anatomical and chemical pathways for pain and memory, perhaps some of the neurocognitive issues pain patients suffer from can be more easily explained in understanding their shared patho-anatomical structures and pathophysiological pathways (Ji, 2003; Luerding, 2008).

There are pathophysiological similarities among various pain syndromes, such as headache and pain, and also between focal/general (i.e., "neuropathic") pains and more diffuse pains such as fibromyalgia (and other central pain disorders or disorders which result from central sensitization) and regional pain syndromes, which mean the potential for efforts to treat such pains may have even more in common than previously thought (Desmeules, 2003; Maletic, 2009; Kindler, 2011; Woolf, 2011).

Indeed, the oral medications commonly used to treat such disorders, epitomized by the complex protocols often used in fibromyalgia (Mease, 2005), are often the same as those used in transdermal options to treat pain. As well as employing the many other options for therapy (Hassett, 2009), such topically applied compounds can be useful in treating even such diffuse pain conditions. Further, there has been a dramatic shift in thinking that previously diagnosed "peripheral" pain syndromes (e.g., "fibromyalgia syndrome,") may in fact have "central" bases which may be perpetuated, if not frankly initiated, by the "peripheral" mechanisms which are felt involved in the generation of most pains (Phillips, 2011; Sarzi-Puttini, 2011; and Staud, 2011). Especially for orofacial pains (Ren, 2011), and for migraines presumptive brainstem origin anatomically (Edvinsson, 2005; Galletti, 2009; Olesen, 2009; D'Andrea, 2010; Burstein, 2011; Bernstein, 2012), there may be either shared or similar anatomical bases for pain generation in such disorders which have previously been felt to be of disparate pathogenetic bases (Sessle, 2000; Romanelli, 2004; Perl, 2011; Ossipov 2012). Potentially this could explain the utility of transdermal treatment in such global pain syndromes.

The similarities between migraine, and its treatment, to other acute and chronic pain syndromes were particularly poignant, especially with the efficacy of indomethacin, in in-vivo migraine models (Ghelardini, 2004). Meningeal nociceptors were inhibited by naproxen (Levy, 2008), and the firing of central trigeminovascular neurons in a headache model was inhibited by applying intravenous naproxen (Jakubowski, 2007). The chemical milieu, for example, involved in the transmission of signals from the thalamus to the cortex is quite complex, with pro- and anti-nociceptive inputs which are used in the generation of those signals, and employing the same neurotransmitters seen in the transmission of pain (Noseda, 2014). Further, the similarities of medication-overuse headache to cutaneous allodynia would be consistent with a shared pathophysiology (de Felice, 2011). The thalamus may, in fact, provide the link for the diffusion and spread of focal pain into more widespread pain, as in a headache model sensitization of thalamic neurons in the rat provided for extracephalic allodynia (Burstein, 2010). Given the complexity of its symptoms, complex regional pain syndrome (CRPS) may represent such a pain syndrome which bridges both the peripheral and the central nervous system (Baron, 2004).

Given the complexity of pain syndromes in both the peripheral and central nervous systems, and in their complex interactions with each other (Melzack, 2001a; Melzack, 2001b; Melzack, 2005; Meeus, 2007; Basbaum, 2009; Latremoliere, 2009; Cheng, 2010; Kuner, 2010; Staud, 2010; De Felice, Pain, 2011; Woolf, 2011; Moayedi, 2013;), and the unique, personal responses, for example, to pain (Ossipov, 2010), an individualized approach to pain management has been recommended to account for this highly complicated problem, one recommendation based on symptoms (Smith, 2002) and one based on mechanisms (von Hehn, 2012).

4. MEDICATIONS/PATHWAYS/MECHANISMS OF ACTION

There are three published sets of guidelines for therapy for neuropathic pain which arise from the collectives: 1) Neuropathic Pain Special Interest Group of the International Association for the Study of Pain; 2) the Canadian Pain Society; and 3) the European Federation of Neurological Societies. They can serve as a reference for the treatment of pain generally, as well as for potential choices for medications which may have a transdermal application as these lists of drug options are quite similar (Moulin, 2007; Attal, 2010; Dworkin, 2010). There is also a similar review of such treatment options, but also including neurostimulation (O'Connor, 2009).

An older but thorough review of the peripheral mechanisms in pain generation outlines well persistent lines of investigation and some crucial current means of treatment (Raja, 1988). That there are such formal guidelines may suggest that ponderous and/or useful advice on proven therapies for pain can thereby be provided.

An analysis of controlled clinical trials for peripheral neuropathic pain (PNP) and CRPS (formerly known as reflex sympathetic dystrophy, RSD), however, reveals the following:

- For PNP there are at least two trials ("consistent support") showing efficacy of: tricyclic antidepressants (TCA), IV and topical lidocaine, IV ketamine, carbamazepine, and topical aspirin;
- There is at least 1 trial ("limited support") showing analgesic efficacy for PO/topical/epidural clonidine and for SQ ketamine;
- There is contradictory data for: mexiletine, phenytoin, topical capsaicin, PO non-steroidal anti-inflammatory drugs (NSAIDs), and IV morphine, although the author of the review of these 92 trials reviewed all of these studies further and felt that mexiletine and IV morphine probably are helpful but NSAIDs are not;
- Notably, there were no long-term results and the etiology of the neuropathy had no apparent effect on the outcome of the intervention (Kingery, 1997).

This dichotomy, then, indicates that there are a variety of problems in treating pain pharmacologically, not the least of which are its diverse etiologies (Ossipov, 2005). Consequently, there are a number of classes of drugs currently employed through oral/other routes of administration, as well as by topical and transdermal means, to try to overcome the many limitations in alleviating pain.

TRPV1 agonists

One of the first classes of drugs includes those acting at transient receptor potential vanilloid -1 (TRPV1) channels, colloquially often referred to as "counterirritants" as this drug class includes such drugs as capsaicin, menthol, and camphor. These are ion channels with greater porosity to divalent cations (e.g., Ca++) and protons than to other (monovalent) cations (K+, Na+) (Tominanga, 2004, and Xia, 2011).

These channels are found in the peripheral nervous system, and thus are felt important in pain generation generally, but they are also found on neurons in the trigeminovascular system where there is release on their activation of calcitonin gene-related peptide (CGRP) and substance P (SP), thereby also implicating these TRPV1 channels in the generation of migraine. There is, then, a large body of literature indicating this inflammatory nature of migraine and that it, like pain, has both "peripheral" and "central" processes and that they share significant pathophysiological chemistries, at least (Edvinsson, 2005; Galletti, 2009; D'Andrea, 2010; Meents, 2010; Burstein, 2011).

TRPV1 channels are activated by: heat, protons (pH), electricity, capsaicin/other vanilloids, prostaglandins, menthol, leukotriene B4, adenosine, and ATP (Haghigi, 2010; Xia, 2011; Kwak 2012; p. 6 of McMahon). They are also involved in the production of opioid-induced hyperalgesia, in a peripheral mechanism (Vardanyan, 2008). The physiology of TRPV1 channels is well-described, including the complex interactions and potentials for treatment therein, by Schumacher (2010). Whether capsaicin has broader but similar actions, or if it is only effective in being active via TRPV1 channels, has been addressed as well (Anand, 2011).

With prolonged TRPV1 receptor activation, as in the repetitive application of these agents to the skin, there is pore dilation: the size of the channel increases to the point that it now is permeable to large macromolecules. This is found in another TRP channel subfamily, as well (Chung, 2008; McMahon, p. 38). This may be potentially exploitable for therapy as, e.g., compounds which are relatively impermeable may be able to be delivered through opened TRP channels (also providing for a synergistic effect in pain relief) (Binshtok, 2007; McMahon, p. 38).

Therapeutically, two separate Cochrane Reviews did not show great efficacy for chronic neuropathic pain in adults for low-dose capsaicin, though there was some benefit for high concentrations of capsaicin (Derry, 2012; Derry, 2013); and they noted fairly common side effects, firstly by inducing pain on the initial dramatic release of substance P, and also skin irritation, which would be as expected given that the capsaicin was given topically and this massive, persistent release of substance P on its topical application would easily be seen as potentially locally irritating. There is an indication elsewhere, though, that local, high-dose capsaicin does show some efficacy not seen in low-dose paradigms (Gunthorpe, 2009; Xia, 2011; Anand, 2011; Maihofner, 2013).

The high-dose capsaicin paradigm was also felt helpful in managing the polyneuropathy of patients with human immunodeficiency virus (HIV) infection and in patients with postherpetic neuralgia (PHN) (Simpson, 2008; Simpson, 2010; Simpson, 2014); the original study in 2008 showed pain relief for > 12 weeks from a single application in a fairly large group of patients with the painful HIV neuropathy. Two summaries (Noto, 2009; McCormack, 2010) of a few studies lend support to the use of the high-dose protocol. One study looked at applying very low-dose capsaicin to patients without a migraine with head tenderness and then the same patients with a migraine; though a small group of patients in total

was looked at, each application reduced the pain (Cianchetti, 2010). In general, though, the limitations of capsaicin from both efficacy and side effect standpoints preclude its inclusion in compounded topical preparations designed for chronic pain management. However, the use of topically applied medications to treat migraine has started and continues (Rapoport, 2010).

Menthol is active at TRPV1 channels and is a common ingredient in, for example, many over-the-counter topical preparations. Topical 10% menthol solution was found a safe and effective treatment for the abortive treatment of migraine (Haghighi, 2010). It, and a methyl salicylate compound, were found helpful for muscle strain (Higashi, 2010). However, results were not very robust in a cold allodynia model (Wasner, 2008). There are, indeed, a number of over-the-counter "rubefacients" which are commonly used, often employing menthol or camphor, but we know that topical or transdermal administration of medications and not just these TRPV1 agonists provides relief greater for chronic and especially neuropathic pains than what simply applying such a limited cream to a sore body part may do (Ickowicz, 2009).

Resolvins, as well, may play a role in the inflammatory production of pain. They are products of COX-II or cytochrome p45 followed by lipoxygenase-mediated oxidation—they have their analgesic potential through both central and peripheral receptor activation, inhibiting the activity of the TRPA1 and TRPV1 channels, among other ways of affecting pain (Xu, 2010; Ji, 2011; Park, 2011; McMahon, p. 53).

Classical anti-inflammatories

A second, and potentially the most important etiopathogenically, class of helpful analgesic drugs are the anti-inflammatories (NSAIDs and COX-II inhibitors). Classically, diclofenac has been the most widely employed of these, but other common options are: ketorolac, flurbiprofen, ketoprofen, and meloxicam. Diclofenac is actually the most utilized NSAID worldwide (Atkinson, 2013); there are numerous studies documenting its efficacy in osteoarthritis, epicondylitis, and back/shoulder/foot/elbow pains (Skoutakis, 1988; Jenoure, 1997; Brühlmann, 2006; Lionberger, 2010; McCarberg, 2010). One advantage of diclofenac applied topically is that it accumulates at the site of its application and thus better local tissue concentrations are possible via the topical route as opposed to PO administration (Dominkus, 1996; Rolf, 1999). The low plasma levels of diclofenac when given by topical administration made these preparations more tolerable, and thus a better option for elderly patients (Petersen, 2009; McCarberg, 2010). Similarly, it was concluded that for elderly patients intolerant of PO NSAIDs that topical NSAIDs can provide "targeted pain relief, reduce stiffness, maximize function, and mitigate oral NSAID risks" (Atkinson, 2013).

Generally the NSAIDs have a primary role in pain management, and their mechanisms of action thus are of great interest. We have known about these pathways for more than forty years (Vane, 1971). The prostaglandin G/H synthases, now better known as cyclooxygenases (COXs), were genetically sequenced over the late 1980's-early 1990's (McMahon, p. 444), with the eventually discovered subtypes (Vane, 1994). These inflammatory pathways on which the NSAIDs and COX-IIs operate do not exist independently of the other pathways generating pain, but are interwoven into the vast array of cascading biochemical processes effecting the perception of pain.

Common thematically, then, is the appreciation of the incredibly complex and interrelated sources of pain's origin and, then, potentially its effective treatment. This includes the inflammatory mediators and extends to all of the other chemical pathways. A second thematic commonality in studying pain and pain treatment is the shared, or at least greatly analogous, anatomical pathways and chemical mediators of pains, generally, which includes migraine. For example, it has been shown that there is an upregulation of COX-II from pro-inflammatory mediators, and the complicated cascade poses, then, the potential for treatment in a multitude of sites (Capuano, 2009). This is similar to the peripheral pathophysiology of other, those thought to be more peripheral in their onset, pain syndromes.

Indeed, a recent study in chronic headache patients looked at the expression of mRNAs which encode inflammatory proteins and proteins involved in immune responses, finding preferential expression in those with chronic migraine over control subjects. This provides evidence that inflammation, acting from the periphery, is crucial in headache generation (Burstein, 2014), and, if headache and pain share, as it seems, much of their pathophysiology, similar findings should be had for other forms of pain.

The relevant inflammatory molecules produced in the pathways affected by NSAIDs are the eicosanoids, which include prostaglandins (PGs), leukotrienes, and thromboxanes (McMahon, p. 444). They do not activate receptors directly (save some exceptions for certain prostaglandins) but enhance the sensation of pain in response to natural stimuli and other endogenous chemicals by increasing the frequency of action potential firing (Moller, p. 14). Specifically, they reduce the threshold for initiation of action potentials and increase the excitability of sensory neurons by decreasing the threshold for activation of a nociceptor-specific, voltage-activated sodium current (Moller, pp. 14-15).

NSAIDs do not affect normal pain thresholds but attenuate the abnormal pain responses in inflammatory conditions (Moller, p. 52).

On injury or stimulation from inflammatory molecules, phospholipase A2 enzyme is activated. This releases arachidonic acid from cell membranes, which can then proceed down two

primary paths involving enzymes cyclooxygenase (COX; which has two primary types, I and II) and lipoxygenase (LOX), which do compete with each other (Omoigui, 2009).

The cyclooxygenase pathway has been the one of primary interest so far for pain syndromes, and inflammation generally, as it produces prostaglandins, prostacyclin (inhibit platelet aggregation) and thromboxane. The lipoxygenase pathway produces leukotrienes, previously having its emphasis in allergic phenomena (Omoigui, 2009) though the primary ones involved in pain are LTD4 and LTB4 (Moller, p. 15). Leukotriene antagonists were found helpful, effective, and safe (Riccioni, 2007), and while better known as being more involved in migraine (Saberi, 2012), the complex, but shared, pathophysiological bases for migraine and pain potentially expand the role for leukotriene antagonists in pain relief more generally.

COX activity, from both COX-I and COX-II, produces prostaglandins D, E, and F, which have a number of effects but most importantly sensitize peripheral nociceptors and eventually can lead to hypersensitivity. They are potent in their actions (Omigui, 2009). Prostaglandins that primarily play a role in inflammatory pain and hyperalgesia are PGI2, PGE1, PGE2, and PGD2 (Moller, p. 14).

COX-I is constitutively expressed, found in all tissues; COX-II is an enzyme induced in peripheral tissues by inflammation (Moller p. 14 and p. 52; Vane, 1994; Wallace, 2002), though COX-I and -II are constitutively expressed on DRG neurons and in the spinal cord. In the periphery, COX-II expression is induced in cells involved in inflammation (macrophages, monocytes, and synoviocytes) (Moller, p. 52).

NSAIDs, COX-II inhibitors, and acetaminophen inhibit COX-I and COX-II. The latter results in the relief of pain as COX-II is involved in the production of the swelling and pain from inflammation, but that they inhibit COX-I results in many of the side effects, particularly the GI side effects, as COX-I is involved in gastric protection constitutively. This results in decreased synthesis of PGs, which prevents the enhancement of pain by the PG-induced sensitization of nociceptors (McMahon, p. 142).

NSAIDS
COX-II inhibitors slow the production of PGE2.

NSAIDS Miss LOX Pathway
The LOX pathway continues to produce large amounts of PIM, even with COX inhibition.

In addition to using more "classical" or otherwise well-known anti-inflammatories, Transdermal Therapeutics employs tranilast and pentoxifylline (Trental) in each analgesic formulation, both of which have anti-inflammatory activity (Mulleman, 2006; Shaw, 2009; Rogosnitsky, 2012; Nasiri-Toosi, 2013).

Tranilast is better known as an anti-allergy drug used in asthma, autoimmune diseases, and it may, as well, have efficacy against proliferative disorders, various types of cancers, and keloid formation (Rogosnitsky, 2012). It has also been found to be helpful in treating adhesions found postsurgically, most likely through interfering with a number of the processes found in the inflammatory cascade resulting, eventually, in adhesion formation (Petrilli, 2008). Further, a topically applied preparation with tranilast nanoparticles decreased the paw edema in a rat model of arthritis (Nagai, 2014). Pentoxifylline, more notable for its use for peripheral arterial disease, was found to reverse the CRPS-like proinflammatory changes in a rat model (Wei, 2009). It can also block glial activation (Tawfik, 2008). The roles of microglia are under investigation (Calvo, 2012 and Schomberg, 2012) and include, for example, a role in producing cutaneous allodynia after nerve injury (Inoue, 2004). These additional anti-inflammatory agents should provide, then, even greater benefits on treating pain, especially pain resulting from an inflammatory source.

Other anti-inflammatories

In addition to the eicosanoids, the most important for pain being the prostaglandins, there are a number of other inflammatory mediators which have important algogenic roles. Some of these agents can directly activate nociceptors, whereas others act indirectly via inflammatory cells, which in turn release algogenic agents. The variety of chemical mediators released during inflammation can have a synergistic effect in potentiating nociceptor responses (McMahon, p. 14). A brief look at some of these will help in understanding the

striking complexity of the inflammatory milieu responsible for so much of the burden of pain.

Protons, or more generally acidity or the changes in acidity, are important in the production of pain, though this pathway is without clear therapeutic options at this time. There is a class of acid-sensing ion channels (ASICs) which can sense low pH levels, moderate decreases, while TRPV1 channels are activated by severe acidosis (pH <6). ASICs are felt to potentially play a role in mediating or modulating pain based on indirect evidence involving peripheral neurons. (Wood, 2004; Deval, 2010; McMahon, p. 16 and 56) though they are implicated, as well, in migraine (Yan, 2013). They are found centrally and peripherally, and they do look to be implicated in pain generation for a number of different pain syndromes (Sluka, 2009). ASICs are implicated with a number of other mediators of pain at less severe pH changes than when the TRPV1 channels are implicated in generating pain, suggesting complementary roles for these receptors (Deval, 2010).

Serotonin (5HT) is not just important in nociception as a neurotransmitter in the central nervous system. Mast cells release platelet-activating factor (PAF), which leads to the release of 5HT which can potentiate the pain induced by bradykinin (Moller, p. 16). Platelets can also release 5HT (McMahon, p. 54). Exemplifying the interrelationship of the inflammatory chemical mediators, many of the cells which show serotonergic activity felt related to pain reception also express the TRPV1 receptor, and such a relationship with migraine has been well-described for at least 50 years (Sicuteri, 1963; McGovern, 1964; Cady, 2009; Mehle, 2012).

Histamine can be released from mast cells on the release of SP from nociceptors. It also induces vasodilatation and edema. It is known to cause pruritus but its role in pain is murkier. Similar to leukotrienes, which may be more well-known in their relationship with migraine due to associations with allergic phenomena (Levy, 2007), histamine is being investigated in headache issues (Alstadhaug, 2014) but may be found to play roles in pain issues more largely (Levy, 2012).

Purines are an important class of inflammatory molecules, as well. Adenosine and adenosine triphosphate (ATP) levels are found to be high at inflammatory sites. Platelets may be the source of these high levels, potentially leaking it at, e.g., sites of tissue injury. The pain produced by ATP is dependent on capsaicin-sensitive neurons (McMahon, p. 16).

Cytokines, especially the interleukins IL-1β and IL6, particularly) and TNFα (de Oliveira, 2011), are felt to generate pain through at least the following mechanisms:

- Affecting the properties of ion channels in sensory neurons;
- Stimulating the release of, e.g., PG, neurotrophins, and ATP; and
- Longer term, by causing new gene transcription (McMahon, p. 17).

Interfering with the role cytokines (as well as glia and neurotrophins) play in pain has been explored (Dray, 2008), as well as in pain generally but specifically with respect to the trigeminal system (Dussor, 2005). Increased levels of TNFα were associated with pain in an allodynia rat model, which was reduced on anti-TNF treatment, suggesting a role for nociceptive sensitization in patients with CRPS (Sabsovich, 2008). Further, adipocytes are implicated in the inflammation associated with obesity, as well as with migraine; given the superior depth of penetration of the compounds from Transdermal Therapeutics by employing micelles to carry the medications, potentially the anti-inflammatory medications in the compounds are blocking inflammation at a cellular level in the fatty tissue under the dermis (Bigal, 2007; Peterlin, 2009; Ianonne, 2010).

Neurotrophins, especially nerve growth factor (NGF), are important inflammatory mediators, as NGF is not only necessary for the survival of nociceptors during development but may also play an important role during inflammatory processes in adult animals (McMahon, p. 14). Sources of NGF include: fibroblasts, keratinocytes, Schwann cells, and inflammatory cells. There are several pathways which NGF employs to affect pain.

NGF can amplify inflammatory processes by stimulating mast cells to release histamine and 5HT, and it can act directly on afferent terminals. It modulates the activity of ligand- and voltage-gated ion channels, such as ASICs and TRPV1. Further, it can alter the distribution of α-δ fibers, making a greater proportion of them have nociceptor properties (McMahon, pp. 17-18). Thus, there are complicated roles for NGF, and neurotrophins generally (McMahon, 2004), and while we are awaiting their better definition, these pathways are potentially amenable to treatment with NSAIDs and opioids (Eibl, 2012).

A specific vasodilator felt important in nociception generally is nitric oxide (NO). It is best known for its role in migraine generation (de Felice, 2010), and its role in pain generation is awaiting better definition.

Bradykinin is an inflammatory mediator which may be best known for its involvement therapeutically in hypertension and therapeutic modulation by angiotensin converting enzyme (ACE) inhibitors. ACE inhibitors are recently being used as headache preventative agents. Potentially similar effects on pain from bradykinin modulation can be had. It may be important in the hyperalgesia associated with persistent inflammation (Luo, 2008).

There are currently known a number of potential mechanisms whereby it acts in nociception. It can act directly on sensory nerves and can indirectly cause pain via evoking the release of other inflammatory mediators from non-neuronal cells. It can have the pain it produces potentiated by serotonin. It can enhance the heat-gated current mediated by TRPV1 (McMahon, pp. 16, 50, 51). Of the several posited mechanisms active in its role in pain, two of potentially the most important are arachidonic acid production (thereby potentiating pain by amplifying through COX-mediation inflammation) and TRPV1 channel modulation (McMahon, p. 16). There are no specific bradykinin antagonists in use clinically at this time, but there is at least one other potential agent, aloe, which may have benefits on pain acting through bradykinin (Yagi, 1982).

A summary of effects anatomically includes:

- Inflammatory mediators involved in sensitizing adjacent C-fibers of the peripheral nervous system include: glutamate, CGRP, SP, cytokines, PG, LT, and NO;
- Activators of C-fibers include: 5HT, bradykinin, and histamine; and
- Sensitizers of C-fibers include: PG, SP, and LT (Kerstman, 2013).

The crucial, primary role of the inflammatory milieu prompted Omoigui to summarize things in the proposed new "law of pain: the origin of all pain is inflammation and the inflammatory response." The import, then, of these mediators in causing pain, and their interrelationships, can be found in the two exhaustive reviews from 2007. This is echoed in a more recent review (Ellis, 2013), as well.

Ion Channels

There are various ion channels which are integral to algogenesis.

Perhaps as well-known as NSAIDs in topical medicine are the local anesthetics. There are, as well, other sodium-channel blockers which are effective transdermal analgesics, including many anticonvulsants and certain antidepressants. That lidocaine and related systemically active local anesthetics are not available in oral form limits their clinical utility, but certainly they can be used topically. Further, the topical availability of many anticonvulsants and antidepressants which block sodium channels in the periphery provides a number of compounds which can be potentially effective in treating pain through this mechanism. Even when used orally, at doses which are much lower than those which can be attained through intravenous administration, sodium channel antagonists do not block axonal conduction but are thought to block ectopic/other neuronal firing which leads to pain, explaining their being occasionally called "membrane stabilizers", though the exact locus (synapse, or membrane, or both) of where these agents exert their analgesic effects is not known with certainty (McMahon, p. 886).

Sodium channels play a crucial role in the model of inflammatory pain (Linley, 2010; Liu, 2011; Levinson, 2012), and they are especially well-known for migraine pain and even visceral pain (Cregg, 2010), though given their localization to dorsal root ganglion neurons (Chung, 2004), this would suggest a highly significant role in the peripheral generation and maintenance of pain. Further, it is felt that mechanical allodynia and hyperalgesia are due to an increase in sodium channels (Backonja, 1998). They are felt to be the primary site of action of TCAs, working much like local anesthetics at the site of nerve injury in the periphery, which is felt to be the site of the generation of the ectopic discharges (Galer, 1998; Amir, 2006). Sodium channels are felt, along with calcium channels, to potentially be the most streamlined locus of treating the disparate sources of pain as many of the various nociceptive pathways seem to eventually converge on sodium channel activation (Ossipov, 2005). Diclofenac and pregabalin may, in particular, have effects on potassium channels (Verma, 2014).

Topically administered lidocaine has been shown to be an effective analgesic, and with a reasonably accurate physiological mechanism (Meng, 2011). This includes use for neuropathic pain in a group of cancer patients, though their pain was not necessarily related to their cancer diagnosis or its treatment (Ramírez, 2013). Topical bupivacaine was felt to be a promising alternative to lidocaine (Kuhn, 1996; Smith, 1996; Keyes, 1998), and it is a longer-acting local anesthetic so may be a better, more convenient option for patients (Heavner, 2007). The potential for reduction of centrally based neuropathic pain by either local effects on the central pain processes, or perhaps both local and central effects, was entertained to explain the rapid (in ca. 12 hours) pain freedom achieved with application of a 5% lidocaine patch to a patient with metastatic cancer and pain felt from the spinal cord pathology (Hans, 2008). The safety of topical lidocaine was well-established in a study looking at normal patients and those with PHN and acute zoster, and the bioavailability levels of topically administered lidocaine was only 3% (Campbell, 2002).

Anticonvulsants are commonly employed in a variety of pain syndromes, including neuropathic pain, and have a diverse range of mechanisms of action (Tremont-Lukats, 2000; Angehagen, 2003), one of which for many anticonvulsants is sodium channel blocking. Agents considered to have sodium channel blockade as a major mechanism of action include: carbamazepine, valproate, phenytoin, topiramate, lamotrigine, lacosamide (McMahon, p. 491). Anticonvulsants bind to the local anesthetic binding site on the α subunit of the sodium channel (McMahon, p. 493). There are at least 9 sodium channel subtypes (McMahon, p. 492), and all the currently available sodium channel blocking AEDs are nonselective for these various subtypes save perhaps lacosamide (Sheets, 2008;

McMahon, p. 492). Primarily most anticonvulsants exert their antinociceptive effects via sodium as well as calcium channel blockade, directly for voltage-gated sodium channels, indirectly for voltage-gated calcium channels (VGCC) (McMahon, p. 491).

The sodium channel blockade may be particularly important for the central effects of these agents on nociception, but when administered orally this may be—given that sodium channels are of primary importance for all other central functions—the source of their side effects, as well (Castro, 2009; McMahon, p. 493), which include sedation, dizziness, ataxia, convulsions and cognitive dysfunction. The following summarizes the results for pain management for commonly used, orally administered, anticonvulsants, and we note, as well, that they are not commonly employed in topical preparations:

- Carbamazepine:
  - Mixed, better for trigeminal neuralgia (TN);
- Oxcarbazepine:
  - Good for TN, possibly helpful for diabetic polyneuropathy (DPN);
- Valproic acid:
  - Good for headache, not so much for pain (similar to topiramate);
- Lamotrigine:
  - Mixed (Ettinger, 2007);
- Lacosamide:
  - No known studies;
- Phenytoin
  - Mixed results.

The tricyclic/heterocyclic antidepressants are widely employed as analgesics in oral and topically applied formulations. Sodium channel blockade may be its primary mechanism of action in the periphery, while for its CNS effects, with any systemic absorption, may be in altering 5HT and norepinephrine (NE) activity in brainstem/dorsal horn sites (Galer, 1998).

While perhaps using antidepressants in chronic pain may have originally been to treat the depression often associated (McMahon, p. 465), there has been considered a dissociation between effective treatment and pain treatment since at least the early 1970's (Merskey, 1972) and more strongly it is felt that their effects on pain are independent of any antidepressant effect (McCleane, 2007).
An analysis of studies of oral antidepressant drugs and reported results of their trials indicates that the most effective antidepressants appear to be desipramine, amitriptyline, and nortriptyline (a metabolite of amitriptyline). Further, drugs acting primarily or solely through serotonergic mechanisms are less effective than those with concomitant noradrenergic effects at least centrally. The drugs which are more clearly serotonergically active are not as good at pain relief as those agents which appear to have at least central activity against serotonin and norepinephrine (McMahon, p. 476 and 1008).

There are a number of postulated central actions of these agents, though most importantly from a topical perspective there should be most importantly peripheral actions (Butler, 1985 and McMahon, p. 476) in the inflammatory milieu as well as possibly other antagonistic mechanisms of action (e.g., opioids, substance P [SP], calcium channels) and potentially agonistic mechanisms of action (potassium channel activation, GABAb potentiation) as well as what is noted as recent possibilities that they may be NMDA antagonists or sodium channel blockers (McMahon, p. 476). Thus, the tricyclic antidepressants (TCAs) may act as local anesthetics (Sudoh, 2003; Amir, 2006; and McMahon, p. 476).

While there may be no definitive proof for how they affect their antinociceptive properties, they do: block NE reuptake; block 5HT uptake; block hyperalgesia induced by NMDA agonists; and block sodium channels (Kerstman, 2013). They also increase endorphin release and bind at histamine, cholinergic, and adrenergic neurotransmitter sites (Galer, 1998). Thus, there are a number of postulated mechanisms of action in the periphery for antidepressants which include the block of NE, 5HT, potentially histamine, excitatory amino acids, adenosine, and sodium channels, along with potentially mimicking or enhancing the properties of opioids. These multiple mechanisms of action in the periphery were felt to make the topical applications of antidepressants an attractive option for using antidepressants via this route of administration (Sawynok 2001). The best known of these transdermally used drugs include: amitriptyline, protriptyline, nortriptyline, trazodone, and doxepin.

A whole new class of drugs which are effective analgesics arose with the launch of gabapentin. It has a number of mechanisms of action (may affect potassium channels, increase GABA, decrease SP release, and decrease CGRP release (Verma, 2014)) which are potentially important for pain relief, though its primary mechanism of action is the blockade of voltage-gated calcium channels (Micheva, 2006; Hendrich, 2008; McMahon, p. 496). There are two drugs in this class, the "gabapentinoids:" gabapentin (GBP) and pregabalin (PGB). Both of these drugs are approved for seizures, as well as GBP for neuropathic pain including PHN, and PGB also for DNP, post-herpetic neuralgia (PHN), and fibromyalgia syndrome (FMS) (Ettinger, 2007; Taylor, 2007; McMahon, p. 496).

It is now known that the specific primary mechanism of action of both gabapentin and pregabalin–although both drugs are derived from GABA, neither has any effect on GABA receptors, channels,

or transporters—is calcium channel antagonism by binding to the α-2-δ subunit of the VGCC (McMahon, p. 496), presynatpically, and thus they decrease glutamate and SP release (Hendrich, 2008; Rogawski, 2008; Thorpe, 2010; Kerstman, 2013). Most of the antinociceptive effects of the gabapentinoids are felt to be due to their central effects (McMahon, p. 497), though there are appropriate calcium channels (Cav2.2 channels) found on dorsal root ganglion (DRG) neurons which preferentially also express markers for TRPV1 and Nav`1.8 (Bell, 2004; McMahon, p. 497).

Two large multicenter, double-blind, placebo-controlled clinical trials reported in 1998 demonstrated that gabapentin at a target dose of 3600 mg/day reduces pain in patients with PHN and DNP (McMahon, p. 1006), and there have been numerous similar clinical trials of gabapentin for other types of neuropathic pain, including for those patients with PHN, DNP, mixed NP syndromes, phantom limb pain, Guillain-Barré syndrome, and acute and chronic spinal cord injury pain (McMahon, pp. 1006-1007). Given its success clinically, in the beginning of this century gabapentin came to be used more frequently than any other anticonvulsant for chronic pain (McMahon, p. 1007).

In 2004, pregabalin, another member of this class of drugs that modulates the α_2-δ binding site, was launched in the United States for the treatment of both DPN and PHN, the first drug FDA-approved for such (Ettinger, 2007; McMahon, p. 1007; Verma, 2014). For PHN, a multicenter, parallel-group, double-blind, placebo-controlled, 8-week randomized clinical trial of 300 and 600 mg/day was conducted and showed pain relief vs. placebo which was sustained over the 13-week observation period, as well as improved sleep and was felt well-tolerated. Thus, for PHN there are numerous guidelines for using pregabalin along with a TCA/SNRI for PHN (McMahon, p. 1007; Verma, 2014).

Aside from any action on calcium channels, in the periphery or centrally, there are other calcium channel blocking agents which have use for pain of various types in addition to their cardiac effects and effects on hypertension, and these are more well-known in treating pain for their inclusion in transdermal preparations. T-type voltage-gated calcium channels have both central and peripheral distributions, making them especially amenable, perhaps, to treatment for a number of pain syndromes (Todorovic, 2011). Examples of these agents include: verapamil; nifedipine; and levetiracetam, which specifically is an SV2A-binding agent (McMahon, p. 1007 and Lynch, 2004).

Another class of agents, perhaps more well-known for effects on hypertension, are α-2-agonists, the most well-known example of which is clonidine. Clonidine can induce peripheral antinociception by an α-2-adrenoceptor-mediated local release of enkephalin-like substances and by reducing presynaptic norepinephrine release from sympathetic nerves (McMahon, p. 497). It also may interact with NMDA receptors, illustrating that while thinking of the complexity of the inflammatory milieu is crucial, the interrelationship of the multiple pathways in pain generation and the pharmacology of manipulating these for analgesia provides for a better approach therapeutically (Fan, 2014).

Most of the agents employed to treat pain, and headache, are those which decrease or block channel activation or use; are anti-inflammatory; or affect excitatory neurotransmitter release or uptake. The most notable agonist class of medications includes those which potentiate GABA. Examples of such GABAergic drugs: tiagabine, topiramate, zonegran, clonazepam (and the other benzodiazepines), baclofen, eszopiclone, and valproic acid (we note that most do have multiple mechanisms of action) (McMahon, p. 497). Specific GABAa agonists include the benzodiazepines, and baclofen and eszopiclone. Chloride channels have a complicated physiology, and may be particularly associated with allodynia and hyperalgesia, along with their having an interrelationship with GABAa receptors, and possibly a glycinergic mechanism in the modulation of pain (Price, 2009).

Glutamate

Glutamate antagonists currently used for pain are those which act on NMDA receptors. They have a complicated physiology generally and with the clinical availability of strong (ketamine) and much weaker (the rest) antagonists (Lipton, 2004), there are often significant differences among these individual agents. Ketamine is the most potent of these agents, and has shown the best promise of those currently available (Jamero, 2011). With respect to pain, we have the longest use with ketamine, though the use of NMDA antagonists has expanded from chronic and acute pain treatment into now the prevention of pain (Helmy, 2001; McCartney, 2004). Their physiology is complicated, as, for example, there are multiple binding sites of agonists at the glutamate receptors, and the details of this interrelationship with glycine and with GABA agonists for pain treatment is not fully defined (Wood, 2005).

There are numerous potential mechanisms of action of ketamine with respect to its analgesic properties. The prevention of intraneuronal calcium influx by blocking NMDA receptors has been felt to be the most important (Sawynok, 2014). These receptors have been best known to be in the spinal cord, accounting for their enlarging use in pain with central sensitivity or of otherwise a central origin as they are also felt to be the key for the transition from peripheral to central sensitization (Eide, 2000; Zhou, 2011).

There are peripheral NMDA receptors which can be exploited with the topical administration of ketamine. By using ketamine locally, the other peripheral mechanisms of action can play a larger role as the ketamine can attain higher concentrations in the local tissues and thus exploit these mechanisms which would otherwise be unavailable

to intravenous or oral routes of ketamine administration (Sawynok, 2014). These other mechanisms of action are felt to include actions through: opioid receptors; NE/dopamine (DA)/5HT transporter blockade; Na-/Ca-channel blockade (McMahon, p. 886); and the inhibition of the production of inflammatory mediators (Sawynok, 2014). Especially that a review article could not recommend IV and orally available NMDA receptor antagonists for the treatment of pain in a review of twenty-eight studies (Collins, 2010), we must get a better understanding of their role in antinociception, but this should not be taken to mean they are not helpful in treating pain, just that certainly further study is needed.

That NMDA antagonists have both central and peripheral effects was illustrated in a study of dextromethorphan, memantine, and ketamine administered systemically, with the effects felt centrally mediated, and locally, which was felt to involve local processes (Sawynok, 2002). Again, that there are peripheral NMDA receptors expands the possibility of treating through, for example, locally administered agents and not just those directed at the central nervous system (Petrenko, 2003).

The best known excitatory amino acid in the nociceptive milieu is glutamate (Petrenko, 2003; Osikowicz, 2013). Its peripheral sources include: plasma, macrophages, epithelial and dendritic cells in the skin, and Schwann cells; further, the peripheral processes of the primary afferents contain glutamate, so with nociceptor stimulation there should be the peripheral release of glutamate from the terminals of these afferent neurons. There are two different receptor types for glutamate:

- ligand-gated ion channels (ionotropic glutamate receptors); and
- via G protein-coupled metabotropic receptors, which are the most widely found receptors in the periphery, with the former more likely to produce side effects so therapeutic emphasis is on the latter (Montana, 2011).

Peripheral, not central, administration of a glutamate antagonist reduced inflammatory hyperalgesia, and one particular glutamate receptor subtype activates phospholipase C (PLC), which leads to the release of Ca++ from intracellular stores and then activation of PKC (Walker, 2001). Other effects of glutamate include: inhibition of glial activation, along with effects on potassium currents and on neurotransmitter release (Montana, 2011). There is also a complicated loss of central inhibition for central sensitization's production and perpetuation of pain which may be amenable to NMDA antagonism (Cheng, 2010).

The NMDARs have some unique properties:

- The cation channel (especially porous to calcium) controlled by the receptor is also highly permeable to monovalent ions;
- The most efficient activation of the NMDAR occurs with simultaneous binding of glutamate and glycine, which is, then, glutamate's coagonist;
- At rest, the channel is blocked by magnesium, only opening on concomitant depolarization and binding of agonist (more efficiently with both coagonists binding) (Petrenko, 2003; Osikowicz, 2013).

Elevated glutamate levels are associated with neuropathic pain and accompanied by lowered efficacy of opioids and often depressed mood or frank depression (Osikowicz, 2013). There are complicated roles of metabotropic glutamate receptors, and even potentiation of pain, depending on where the receptors are located (Montana, 2011), though there is the additional advantage that glutamate targets for pain relief are able to potentiate the analgesic properties of other medications, such as opioids and antidepressants (Zhour, 2011; Osikowicz, 2013). This potentially represents another avenue in which polypharmacy can be utilized.

There were a number of neurocognitive side effects from NMDA antagonism in previous therapeutic trials, and these may limit their use by routes other than being topically applied. Having more receptor-selective treatment options may be a solution, or by preventing their having significant serum levels, the seeming reason for the centrally-based side effects, by using them in transdermal compounded preparations would be an alternative way to employ these medications (Petrenko, 2003).

Studies so far show the most consistent benefit from ketamine and methadone, which have the potential with oral administration for more side effects, with the weaker NMDA antagonists being more attractive from a tolerability standpoint but most without consistent, clear benefit on treating chronic pain (Jamero, 2011).

Other agents which work via glutamate blockade include amantadine, dextromethorphan, memantine, methadone (Jamero, 2011), and magnesium, with only the first two currently having availability for use in topical preparations and with only memantine in the future having a reasonable role for use in topical preparations. Methadone will probably continue to have fairly limited use generally in pain management. There has recently been an expansion of the use of dextromethorphan (Siu, 2007), and there was some analgesic effect noted in more than one study (Goldstein, 2002), looking at its use for DPN and PHN.

Memantine is an important drug currently for pain from an orally administered route, especially for central sensitivity and other centrally mediated pains. It was found to be a safe and well-tolerated

medication, primarily in studying patients with dementia (Farlow, 2008; Thomas, 2009; Babai, 2010; Jones, 2010) and even in bipolar patients (Keck, 2009), with some evidence of help with pain and headache (Mobius, 2004; Kavirajan, 2009). It is an uncompetitive NMDA antagonist, so it works better at antinociception at higher concentrations (Lipton, 2004). A review of memantine's use in neuropathic pain could not recommend its routine use (Rogers, 2009). A recent review of 28 studies using NMDA antagonists (IV ketamine for CRPS; PO memantine in PHN, and IV ketamine/PO memantine in postamputation pain) could reach no conclusions about the use of those agents via those routes for the pain conditions studied, though the authors noted there seemed to be growing evidence generally that such, especially ketamine, were efficacious (Collins, 2010). Case reports, though, indicate often marked help (Hackworth, 2008), and memantine and gabapentin had similar analgesic effects in a rat model of neuropathic pain (Chen, 2009). Magnesium, like many of the drugs used for pain, has a more well-known alternative role: it is a helpful agent for migraineurs. However, there is a body of literature looking at its use in, for example, a peri-/post-operative pain setting (Koinig, 1998; Telci, 2002; Lysakowski C., 2007; Suzuki, 2009).

Having more than one available agent in this class, as in others, may be important in that we know already that there is potentiation of analgesia with the application of magnesium and ketamine, each acting through glutamate receptors (Hong-Tao, 2001). Potentially, given the complex interactions with the plethoric mediators of pain, such synergy may be commonly found both within a class of drugs and more broadly among many drug classes. This would provide for using "rational polypharmacy" in pain management, and the transdermal route remains ideally suited for exploiting a multipronged approach to treating pain.

Opioids

Lastly, we should briefly consider the endogenous opioid systems and ways to use this pathway to more effectively treat pain. The primary elements of the peripheral system include peripheral inflammation and the leukocyte-derived opioids at these sites. The inflammation causes an increase in the release of the peripheral leukocyte-derived opioids along with an increase in the peripheral opioid receptors which are expressed by primary sensory neurons and an improvement (mediated by bradykinin) in the efficiency of the opioid receptors. Potentially, by treating through the peripheral opioid analgesic system, it is possible to avoid the central side effects of opioids: sedation, respiratory depression, addiction. However, the central effects of opioids do play a large role in the totality of opioid-induced analgesia.

Again, like many of the drugs used to treat pain, there are a number of effects of peripheral opioid activity:

- Reduction in nociceptor excitability;
- Impairment of action potential propagation;
- Inhibition of release of excitatory neurotransmitters;
- Inhibition of release of proinflammatory neuropeptides (SP, CGRP).

Such effects are due to a variety of effects otherwise that peripherally administered opioids have, such as:

- α-2-adrenergic antagonism;
- Analgesia via adenosine pathways; and
- TRPV1 antagonism (Machelska, 2003a; Machelska, 2003b; Brack, 2004; Labuz, 2007; Machelska, 2007; Smith, 2008; Moller, 2012).

Tramadol is an atypical analgesic that weakly inhibits norepinephrine and serotonin reuptake (McMahon, p. 1010; Kerstman, 2013). There have been two studies for the use of tramadol in neuropathic pain; a study of its use in DNP in combination with acetaminophen (a combination often employed orally); and one study showing help (along with amitriptyline) in phantom limb/stump pain (McMahon, p. 1010).

Many of the same approaches to pain generally are the same as those used for migraine (some other specific pain syndromes), given their shared pathophysiological chemistry and similar patho-anatomical bases, including having both peripheral and central components (Burstein, 2000; Burstein, 2003; Yarnitsky, 2003; Landy, 2004; Silberstein, 2004; Edvinsson, 2005; Olesen, 2009; Edelmayer, 2009; Galletti, 2009; Burstein, 2010; d'Andrea, 2010; Burstein, 2011; Noseda, 2011; Burstein, 2012).

5. TRANSDERMAL THERAPY

Certain medications delivered orally or otherwise have been found helpful for treating various pain syndromes. As discussed in detail, this includes: anti-inflammatories, anticonvulsants, and heterocyclic antidepressants for postherpetic neuralgia (PHN), diabetic polyneuropathy (DPN), and trigeminal neuralgia (TN) (Backonja, 2004 and Eisenberg 2007). However, there is a paucity of data involving even such commonly used oral agents in alleviating pain (Backonja, 2004 and Eisenberg 2007).

The COX-II controversy in 2004 brought a re-evaluation of pain treatment which has resulted in a renewed interest in topical preparations for pain (Stanos, 2007). Potentially, the recent changes in drug schedule classification for oral tramadol ("Drug Abuse") and oral hydrocodone ("Federal Register") will have similar effects. There are a number of reasons, as well, without such changes that a transdermal route of treatment for pain is particularly appealing. The well-known safety of topical preparations, though, represents

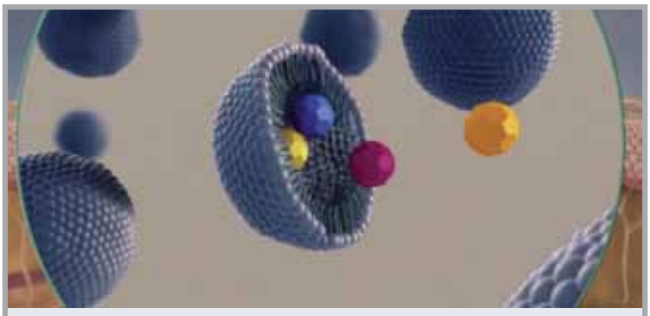
Joseph Vaughan, M.D.
UT Southwestern Medical Center, Dallas, Texas

one of the primary advantages, and probably the most appreciated, of using this route of administration. Others include:

- Avoiding first-pass metabolism/pH/gastric emptying time variables involved with oral administration;
- Reduction of drug concentration peaks and troughs;
- Reduction of side effects due to reduced serum concentrations;
- Easy discontinuation in the event of side effect occurrence;
- Maintenance of sustained and controlled drug delivery over a prolonged period;
- Target site is directly addressed;
- Convenient administration;
- Painless administration;
- Better patient compliance; and
- Can be used when oral dosing is not feasible or possible (Brown, 2006; Stanos, 2007; Galkwad, 2013).

There can be local effects, and accumulation of drugs in target tissues, without the production of systemic side effects in using topical preparations (Stanos, 2007; Argoff, 2002). While there is accumulating evidence of at least some efficacy for a variety of pain syndromes for a variety of medications, as we have no great evidence to provide good recommendations for even the gold standard drug delivery—via the intravenous route—one must remain flexible in the fight against pain (Kosharskyy, 2013). Certainly exploiting the skin as a way to treat pain is flexible, and the compounding of specialized transdermal preparations has its own characteristics which provide even more flexibility and potentially more effective, safer pain management.

Transdermal Therapeutics uses technology in trying to effectively provide medications for topical pain treatment, and this gives their products a distinct advantage in the realm of topically applied preparations (Desai, 2010; Paudel, 2010; Reddy, 2014). A potential limitation of transdermal drug delivery is the stratum corneum, which prevents diffusion for molecules < 500Da (Stanos, 2007). Transdermal Therapeutics uses micelles for drug delivery and avoids this otherwise effective barrier to drug administration (Narang, 2007), thereby allowing the drugs in the compounds to cross this potential barrier and reach the target tissues. This potential barrier, then, is overcome by using this technological advantage. As there are no real skin changes as we age, especially for older patients a transdermal route may remain a great option (Ickowicz E., 2009), and by using micelles we can avoid potential issues with the technologies commonly employed in the patches. In using micelles for drug delivery, getting the various drugs deep to the stratum corneum can also potentially treat the adipocytokine-mediated role in generating pain (Peterlin, 2009). Thus, using a transdermal route which permits the delivery of medications to the target tissues is a great option for a number of painful conditions regardless of the age of the patient.



Nanotechnology Drug Delivery
Micelles envelop hydrophilic medications to transport them through the stratum corneum and subcutaneous tissues.

Given the multiple mechanisms of action of the currently available medications, and the often refractory nature of the pain syndromes for which they are employed, transdermally directed compounds can take advantage of "rational polypharmacy." Further, pain, especially neuropathic pain, can present in a variety of fashions, and as such requires treatment capable of handling the heterogeneity of its presentations (Galluzzi, 2007). Thus, polypharmacy would be preferred to, for example, the use of a single oral agents being started, titrated to efficacy and/or intolerable side effects, then off-titration along with the institution of an alternative or additional oral agent (Galluzzi, 2009) as the former would be more likely to reach our target of pain reduction or relief much faster.

A Cochrane review (Matthews, 2009) found that rubefacients ("counterirritants," or TRPV1 antagonists plus salicylates) had efficacy about the same as topical NSAIDs for chronic conditions but had no real role for acute injuries. However, a case report of marked pain reduction from a chemotherapy-induced neuropathy by employing a compound containing ketamine 5%/clonidine 0.5%/gabapentin 6% illustrates both the success which can be attained by using polypharmacy and the importance of finding the right dose of the component medications as this patient's pain was further improved on increasing the concentration of ketamine to 10% (Prommer, 2009). Another study found that doxepin, capsaicin, and a combination of both helped with analgesia in chronic neuropathic pain (McCleane, 2000), and another found that a chemotherapy-induced neuropathy was helped with a compound containing baclofen, amitriptyline, and ketamine (Barton, 2011).

Even within glutamate antagonists polypharmacy could be considered. There was a potentiation of analgesia with the application of magnesium and ketamine, which act through glutamate receptors (Hong-Tao, 2001), for example. As there are often options within different classes of compounds, this kind of synergy may be found in classes with other mechanisms of action. Potentially, given the complex interactions among the plethoric mediators of pain, such synergy is even more likely to be found among agents of many different classes of medications. This would provide for an additional argument for employing broad polypharmacy among the number of classes of medications, similar to the role "rational polypharmacy" plays in many other disorders, including epilepsy. The lack of side effects, tolerability, and ease of use of topical medications would suggest an even better overall paradigm for using multiple agents applied topically to treat pain. Transdermal Therapeutics embraces the significant role peripheral inflammation plays in both acute and chronic pain. Indeed, NSAIDs in topical preparations have the largest amount of evidence for their use (Stanos, 2007), with several trade name preparations being currently available in the U.S. (McPherson, 2013).

Topical NSAIDs were found helpful in acute and chronic pain, musculoskeletal injuries acutely, and osteoarthritis and tendinitis for chronic conditions in a review which analyzed 86 trials which included 10,160 patients (Moore, 1998). A Cochrane review of acute pain from musculoskeletal conditions (sprains, strains, or sports/overuse-type injuries) found that topical NSAIDs can be useful analgesics without the systemic side effects found by using oral NSAIDs (Massey, 2010). In an exhaustive Cochrane review of chronic knee or hand arthritis, topical NSAIDs were efficacious in treating pain and about equivalent to the oral administration of NSAIDs (Derry, 2012). Given some limitations, Heyneman et al. felt that there could be equivalent efficacy of topical and oral NSAIDs, with a superior efficacy profile for the topical formulations, on specifically being used to treat rheumatic diseases (Heyneman, 2000).

Of the many recommendations from the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT), an assignation of a level of evidence of Ia (high level of recommendation, through the meta-analysis of randomized clinical trials) was given to their conclusion that local treatments, especially for mild to moderate pain and if pauciarticular, were preferred to systemic treatments, especially for topical NSAIDs and capsaicin, which they felt were both safe and effective (Zhang, 2007). This was also followed by the often enumerated cautions regarding the use of oral NSAIDs.

Similarly, the American College of Rheumatology made the following pharmacologic recommendations:

- For the initial management of hand OA, topical capsaicin, topical NSAIDs were conditionally recommended for use, with the use of topical NSAIDs preferred to that of oral NSAIDs; and
- For the initial management of knee OA, topical NSAIDs were conditionally recommended (Hochberg, 2012).

More recently, topical NSAIDs, and in particular diclofenac (the only NSAID which is approved for topical use in the U.S.), were felt to be an important option for treatment in patients with osteoarthritis, especially in those groups of patients at high risk for side effects from using oral NSAIDs (e.g., the elderly, those patients with a history of GI bleeding) (Farlow, 2011; Stanos, 2013). Further, the lack of cardiovascular effects of topically administered NSAIDs was especially emphasized (Barkin, 2009; Barkin 2010). The relative lack of attaining significant serum levels, even in damaged skin (first degree sunburn, which was accompanied by pain) was also established, and that the serum levels of both topical applications (normal skin, sunburned skin) were each <3% of those attained with oral administration of diclofenac (Magnette, 2004).

A Cochrane review showed that patients with rheumatoid arthritis, a significantly inflammatory connective tissue disease, also demonstrated some help with topical capsaicin (Richards, 2012). Without the advantage of having extensive controlled trials of compounded transdermal preparations, there is a growing body of such, and with the available studies using formulations which do not even take advantage of using micelles as a technologically superior delivery method, we feel that topically applied compounds are a reasonable method of treating a number of pain syndromes. For example, treatment of PHN/localized neuropathic pain with topical lidocaine patches, neuropathic pain with topical lidocaine, and even capsaicin cream has been shown to be effective (Galluzzi, 2007; Finnerup, 2007; Zin, 2008; Galluzzi, 2009). Indeed, Finnerup et al. recommend the lidocaine patch as first-line therapy for PHN and localized neuropathic pain with allodynia (Finnerup, 2007). An evidence-based algorithm for the treatment of neuropathic pain has been presented, in fact (Finnerup, 2007) making similar recommendations (then followed by gabapentinoids and antidepressants). Neuropathic pain in older adults is also felt to be a potential candidate for treatment by transdermal preparations (McCarberg, 2012).

Topical lidocaine was recommended as first-line treatment for neuropathic pain by the Neuropathic Pain Special Interest Group of the International Association for the Study of Pain. Further, this study particularly noted the multiple negative results of studies for individual agents used to treat pain (Dworkin, 2010). This would be consistent with using a broader palate of drugs in trying to treat pain in trying to avoid the oft-found failure to respond to a single oral agent.

Glutamate antagonism, e.g., with ketamine, also requires good randomized trial data, though a recent review (Watson 2010) points out the paucity of such studies for oral/other analgesics generally. After their pilot study of lower doses of each agent suggested a longer term benefit (Lynch, 2003), through its use alone in a 1% concentration of ketamine, the use of 2% amitriptyline alone, and their use in combination did produce analgesia in patients with neuropathic pain syndromes without evidence of significant systemic absorption (Lynch, 2005). We note that Transdermal Therapeutics has as its default concentrations 4% for amitriptyline and 10% for ketamine, and this may provide for greater efficacy of such compounds as has been previously suggested (Kopsky, 2011).

Similarly, using doxepin alone, capsaicin alone, and their combination produced similar levels of efficacy among the three options, though the combination produced its analgesia more rapidly (McCleane, 2000).

Sawynok's recent review of topical analgesics (Sawynok, 2014) is an excellent summary of currently available information as well as considerations of unique patient populations and the future of this form of therapy for pain. Indeed, enlarging the possible roles for topical preparations even more, employing topical analgesic preparations in the specific instance of immediate postoperative pain has been evaluated (McCleane, 2010).

6. DIAGNOSES FOR TRANSDERMAL TREATMENT

There are a number of painful diagnoses which can potentially benefit from transdermal therapy. These include:

- Stump pain, DPN, HIV neuropathy, and perhaps chronic myosfascial pain, for which topical lidocaine 5% can be helpful (Argoff, 2002);
- Cutaneous pain, muscle pain, chronic rheumatological diseases (McCleane, 2008);
- Sports injury pain (strains, sprains, OA, and post-op pain: NSAIDs (Stanos, 2007; Argoff , 2012; Massey, 2010)
- CRPS I (McCleane, 2002).
- Neuropathies represent one of the most common neurological disorders, with an incidence range from 2.4% in the general population to 8% in an older population, with a point-prevalence of neuropathic pain estimate of 5-7% (McMahon, p. 1004). Of all patients with diabetes, the point-prevalence of DPN is estimated at 10-20% (McMahon, p.1004). The list of peripheral and central nervous system diseases than can cause acute or chronic neuropathic pain is lengthy (see below table, modified from McMahon Box 70-1, p. 1004)

  - Peripheral neuropathic pain: acute and chronic inflammatory:
    - Demyelinating polyradiculoneuropathy;
    - Alcoholic polyneuropathy;
    - Chemotherapy-induced polyneuropathy;
    - Complex regional pain syndrome (CRPS) type 2;
    - Entrapment neuropathies;
    - Herpes zoster;
    - HIV-associated sensory neuropathy;
    - Iatrogenic neuralgias;
    - Idiopathic sensory neuropathy;
    - Nutritional deficiency-related neuropathies;
    - Painful diabetic neuropathy (PDN)/diabetic polyneuropathy (DPN);
    - Phantom limb pain;
    - Post-herpetic neuralgia (PHN);
    - Post-traumatic neuralgias;
    - Radiculopathy (cervical, thoracic, lumbosacral);
    - Toxic exposure-related neuropathies;
    - Trigeminal neuralgia (TN); and
    - Vasculitis neuropathy.

  - Central neuropathic pain:
    - Central post-stroke pain;
    - Compressive myelopathy;
    - HIV myelopathy;
    - MS-related pain;
    - Parkinson's disease-related pain;
    - Post-radiation myelopathy;
    - Post-traumatic spinal cord injury pain; and
    - Syringomyelia.

Perhaps the most commonly thought of neuropathic indication for transdermal therapy is postherpetic neuralgia (McMahon, p. 1005), and this is particularly important for the medically complicated patient as often PHN occurs in the older patient, who may or may not have oral polypharmacy as a potential complication of trying to treat their pain, as well as hepatic, renal, and other considerations (Bruckenthal, 2013).

The treatment of neuropathic pain in diabetes has been well-described recently (Smith, 2011), with the emphasis on orally available agents but also exploring the commonly known topical options. The agents explored, however, and their coverage of polypharmacy, do suggest that using the oral options commonly employed in a topical, perhaps polypharmaceutical preparation, may be efficacious.

The use of topical medications for pain from osteoarthritis has been well-described for quite a while, as noted earlier. TMJ, neck pain, back pain, and facial pain/other painful cranial neuralgias are further considerations for using topical therapy.

It has been suggested that topical options can at least represent an important option in a multimodal approach to pain (de Leon-Casasola, 2007). This is certainly true. Hopefully by using the appropriate drug choices, probably in a polypharmaceutical approach, in a transdermal preparation which can get good skin penetration, these tools can hopefully play an even larger role.

The ability to employ rational polypharmacy makes transdermal preparations an excellent option for a number of acute and chronic painful conditions. This ability to employ polypharmacy can overcome poorly understood failures of certain oral medications to effectively treat certain conditions.

For example:

- Carbamazepine is still considered the first choice by many for initiating treatment for trigeminal neuralgia (see the 3 sets of guidelines: (Mayo Clin Proc 2010; 85(3) (suppl): S3-S14; Pain Res Manage Spring 2007; 12(1) 13-21; and Eur J Neurol. 2010 Sep;17(9):1113-e88), but it is not very effective for PHN or for polyneuropathies (Ettinger, 2007);

- NMDA blockade for CRPS is often helpful, as well as for DPN, but it is felt of no help for PHN (Zhou, 2011);

- Topiramate has very many mechanisms of action and is an FDA-approved headache preventative medication, but it is a poor choice for pain otherwise, very much like valproic acid which is also FDA-approved for migraine prevention but is felt generally not effective for other pain syndromes (Ettinger, 2007).

Thus, painting a broader brush in both the numbers of agents to be compounded into a transdermal preparation as well as exploiting multiple mechanisms of action should provide for more effective pain relief.

There are many excellent review articles which look at the pathophysiology of pain and the spectrum of drug choices which can be helpful for various painful conditions (Sawynok, 2003; Stanos, 2007; McCleane, 2007; McCleane, 2008; Ossipov, 2012; Sawynok, 2013). Further, there are detailed paradigmatic research protocols to expedite the search for better understanding of pain and how to more effectively treat it (Antunes-Martin, 2013).

7. REFERENCES

Alstadhaug, K. B. (2014). Histamine in migraine and brain. Headache: *The Journal of Head and Face Pain*, 54(2), 246-259.

Amir, R., Argoff, C. E., Bennett, G. J., Cummins, T. R., Durieux, M. E., Gerner, P., ... & Strichartz, G. R. (2006). The role of sodium channels in chronic inflammatory and neuropathic pain. *The Journal of Pain*, 7(5), S1-S29.

Anand, P., & Bley, K. (2011). Topical capsaicin for pain management: therapeutic potential and mechanisms of action of the new high-concentration capsaicin 8% patch. *British Journal of Anaesthesia*, 107(4), 490-502.

Ängehagen, M., Ben-Menachem, E., Rönnbäck, L., & Hansson, E. (2003). Novel mechanisms of action of three antiepileptic drugs, vigabatrin, tiagabine, and topiramate. *Neurochemical Research*, 28(2), 333-340.

Anitescu, M., Benzon, H. T., & Argoff, C. E. (2013). Advances in topical analgesics. *Current Opinion in Anesthesiology*, 26(5), 555-561.

Antunes-Martins, A., Perkins, J. R., Lees, J., Hildebrandt, T., Orengo, C., & Bennett, D. L. (2013). Systems biology approaches to finding novel pain mediators. *Wiley Interdisciplinary Reviews: Systems Biology and Medicine*, 5(1), 11-35.

Argoff, C. (2002) Pharmacologic management of chronic pain. *Journal of American Osteopathic Association*, 102(9 Supplement 3), S21–S27.

Argoff, C., Albrecht, P., Irving, G., & Rice, F. (2009). Multimodal analgesia for chronic pain: rationale and future directions. *Pain Medicine*, 10(S2), S53-S66.

Argoff, C. E. (2013, February). Topical analgesics in the management of acute and chronic pain. *Mayo Clinic Proceedings* (Vol. 88, No. 2, pp. 195-205). Elsevier.

Argoff C.E. (2013). Introduction to topical analgesics in the management of acute and chronic pain: special report. *Postgraduate Medicine*, 125(4): 3-6.

Arnstein, P. M. (2013). The future of topical analgesics. *Postgraduate Medicine*, 125(4 Suppl 1), 34-41.

Atkinson, T. J., Fudin, J., Pandula, A., & Mirza, M. (2013). Medication pain management in the elderly: unique and underutilized analgesic treatment options. *Clinical Therapeutics*, 35(11), 1669-1689.

Attal, N., Cruccu, G., Baron, R., Haanpää, M., Hansson, P., Jensen, T. S., & Nurmikko, T. (2010). EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *European Journal of Neurology*, 17(9), 1113-e88.

Babai, S., Auriche, P., & Le-Louët, H. (2010). Comparison of adverse drug reactions with donepezil versus memantine: *analysis of the French Pharmacovigilance Database. Therapie*, 65(3), 255-259.

Backonja, M. M., & Galer, B. S. (1998). Pain assessment and evaluation of patients who have neuropathic pain. *Neurologic Clinics*, 16(4), 775-789.

Backonja, M. M., & Serra, J. (2004). Pharmacologic Management Part 1: Better-Studied Neuropathic Pain Diseases. *Pain Medicine*, 5(s1), S28-S47.

Barkin, R. L. (2009). Reducing cardiovascular risks of nonsteroidal anti-inflammatory drugs by using topical formulations. *The American Journal of Cardiology*, 104(9), 1315.

Barkin, R. L., Beckerman, M., Blum, S. L., Clark, F. M., Koh, E. K., & Wu, D. S. (2010). Should nonsteroidal anti-inflammatory drugs (NSAIDs) be prescribed to the older adult?. *Drugs & Aging*, 27(10), 775-789.

Barkin, R. L. (2013). The pharmacology of topical analgesics. *Postgraduate Medicine*, 125(4 Suppl 1), 7-18.

Baron, R. (2004). Mechanistic and clinical aspects of complex regional pain syndrome (CRPS). *Pathological Pain: From Molecular to Clinical Aspects*, 148, 220.

Barton, D. L., Wos, E. J., Qin, R., Mattar, B. I., Green, N. B., Lanier, K. S., ... & Loprinzi, C. L. (2011). A double-blind, placebo-controlled trial of a topical treatment for chemotherapy-induced peripheral neuropathy: NCCTG trial N06CA. *Supportive Care in Cancer*, 19(6), 833-841.

Basbaum, A. I., Bautista, D. M., Scherrer, G., & Julius, D. (2009). Cellular and molecular mechanisms of pain. *Cell*, 139(2), 267-284.

Bell, T. J., Thaler, C., Castiglioni, A. J., Helton, T. D., & Lipscombe, D. (2004). Cell-specific alternative splicing increases calcium channel current density in the pain pathway. *Neuron*, 41(1), 127-138.

Bigal, M. E., Lipton, R. B., Holland, P. R., & Goadsby, P. J. (2007). Obesity, migraine, and chronic migraine: Possible mechanisms of interaction. *Neurology*, 68(21), 1851-1861.

Binshtok, A. M., Bean, B. P., & Woolf, C. J. (2007). Inhibition of nociceptors by TRPV1-mediated entry of impermeant sodium channel blockers. *Nature*, 449(7162), 607-610.

Borsook, D., & Burstein, R. (2012). The enigma of the dorsolateral pons as a migraine generator. *Cephalalgia*, 32(11), 803-812.

Brack, A., Rittner, H. L., Machelska, H., Leder, K., Mousa, S. A., Schäfer, M., & Stein, C. (2004). Control of inflammatory pain by chemokine-mediated recruitment of opioid-containing polymorphonuclear cells. *Pain*, 112(3), 229-238.

Brown, M. B., Martin, G. P., Jones, S. A., & Akomeah, F. K. (2006). Dermal and transdermal drug delivery systems: current and future prospects. *Drug Delivery*, 13(3), 175-187.

Bruckenthal, P., & Barkin, R. L. (2013). Options for treating postherpetic neuralgia in the medically complicated patient. *Therapeutics and Clinical Risk Management*, 9, 329.

Bruehl, S. (2010). An update on the pathophysiology of complex regional pain syndrome. *Anesthesiology*, 113(3), 713-725.

Brühlmann, P., Vathaire, F. D., Dreiser, R. L., & Michel, B. A. (2006). Short-term treatment with topical diclofenac epolamine plaster in patients with symptomatic knee osteoarthritis: pooled analysis of two randomized clinical studies. *Current Medical Research and Opinion®*, 22(12), 2429-2438.

Burstein, R., Cutrer, M. F., & Yarnitsky, D. (2000). The development of cutaneous allodynia during a migraine attack clinical evidence for the sequential recruitment of spinal and supraspinal nociceptive neurons in migraine. *Brain*, 123(8), 1703-1709.

Burstein, R., Collins, B., & Jakubowski, M. (2004). Defeating migraine pain with triptans: a race against the development of cutaneous allodynia. *Annals of Neurology*, 55(1), 19-26.

Burstein, R., Jakubowski, M., Garcia-Nicas, E., Kainz, V., Bajwa, Z., Hargreaves, R., ... & Borsook, D. (2010). Thalamic sensitization transforms localized pain into widespread allodynia. *Annals of Neurology*, 68(1), 81-91.

Burstein, R., Jakubowski, M., & Rauch, S. D. (2011). The science of migraine. *Journal of Vestibular Research*, 21(6), 305-314.

Bernstein, C., & Burstein, R. (2012). Sensitization of the trigeminovascular pathway: perspective and implications to migraine pathophysiology. *Journal of Clinical Neurology*, 8(2), 89-99.

Burstein, R., Perry, C., Blake, P., Buettner, C., & Bhasin, M. (2014). EHMTI-0354. Abnormal expression of gene transcripts linked to inflammatory response in the periosteum of chronic migraine patients: implications to extracranial origin of headache. *The Journal of Headache and Pain*, 15(1), 1-1.

Butler, S. H., Weil-Fugazza, J., Godefroy, F., & Besson, J. M. (1985). Reduction of arthritis and pain behaviour following chronic administration of amitriptyline or imipramine in rats with adjuvant-induced arthritis. *Pain*, 23(2), 159-175.

Cady, R. K., & Schreiber, C. P. (2009). Sinus problems as a cause of headache refractoriness and migraine chronification. *Current Pain and Headache Reports*, 13(4), 319-325.

Calvo, M., & Bennett, D. L. (2012). The mechanisms of microgliosis and pain following peripheral nerve injury. *Experimental Neurology*, 234(2), 271-282.

Campbell, B. J., Rowbotham, M., Davies, P. S., Jacob, P., & Benowitz, N. L. (2002). Systemic absorption of topical lidocaine in normal volunteers, patients with post-herpetic neuralgia, and patients with acute herpes zoster. *Journal of Pharmaceutical Sciences*, 91(5), 1343-1350.

Campbell, J. N., & Meyer, R. A. (2006). Mechanisms of neuropathic pain. *Neuron*, 52(1), 77-92.

Capuano, A., De Corato, A., Lisi, L., Tringali, G., Navarra, P., & Dello Russo, C. (2009). Proinflammatory-activated trigeminal satellite cells promote neuronal sensitization: relevance for migraine pathology. *Mol Pain*, 5(43), 8069-5.

Castro, M. J., Stam, A. H., Lemos, C., De Vries, B., Vanmolkot, K. R. J., Barros, J., ... & Van Den Maagdenberg, A. M. J. M. (2009). First mutation in the voltage-gated NaV1. 1 subunit gene SCN1A with co-occurring familial hemiplegic migraine and epilepsy. *Cephalalgia*, 29(3), 308-313.

Chaparro, L. E., Wiffen, P. J., Moore, R. A., & Gilron, I. (2012). Combination pharmacotherapy for the treatment of neuropathic pain in adults. *The Cochrane Library*.

Chen, S. R., Samoriski, G., & Pan, H. L. (2009). Antinociceptive effects of chronic administration of uncompetitive NMDA receptor antagonists in a rat model of diabetic neuropathic pain. *Neuropharmacology*, 57(2), 121-126.

Cheng, H. T. (2010). Spinal cord mechanisms of chronic pain and clinical implications. *Current Pain and Headache Reports*, 14(3), 213-220.

Chung, J. M., & Chung, K. (2005). Sodium channels and neuropathic pain. Pathological Pain: *From Molecular to Clinical Aspects*, 269, 19.

Chung, M. K., Güler, A. D., & Caterina, M. J. (2008). TRPV1 shows dynamic ionic selectivity during agonist stimulation. *Nature Neuroscience*, 11(5), 555-564.

Cianchetti, C. (2010). Capsaicin jelly against migraine pain. *International Journal of Clinical Practice*, 64(4), 457-459.

Collins, S., Sigtermans, M. J., Dahan, A., Zuurmond, W. W., & Perez, R. S. (2010). NMDA receptor antagonists for the treatment of neuropathic pain. *Pain Medicine,* 11(11), 1726-1742.

Cregg, R., Momin, A., Rugiero, F., Wood, J. N., & Zhao, J. (2010). Pain channelopathies. *The Journal of Physiology*, 588(11), 1897-1904.

D'Andrea, G., & Leon, A. (2010). Pathogenesis of migraine: from neurotransmitters to neuromodulators and beyond. *Neurological Sciences*, 31(1), 1-7.

De Felice, M., Ossipov, M. H., Wang, R., Dussor, G., Lai, J., Meng, I. D., ... & Porreca, F. (2010). Triptan-induced enhancement of neuronal nitric oxide synthase in trigeminal ganglion dural afferents underlies increased responsiveness to potential migraine triggers. *Brain*, 133(8), 2475-2488.

De Felice, M., Ossipov, M. H., & Porreca, F. (2011). Update on medication-overuse headache. *Current Pain and Headache Reports*, 15(1), 79-83.

De Felice, M., Sanoja, R., Wang, R., Vera-Portocarrero, L., Oyarzo, J., King, T., ... & Porreca, F. (2011). Engagement of descending inhibition from the rostral ventromedial medulla protects against chronic neuropathic pain. *Pain*, 152(12), 2701-2709.

De Leon-Casasola, O. A. (2007). Multimodal approaches to the management of neuropathic pain: the role of topical analgesia. *Journal of Pain and Symptom Management*, 33(3), 356-364.

De Oliveira, C. M. B. D., Sakata, R. K., Issy, A. M., Gerola, L. R., & Salomão, R. (2011). Cytokines and pain. *Revista Brasileira de Anestesiologia*, 61(2), 260-265.

Derry, S., Moore, R. A., & Rabbie, R. (2012). Topical NSAIDs for chronic musculoskeletal pain in adults. *The Cochrane Library*.

Derry, S., & Moore, R. A. (2012). Topical capsaicin (low concentration) for chronic neuropathic pain in adults. *The Cochrane Library*.

Derry, S., Rice, A. S., Cole, P., Tan, T., & Moore, R. A. (2013). Topical capsaicin (high concentration) for chronic neuropathic pain in adults. *The Cochrane Library*.

Desai, P., Patlolla, R. R., & Singh, M. (2010). Interaction of nanoparticles and cell-penetrating peptides with skin for transdermal drug delivery. *Molecular Membrane Biology*, 27(7), 247-259.

Desmeules, J. A., Cedraschi, C., Rapiti, E., Baumgartner, E., Finckh, A., Cohen, P., ... & Vischer, T. L. (2003). Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. *Arthritis & Rheumatism*, 48(5), 1420-1429.

Deval, E., Gasull, X., Noël, J., Salinas, M., Baron, A., Diochot, S., & Lingueglia, E. (2010). Acid-sensing ion channels (ASICs): pharmacology and implication in pain. *Pharmacology & Therapeutics*, 128(3), 549-558.

Devor, M. (2006) Chapter 19: "Pathophysiology of Nerve Injury," in Handbook of Clinical Neurology, Vol. 81 (3rd series), *Pain*, 261-274.

Dominkus, M., Nicolakis, M., Kotz, R., Wilkinson, F. E., Kaiser, R. R., & Chlud, K. (1996). Comparison of tissue and plasma levels of ibuprofen after oral and topical administration. *Arzneimittel-Forschung*, 46(12), 1138-1143.

Dray, A. (2008). Neuropathic pain: emerging treatments. *British Journal of Anaesthesia*, 101(1), 48-58.

Drug Abuse (NIDA), the FDA Acts as the Lead Agency (n.d.):n. pag. 02 July 2014. Web. http://www.deadiversion.usdoj.gov/fed_regs/rules/2014/fr0702.htm, accessed 01 Dec. 2014.

Dussor, G. O., Price, T. J., Louria, M. D., Candelario-Soto, D. , Jeske, N. A., Patwardhan, A. M., ... & Flores, C. M. (2005). Treatment of trigeminal ganglion neurons in vitro with NGF, GDNF or BDNF: effects on neuronal survival, neurochemical properties and TRPV1-mediated neuropeptide secretion. *BMC Neuroscience*, 6(1), 4.

Dworkin, R. H., O'Connor, A. B., Audette, J., Baron, R., Gourlay, G. K., Haanpää, M. L., ... & Wells, C. D. (2010, March). Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *In Mayo Clinic Proceedings* (Vol. 85, No. 3, pp. S3-S14). Elsevier.

Edelmayer, R. M., Vanderah, T. W., Majuta, L., Zhang, E. T., Fioravanti, B., De Felice, M., ... & Porreca, F. (2009). Medullary pain facilitating neurons mediate allodynia in headache-related pain. *Annals of Neurology*, 65(2), 184-193.

Edvinsson, L., & Uddman, R. (2005). Neurobiology in primary headaches. *Brain Research Reviews*, 48(3), 438-456.

Eibl, J. K., Strasser, B. C., & Ross, G. M. (2012). Structural, biological, and pharmacological strategies for the inhibition of nerve growth factor. *Neurochemistry International*, 61(8), 1266-1275.

Eide, P. K. (2000). Wind-up and the NMDA receptor complex from a clinical perspective. *European Journal of Pain*, 4(1), 5-15.

Eisenberg, E., River, Y., Shifrin, A., & Krivoy, N. (2007). Antiepileptic drugs in the treatment of neuropathic pain. *Drugs*, 67(9), 1265-1289.

Ellis, A., & Bennett, D. L. H. (2013). Neuroinflammation and the generation of neuropathic pain. *British Journal of Anaesthesia*, 111(1), 26-37.

Ettinger, A. B., & Argoff, C. E. (2007). Use of antiepileptic drugs for nonepileptic conditions: psychiatric disorders and chronic pain. *Neurotherapeutics*, 4(1), 75-83.

Fan, Q. Q., Li, L., Wang, W. T., Yang, X., Suo, Z. W., & Hu, X. D. (2014). Activation of α2 adrenoceptors inhibited NMDA receptor-mediated nociceptive transmission in spinal dorsal horn of mice with inflammatory pain. *Neuropharmacology*, 77, 185-192.

Farlow, M. R., Graham, S. M., & Alva, G. (2008). Memantine for the treatment of Alzheimer's Disease. *Drug Safety*, 31(7), 577-585.

Farlow, M. R., & Somogyi, M. (2011). Transdermal patches for the treatment of neurologic conditions in elderly patients: a review. *The Primary Care Companion to CNS Disorders*, 13(6).

Finch, P. M., Knudsen, L., & Drummond, P. D. (2009). Reduction of allodynia in patients with complex regional pain syndrome: a double-blind placebo-controlled trial of topical ketamine. *Pain*, 146(1), 18-25.

Finnerup, N. B., Otto, M., Jensen, T. S., & Sindrup, S. H. (2007). An evidence-based algorithm for the treatment of neuropathic pain. *Medscape General Medicine*, 9(2), 36.

Galer, B. S. (1998). Painful polyneuropathy. *Neurologic Clinics*, 16(4), 791-811.

Gaikwad, A. K. (2013). Transdermal drug delivery system: formulation aspects and evaluation. *Comprehensive Journal of Pharmacology Sciences*, 1(1), 1-10.

Galletti, F., Cupini, L. M., Corbelli, I., Calabresi, P., & Sarchielli, P. (2009). Pathophysiological basis of migraine prophylaxis. *Progress in Neurobiology*, 89(2), 176-192.

Galluzzi, K. E. (2007). Managing neuropathic pain. JAOA: *Journal of the American Osteopathic Association*, 107(suppl 6), ES39-ES48.

Galluzzi, K. E. (2009). Managing herpes zoster and postherpetic neuralgia. JAOA: *Journal of the American Osteopathic Association*, 109(6 suppl 2), S7-S12.

Gangadharan, V., & Kuner, R. (2013). Pain hypersensitivity mechanisms at a glance. *Disease Models & Mechanisms*, 6(4), 889-895.

Ghelardini, C., Galeotti, N., Grazioli, I., & Uslenghi, C. (2004). Indomethacin, alone and combined with prochlorperazine and caffeine, but not sumatriptan, abolishes peripheral and central sensitization in in vivo models of migraine. *The Journal of Pain*, 5(8), 413-419.

Goldstein, F. J. (2002). Adjuncts to opioid therapy. *Journal of American Osteopathic Association*, 102(9; SUPP/3), S15-S20.

Gunthorpe, M. J., & Chizh, B. A. (2009). Clinical development of TRPV1 antagonists: targeting a pivotal point in the pain pathway. *Drug Discovery Today*, 14(1), 56-67.

Hackworth, R. J., Tokarz, K. A., Fowler, I. M., Wallace, S. C., & Stedje-Larsen, E. T. (2008). Profound pain reduction after induction of memantine treatment in two patients with severe phantom limb pain. *Anesthesia & Analgesia*, 107(4), 1377-1379.

Haghighi, A., Motazedian, S., Rezaii, R., Mohammadi, F., Salarian, L., Pourmokhtari, M., ... & Miri, R. (2010). Cutaneous application of menthol 10% solution as an abortive treatment of migraine without aura: a randomised, double-blind, placebo-controlled, crossed-over study. *International Journal of Clinical Practice*, 64(4), 451-456.

Hans, G. H., Robert, D. N., & Van Maldeghem, K. N. (2008). Treatment of an acute severe central neuropathic pain syndrome by topical application of lidocaine 5% patch: a case report. *Spinal Cord*, 46(4), 311-313.

Hassett, A. L., & Gevirtz, R. N. (2009). Nonpharmacologic treatment for fibromyalgia: patient education, cognitive-behavioral therapy, relaxation techniques, and complementary and alternative medicine. *Rheumatic Disease Clinics of North America*, 35(2), 393-407.

Heavner, J. E. (2007). Local anesthetics. *Current Opinion in Anesthesiology*, 20(4), 336-342.

Helmy, S. A., & Bali, A. (2001). The effect of the preemptive use of the NMDA receptor antagonist dextromethorphan on postoperative analgesic requirements. *Anesthesia & Analgesia*, 92(3), 739-744.

Hendrich, J., Van Minh, A. T., Heblich, F., Nieto-Rostro, M., Watschinger, K., Striessnig, J., ... & Dolphin, A. C. (2008). Pharmacological disruption of calcium channel trafficking by the α2δ ligand gabapentin. *Proceedings of the National Academy of Sciences*, 105(9), 3628-3633.

Heyneman, C. A., Lawless-Liday, C., & Wall, G. C. (2000). Oral versus topical NSAIDs in rheumatic diseases. *Drugs*, 60(3), 555-574.

Higashi, Y., Kiuchi, T., & Furuta, K. (2010). Efficacy and safety profile of a topical methyl salicylate and menthol patch in adult patients with mild to moderate muscle strain: a randomized, double-blind, parallel-group, placebo-controlled, multicenter study. *Clinical Therapeutics*, 32(1), 34-43.

Hochberg, M. C., Altman, R. D., April, K. T., Benkhalti, M., Guyatt, G., McGowan, J., ... & Tugwell, P. (2012). American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care & Research*, 64(4), 465-474.

Iannone, F., & Lapadula, G. (2010). Obesity and inflammation-targets for OA therapy. Current Drug Targets, 11(5), 586-598.

"IASP Taxonomy." IASP Taxonomy. IASP – International Association for the Study of Pain, n.d. Web. http://www.iasp-pain.org/Taxonomy, accessed 01 Dec. 2014.

Ickowicz E. (2009). Pharmacological management of persistent pain in older persons. *Journal of the American Geriatrics Society*, 57(8), 1331.

Inoue, K., Tsuda, M., & Koizumi, S. (2004, August). Chronic pain and microglia: the role of ATP. Pathological Pain: From Molecular to Clinical Aspects: *Novartis Foundation Symposium*, 261 (pp. 55-67). John Wiley & Sons, Ltd.

Iwaszkiewicz, K. S., Schneider, J. J., & Hua, S. (2013). Targeting peripheral opioid receptors to promote analgesic and anti-inflammatory actions. *Frontiers in Pharmacology*, 4.

Jakubowski, M., Levy, D., Kainz, V., Zhang, X. C., Kosaras, B., & Burstein, R. (2007). Sensitization of central trigeminovascular neurons: blockade by intravenous naproxen infusion. *Neuroscience*, 148(2), 573-583.

Jamero, D. (2011).The emerging role of NMDA antagonists in pain management. US Pharmacist. 2011. Jobson Publishing. Posted to Medscape.com on 6/22/2011.

Jenoure, P., Segesser, B., Lühti, U., & Gremion, G. (1992). A trial with diclofenac HEP plaster as topical treatment in minor sport injuries. *Drugs Under Experimental and Clinical Research*, 19(3), 125-131.

Jensen, T. S., & Finnerup, N. B. (2014). Allodynia and hyperalgesia in neuropathic pain: clinical manifestations and mechanisms. *The Lancet Neurology*, 13(9), 924-935.

Ji, R. R., Kohno, T., Moore, K. A., & Woolf, C. J. (2003). Central sensitization and LTP: do pain and memory share similar mechanisms? *Trends in Neurosciences*, 26(12), 696-705.

Ji, R. R., Xu, Z. Z., Strichartz, G., & Serhan, C. N. (2011). Emerging roles of resolvins in the resolution of inflammation and pain. *Trends in Neurosciences*, 34(11), 599-609.

Jones, R. W. (2010). A review comparing the safety and tolerability of memantine with the acetylcholinesterase inhibitors. *International Journal of Geriatric Psychiatry*, 25(6), 547-553.

Katz, J., Jackson, M., Kavanagh, B. P., & Sandler, A. N. (1996). Acute pain after thoracic surgery predicts long-term post-thoracotomy pain. *The Clinical Journal of Pain*, 12(1), 50-55.

Kavirajan, H. (2009). Memantine: a comprehensive review of safety and efficacy. *Expert Opinion on Drug Safety*, 8(1), 89-109.

Keck Jr, P. E., Hsu, H. A., Papadakis, K., & Russo Jr, J. (2009). Memantine efficacy and safety in patients with acute mania associated with bipolar I disorder: a pilot evaluation. *Clinical Neuropharmacology*, 32(4), 199-204.

Kerstman, E., Ahn, S., Battu, S., Tariq, S., & Grabois, M. (2013). Neuropathic pain. *Handbook of Clinical Neurology*, 110, 175-187.

Keyes, P. D., Tallon, J. M., & Rizos, J. (1998). Topical anesthesia. *Canadian Family Physician*, 44, 2152.

Kindler, L. L., Bennett, R. M., & Jones, K. D. (2011). Central sensitivity syndromes: mounting pathophysiologic evidence to link fibromyalgia with other common chronic pain disorders. *Pain Management Nursing*, 12(1), 15-24.

Kingery, W. S. (1997). A critical review of controlled clinical trials for peripheral neuropathic pain and complex regional pain syndromes. *Pain*, 73(2), 123-139.

Klauenberg, S., Maier, C., Assion, H. J., Hoffmann, A., Krumova, E. K., Magerl, W., ... & Juckel, G. (2008). Depression and changed pain perception: hints for a central disinhibition mechanism. *Pain*, 140(2), 332-343.

Koinig, H., Wallner, T., Marhofer, P., Andel, H., Horauf, K., & Mayer, N. (1998). Magnesium sulfate reduces intra-and postoperative analgesic requirements. *Anesthesia & Analgesia*, 87(1), 206-210.

Kopsky, D. J., & Keppel Hesselink, J. M. (2012). High doses of topical amitriptyline in neuropathic pain: two cases and literature review. *Pain Practice*, 12(2), 148-153.

Kosharskyy, B., Almonte, W., & Shaparin, N. (2013). Intravenous infusions in chronic pain management. *Pain Physician*, 16, 231-249.

Kuhn, M., Rossi, S. O., Plummer, J. L., & Raftos, J. (1996). Topical anaesthesia for minor lacerations: MAC versus TAC. *The Medical Journal of Australia*, 164(5), 277-280.

Kuner, R. (2010). Central mechanisms of pathological pain. *Nature Medicine*, 16(11), 1258-1266.

Kwak, J. (2012). Capsaicin blocks the hyperpolarization-activated inward currents via TRPV1 in the rat dorsal root ganglion neurons. *Experimental Neurobiology*, 21(2), 75-82.

Labuz, D., Mousa, S. A., Schäfer, M., Stein, C., & Machelska, H. (2007). Relative contribution of peripheral versus central opioid receptors to antinociception. *Brain Research*, 1160, 30-38.

Landmark, C. J. (2008). Antiepileptic drugs in non-epilepsy disorders. *CNS Drugs*, 22(1), 27-47.

Latremoliere, A., & Woolf, C. J. (2009). Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *The Journal of Pain*, 10(9), 895-926.

Levinson, S. R., Luo, S., & Henry, M. A. (2012). The role of sodium channels in chronic pain. *Muscle & Nerve*, 46(2), 155-165.

Levy, D., Burstein, R., Kainz, V., Jakubowski, M., & Strassman, A. M. (2007). Mast cell degranulation activates a pain pathway underlying migraine headache. *Pain*, 130(1), 166-176.

Levy, D., Zhang, X. C., Jakubowski, M., & Burstein, R. (2008). Sensitization of meningeal nociceptors: inhibition by naproxen. *European Journal of Neuroscience*, 27(4), 917-922.

Levy, D., Kainz, V., Burstein, R., & Strassman, A. M. (2012). Mast cell degranulation distinctly activates trigemino-cervical and lumbosacral pain pathways and elicits widespread tactile pain hypersensitivity. *Brain, Behavior, and Immunity*, 26(2), 311-317.

Liebregts, R., Kopsky, D. J., & Hesselink, J. M. K. (2011). Topical amitriptyline in post-traumatic neuropathic pain. *Journal of Pain and Symptom Management*, 41(4), e6-e7.

Linley, J. E., Rose, K., Ooi, L., & Gamper, N. (2010). Understanding inflammatory pain: ion channels contributing to acute and chronic nociception. *Pflügers Archiv-European Journal of Physiology*, 459(5), 657-669.

Lionberger, D. R., & Brennan, M. J. (2010). Topical nonsteroidal anti-inflammatory drugs for the treatment of pain due to soft tissue injury: diclofenac epolamine topical patch. *Journal of Pain Research*, 3, 223.

Lipton, S. A. (2004). Failures and successes of NMDA receptor antagonists: molecular basis for the use of open-channel blockers like memantine in the treatment of acute and chronic neurologic insults. *NeuroRx*, 1(1), 101-110.

Liu, M., & Wood, J. N. (2011). The roles of sodium channels in nociception: implications for mechanisms of neuropathic pain. *Pain Medicine*, 12(s3), S93-S99.

Landy, S., Rice, K., & Lobo, B. (2004). Central sensitisation and cutaneous allodynia in migraine. *CNS Drugs*, 18(6), 337-342.

Luo, M. C., Chen, Q., Ossipov, M. H., Rankin, D. R., Porreca, F., & Lai, J. (2008). Spinal dynorphin and bradykinin receptors maintain inflammatory hyperalgesia. *The Journal of Pain*, 9(12), 1096-1105.

Luerding, R., Weigand, T., Bogdahn, U., & Schmidt-Wilcke, T. (2008). Working memory performance is correlated with local brain morphology in the medial frontal and anterior cingulate cortex in fibromyalgia patients: structural correlates of pain–cognition interaction. *Brain*, 131(12), 3222-3231.

Lynch, B. A., Lambeng, N., Nocka, K., Kensel-Hammes, P., Bajjalieh, S. M., Matagne, A., & Fuks, B. (2004). The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levetiracetam. *Proceedings of the National Academy of Sciences of the United States of America*, 101(26), 9861-9866.

Lynch, M. E., Clark, A. J., & Sawynok, J. (2003). A pilot study examining topical amitriptyline, ketamine, and a combination of both in the treatment of neuropathic pain. *The Clinical Journal of Pain*, 19(5), 323-328.

Lynch, M. E., Clark, A. J., Sawynok, J., & Sullivan, M. J. (2005). Topical amitriptyline and ketamine in neuropathic pain syndromes: an open-label study. *The Journal of Pain*, 6(10), 644-649.

Lysakowski, C., Dumont, L., Czarnetzki, C., & Tramèr, M. R. (2007). Magnesium as an adjuvant to postoperative analgesia: a systematic review of randomized trials. *Anesthesia & Analgesia*, 104(6), 1532-1539.

Machelska, H., Schopohl, J. K., Mousa, S. A., Labuz, D., Schäfer, M., & Stein, C. (2003). Different mechanisms of intrinsic pain inhibition in early and late inflammation. *Journal of Neuroimmunology*, 141(1), 30-39.

Machelska, H. (2007). Targeting of opioid-producing leukocytes for pain control. *Neuropeptides*, 41(6), 355-363.

Magnette, J. L., Kienzler, J. L., Sallin, D., Ménart, C., Nollevaux, F., & Knops, A. (2004). Diclofenac systemic exposure is not increased when topical diclofenac is applied to ultraviolet-induced erythema. *European Journal of Clinical Pharmacology*, 60(8), 591-594.

Maihofner, C., & Heskamp, M. L. (2013). Prospective, non-interventional study on the tolerability and analgesic effectiveness over 12 weeks after a single application of capsaicin 8% cutaneous patch in 1044 patients with peripheral neuropathic pain: first results of the QUEPP study. *Current Medical Research & Opinion*, 29(6), 673-683.

Maletic V., & Raison, C. L. (2009). Neurobiology of depression, fibromyalgia and neuropathic pain. *Frontiers in Bioscience*, 14, 5291-5338.

Massey, T., Derry, S., Moore, R. A., & McQuay, H. J. (2010). Topical NSAIDs for acute pain in adults. *The Cochrane Library*.

Matthews, P., Derry, S., Moore, R. A., & McQuay, H. J. (2009). Topical rubefacients for acute and chronic pain in adults. *The Cochrane Library*.

McCarberg, B. H., & Argoff, C. E. (2010). Topical diclofenac epolamine patch 1.3% for treatment of acute pain caused by soft tissue injury. *International Journal of Clinical Practice*, 64(11), 1546-1553.

McCarberg, B., Barkin, R. L., & Zaleon, C. (2012). The management of neuropathic pain with a focus upon older adults. *American Journal of Therapeutics*, 19(3), 211-227.

McCarberg, B., & D'Arcy, Y. (2013). Options in topical therapies in the management of patients with acute pain. *Postgraduate Medicine*, 125(4 Suppl 1), 19-24.

McCartney, C. J., Sinha, A., & Katz, J. (2004). A qualitative systematic review of the role of N-methyl-D-aspartate receptor antagonists in preventive analgesia. *Anesthesia & Analgesia*, 98(5), 1385-1400.

McCleane, G. (2000). Topical application of doxepin hydrochloride, capsaicin and a combination of both produces analgesia in chronic human neuropathic pain: a randomized, double-blind, placebo-controlled study. *British Journal of Clinical Pharmacology*, 49(6), 574-579.

McCleane, G. (2002). Topical application of doxepin hydrochloride can reduce the symptoms of complex regional pain syndrome: a case report. *Injury*, 33(1), 88-89.

McCleane, G. (2003). Pharmacological management of neuropathic pain. *CNS Drugs*, 17(14), 1031-1043.

McCleane, G. (2007). Topical Analgesics. *Anesthesiology Clinics*, 25(4), 825-839.

McCleane, G. (2007). Topical analgesics. *Medical Clinics of North America*, 91(1), 125-139.

McCleane, G. (2008). Topical analgesic agents. *Clinics in Geriatric Medicine*, 24(2), 299-312.

McCleane, G. (2010). Topical application of analgesics: a clinical option in day case anaesthesia?. *Current Opinion in Anesthesiology*, 23(6), 704-707.

McCleane, G. (2000). Topical application of doxepin hydrochloride, capsaicin and a combination of both produces analgesia in chronic human neuropathic pain: a randomized, double-blind, placebo-controlled study. *British Journal of Clinical Pharmacology*, 49(6), 574-579.

McCormack, P. L. (2010). Capsaicin Dermal Patch. *Drugs*, 70(14), 1831-1842.

McGovern, J. P. (1964). On etiologic mechanisms and a new classification of allergic headaches. *Headache: The Journal of Head and Face Pain*, 4(2), 205-216.

McMahon, S. B., & Cafferty, W. B. (2004, August). Neurotrophic influences on neuropathic pain. In *Novartis Foundation Symposium* (pp. 68-91). Chichester; New York; John Wiley; 1999.

McPherson, M. L., & Cimino, N. M. (2013). Topical NSAID formulations. *Pain Medicine*, 14(S1), S35-S39.

Mease, P. (2005). Fibromyalgia syndrome: review of clinical presentation, pathogenesis, outcome measures, and treatment. *The Journal of Rheumatology*, 75, 6-21.

Meents, J. E., Neeb, L., & Reuter, U. (2010). TRPV1 in migraine pathophysiology. *Trends in Molecular Medicine*, 16(4), 153-159.

Meeus, M., & Nijs, J. (2007). Central sensitization: a biopsychosocial explanation for chronic widespread pain in patients with fibromyalgia and chronic fatigue syndrome. *Clinical Rheumatology*, 26(4), 465-473.

Mehle, M. E. (2012). Migraine and allergy: a review and clinical update. *Current Allergy and Asthma Reports*, 12(3), 240-245.

Melemedjian, O. K., Asiedu, M. N., Tillu, D. V., Sanoja, R., Yan, J., Lark, A., ... & Price, T. J. (2011). Targeting adenosine monophosphate-activated protein kinase (AMPK) in preclinical models reveals a potential mechanism for the treatment of neuropathic pain. Mol Pain, 7(1), 70.

Melzack, R. (2001). Pain and the neuromatrix in the brain. Journal of Dental Education, 65(12), 1378-1382.

Melzack, R., Coderre, T. J., Katz, J., & Vaccarino, A. L. (2001). Central neuroplasticity and pathological pain. Annals of the New York Academy of Sciences, 933(1), 157-174.

Melzack, R. (2005). Evolution of the neuromatrix theory of pain. The Prithvi Raj Lecture: presented at the third World Congress of World Institute of Pain, Barcelona 2004. Pain Practice, 5(2), 85-94.

Melzack, R., Wall, P. D., & Bonica, J. J. (1994). *Textbook of Pain*. 6th ed. Elsevier/Saunders. Philadelphia. 2013. ISBN: 978-0-7020-4059-7.

Meng, Q. T., Xia, Z. Y., Liu, J., Bayliss, D. A., & Chen, X. (2011). Local anesthetic inhibits hyperpolarization-activated cationic currents. *Molecular Pharmacology*, 79(5), 866-873.

Merskey, H., & Hester, R. A. (1972). The treatment of chronic pain with psychotropic drugs. *Postgraduate Medical Journal*, 48(564), 594-598.

Merskey H. "Part III: Pain Terms, A Current List with Definitions and Notes on Usage" (pp. 209-214) Classification of Chronic Pain, Second Edition, IASP Task Force on Taxonomy, edited by H.Merskey and N. Bogduk, IASP Press, Seattle, 1994.

Micheva, K. D., Taylor, C. P., & Smith, S. J. (2006). Pregabalin reduces the release of synaptic vesicles from cultured hippocampal neurons. *Molecular Pharmacology*, 70(2), 467-476.

Moayedi, M., & Davis, K. D. (2013). Theories of pain: from specificity to gate control. *Journal of Neurophysiology*, 109(1), 5-12.

Mobius, H. J., Stoffler, A., & Graham, S. M. (2004). Memantine hydrochloride: pharmacological and clinical profile. *Drugs of Today*, 40(8), 685-696.

Moller, A.R. Pain: its anatomy, physiology, and treatment. Aage R. Moller, Publishing, Richardson, TX, 2012. ISBN: 13: 978-1466395107.

Montana, M. C., & Gereau IV, R. W. (2011). Metabotropic glutamate receptors as targets for analgesia: antagonism, activation, and allosteric modulation. *Current Pharmaceutical Biotechnology*, 12(10), 1681.

Moore, R. A., Tramer, M. R., Carroll, D., Wiffen, P. J., & McQuay, H. J. (1998). Quantitative systematic review of topically applied non-steroidal anti-inflammatory drugs. BMJ, 316(7128), 333-338.

Moulin, D. E., Clark, A. J., Gilron, I., Ware, M. A., Watson, C. P. N., Sessle, B. J., ... & Velly, A. (2007). Pharmacological management of chronic neuropathic pain–consensus statement and guidelines from the Canadian Pain Society. *Pain Research & Management: The Journal of the Canadian Pain Society*, 12(1), 13.

Moulton, E. A., Burstein, R., Tully, S., Hargreaves, R., Becerra, L., & Borsook, D. (2008). Interictal dysfunction of a brainstem descending modulatory center in migraine patients. *PLoS One*, 3(11), e3799.

Mulleman, D., Mammou, S., Griffoul, I., Watier, H., & Goupille, P. (2006). Pathophysiology of disk-related sciatica. I.—Evidence supporting a chemical component. *Joint Bone Spine*, 73(2), 151-158.

Mulleman, D., Mammou, S., Griffoul, I., Watier, H., & Goupille, P. (2006). Pathophysiology of disk-related low back pain and sciatica. II. Evidence supporting treatment with TNF-α antagonists. *Joint Bone Spine*, 73(3), 270-277.

Nagai, N., & Ito, Y. (2014). Therapeutic effects of gel ointments containing tranilast nanoparticles on paw edema inadjuvant-induced arthritis rats. *Biological Pharmaceutical Bulletin*, 37, 96-104.

Narang, A. S., Delmarre, D., & Gao, D. (2007). Stable drug encapsulation in micelles and microemulsions. *International Journal of Pharmaceutics*, 345(1), 9-25.

Nasiri-Toosi, Z., Dashti-Khavidaki, S., Khalili, H., & Lessan-Pezeshki, M. (2013). A review of the potential protective effects of pentoxifylline against drug-induced nephrotoxicity. *European Journal of Clinical Pharmacology*, 69(5), 1057-1073.

(n.d.): n. pag. Federal Register. Department of Justice, 22 Aug. 2014. Web. 01, https://www.federalregister.gov/articles/2014/08/22/2014-19922/schedules-of-controlledsubstances-rescheduling-of-hydrocodone-combination-productsfrom-schedule. Accessed Dec. 2014.

Nijs, J., Van Houdenhove, B., & Oostendorp, R. A. (2010). Recognition of central sensitization in patients with musculoskeletal pain: Application of pain neurophysiology in manual therapy practice. *Manual Therapy*, 15(2), 135-141.

Noguchi, K., Obata, K., & Dai, Y. (2004). Changes in DRG neurons and spinal excitability in neuropathy. *Pathological Pain: From Molecular to Clinical Aspects*, 148, 103.

Noseda, R., & Burstein, R. (2011). Advances in understanding the mechanisms of migraine-type photophobia. *Current Opinion in Neurology*, 24(3), 197-202.

Noseda, R., Kainz, V., Borsook, D., & Burstein, R. (2014). Neurochemical pathways that converge on thalamic trigeminovascular neurons: potential substrate for modulation of migraine by sleep, food intake, stress and anxiety. *PloS One*, 9(8), e103929.

Noto, C., Pappagallo, M., & Szallasi, A. (2009). NGX-4010, a high-concentration capsaicin dermal patch for lasting relief of peripheral neuropathic pain. *Current Opinion in Investigational Drugs* (London, England: 2000), 10(7), 702-710.

Oatway, M., Reid, A., & Sawynok, J. (2003). Peripheral antihyperalgesic and analgesic actions of ketamine and amitriptyline in a model of mild thermal injury in the rat. *Anesthesia & Analgesia*, 97(1), 168-173.

O'Connor, A. B., & Dworkin, R. H. (2009). Treatment of neuropathic pain: an overview of recent guidelines. *The American Journal of Medicine*, 122(10), S22-S32.

Olesen, J., Burstein, R., Ashina, M., & Tfelt-Hansen, P. (2009). Origin of pain in migraine: evidence for peripheral sensitisation. *The Lancet Neurology*, 8(7), 679-690.

Omoigui, S. (2007). The biochemical origin of pain–proposing a new law of pain: The origin of all pain is inflammation and the inflammatory response. Part 1 of 3–A unifying law of pain. *Medical Hypotheses*, 69(1), 70-82.

Omoigui, S. (2007). The biochemical origin of pain: The origin of all pain is inflammation and the inflammatory response. Part 2 of 3–Inflammatory profile of pain syndromes. *Medical Hypotheses*, 69(6), 1169-1178.

Osikowicz, M., Mika, J., & Przewlocka, B. (2013). The glutamatergic system as a target for neuropathic pain relief. *Experimental Physiology*, 98(2), 372-384.

Ossipov, M. H., & Porreca, F. (2005). Challenges in the development of novel treatment strategies for neuropathic pain. *NeuroRx*, 2(4), 650-661.

Ossipov, M. H., Dussor, G. O., & Porreca, F. (2010). Central modulation of pain. *The Journal of Clinical Investigation*, 120(11), 3779.

Ossipov, M. H. (2012). The perception and endogenous modulation of pain. *Scientifica*, 2012.

Park, C. K., Xu, Z. Z., Liu, T., Lü, N., Serhan, C. N., & Ji, R. R. (2011). Resolvin D2 is a potent endogenous inhibitor for transient receptor potential subtype V1/A1, inflammatory pain, and spinal cord synaptic plasticity in mice: distinct roles of resolvin D1, D2, and E1. *The Journal of Neuroscience*, 31(50), 18433-18438.

Paudel, K. S., Milewski, M., Swadley, C. L., Brogden, N. K., Ghosh, P., & Stinchcomb, A. L. (2010). Challenges and opportunities in dermal/transdermal delivery. *Therapeutic Delivery*, 1(1), 109-131.

Perl, E. R. (2011). Pain mechanisms: a commentary on concepts and issues. *Progress in Neurobiology*, 94(1), 20-38.

Peterlin, B. L. (2009). The role of the adipocytokines adiponectin and leptin in migraine. *JAOA: Journal of the American Osteopathic Association*, 109(6), 314-317.

Petersen, B., & Rovati, S. (2009). Diclofenac epolamine (Flector®) patch. *Clinical Drug Investigation*, 29(1), 1-9.

Petrenko, A. B., Yamakura, T., Baba, H., & Shimoji, K. (2003). The role of N-methyl-D-aspartate (NMDA) receptors in pain: a review. *Anesthesia & Analgesia*, 97(4), 1108-1116.

Petrilli, J., Wadsworth, S., Cooper, K., Rodgers, K. E., Siekierka, J., & diZerega, G. S. (2008, July). Tranilast: a pharmaceutical candidate for reduction of adhesions using a novel approach. *Seminars in Reproductive Medicine* (Vol. 26, No. 4, pp. 341-348).

Phillips, K., & Clauw, D. J. (2011). Central pain mechanisms in chronic pain states–maybe it is all in their head. B*est Practice & Research Clinical Rheumatology*, 25(2), 141-154.

Price, T. J., Cervero, F., Gold, M. S., Hammond, D. L., & Prescott, S. A. (2009). Chloride regulation in the pain pathway. *Brain Research Reviews*, 60(1), 149-170.

Prommer, E. E. (2009). Topical analgesic combinations for bortezomib neuropathy. *Journal of Pain and Symptom Management*, 37(3), e3-e5.

Raja, S. N., Meyer, R. A., & Campbell, J. N. (1988). Peripheral mechanisms of somatic pain. *Anesthesiology*, 68(4), 571-590.

Ramírez, E. L. (2013). Treatment of acute and chronic focal neuropathic pain in cancer patients with lidocaine 5% patches. A radiation and oncology department experience. *Supportive Care in Cancer*, 21(5), 1329-1334.

Rapoport, A. M., Freitag, F., & Pearlman, S. H. (2010). Innovative delivery systems for migraine: the clinical utility of a transdermal patch for the acute treatment of migraine. *CNS Drugs*, 24(11), 929.

Reddy, Y. K., Reddy, D. M., & Kumar, M. A. (2014). Transdermal Drug Delivery System: A Review. *International Journal of Chemical and Physical Sciences,* 2(2), 870-877.

Ren, K., & Dubner, R. (2011). The role of trigeminal interpolaris-caudalis transition zone in persistent orofacial pain. *International Review of Neurobiology*, 97, 207.

Riccioni, G., Bucciarelli, T., Mancini, B., Di Ilio, C., & D'Orazio, N. (2007). Antileukotriene drugs: clinical application, effectiveness and safety. *Current Medicinal Chemistry*, 14(18), 1966-1977.

Richards, B. L., Whittle, S. L., & Buchbinder, R. (2012). Neuromodulators for pain management in rheumatoid arthritis. *The Cochrane Library*.

Richards, N., & McMahon, S. B. (2013). Targeting novel peripheral mediators for the treatment of chronic pain. *British Journal of Anaesthesia*, 111(1), 46-51.

Rogawski, M. A., & Bazil, C. W. (2008). New molecular targets for antiepileptic drugs: α2δ, SV2A, and Kv7/KCNQ/M potassium channels. *Current Neurology and Neuroscience Reports*, 8(4), 345-352.

Rogers, M., Rasheed, A., Moradimehr, A., & Baumrucker, S. J. (2009). Memantine (Namenda) for neuropathic pain. *American Journal of Hospice and Palliative Medicine,* 26(1), 57-59.

Rogosnitzky, M., Danks, R., & Kardash, E. (2012). Therapeutic potential of tranilast, an anti-allergy drug, in proliferative disorders. *Anticancer Research*, 32(7), 2471-2478.

Rolf, C., Engström, B., Beauchard, C., Jacobs, L. D., & Le Liboux, A. (1999). Intra-articular absorption and distribution of ketoprofen after topical plaster application and oral intake in 100 patients undergoing knee arthroscopy. *Rheumatology*, 38(6), 564-567.

Romanelli, P., & Esposito, V. (2004). The functional anatomy of neuropathic pain. *Neurosurgery Clinics of North America*, 15(3), 257-268.

Saberi, A., Nemati, S., Shakib, R. J., Kazemnejad, E., & Maleki, M. (2012). Association between allergic rhinitis and migraine. Journal of Research in Medical Sciences: *The Official Journal of Isfahan University of Medical Science*s, 17(6), 508.

Sabsovich, I., Guo, T. Z., Wei, T., Zhao, R., Li, X., Clark, D. J., ... & Kingery, W. S. (2008). TNF signaling contributes to the development of nociceptive sensitization in a tibia fracture model of complex regional pain syndrome type I. *Pain*, 137(3), 507-519.

Sarzi-Puttini, P., Atzeni, F., & Mease, P. J. (2011). Chronic widespread pain: from peripheral to central evolution. *Best Practice & Research Clinical Rheumatology*, 25(2), 133-139.

Sawynok, J., Esser, M. J., & Reid, A. R. (2001). Antidepressants as analgesics: an overview of central and peripheral mechanisms of action. *Journal of Psychiatry and Neuroscience*, 26(1), 21.

Sawynok, J., & Reid, A. (2002). Modulation of formalin-induced behaviors and edema by local and systemic administration of dextromethorphan, memantine and ketamine. *European Journal of Pharmacology*, 450(2), 153-162.

Sawynok, J. (2003). Topical and peripherally acting analgesics. *Pharmacological Reviews*, 55(1), 1-20.

Sawynok, J. (2014). Topical analgesics for neuropathic pain: Preclinical exploration, clinical validation, future development. *European Journal of Pain*, 18(4), 465-481.

Sawynok, J. (2014). Topical and peripheral ketamine as an analgesic. *Anesthesia & Analgesia*, 119(1), 170-178.

Schlereth, T., & Birklein, F. (2008). The sympathetic nervous system and pain. *Neuromolecular Medicine*, 10(3), 141-147.

Schomberg, D., & Olson, J. K. (2012). Immune responses of microglia in the spinal cord: contribution to pain states. *Experimental Neurology*, 234(2), 262-270.

Schumacher, M. A. (2010). Transient receptor potential channels in pain and inflammation: therapeutic opportunities. *Pain Practice*, 10(3), 185-200.

Sessle, B. J. (2000). Acute and chronic craniofacial pain: brainstem mechanisms of nociceptive transmission and neuroplasticity, and their clinical correlates. *Critical Reviews in Oral Biology & Medicine*, 11(1), 57-91.

Shankland II, W. E. (2011). Factors that affect pain behavior. *The Journal of Craniomandibular & Sleep Practice*, 29(2), 144-154.

Shaw, S. M., Shah, M. K., Williams, S. G., & Fildes, J. E. (2009). Immunological mechanisms of pentoxifylline in chronic heart failure. *European Journal of Heart Failure*, 11(2), 113-118.

Sheets, P. L., Heers, C., Stoehr, T., & Cummins, T. R. (2008). Differential block of sensory neuronal voltage-gated sodium channels by lacosamide [(2R)-2-(acetylamino)-N-benzyl-3-methoxypropanamide], lidocaine, and carbamazepine. *Journal of Pharmacology and Experimental Therapeutics*, 326(1), 89-99.

Shi, X., Wang, L., Li, X., Sahbaie, P., Kingery, W. S., & Clark, J. D. (2011). Neuropeptides Contribute to Peripheral Nociceptive Sensitization by Regulating Interleukin-1 Beta Production in Keratinocytes. *Anesthesia and Analgesia*, 113(1), 175.

Sicuteri, F. (1963). Mast cells and their active substances: their role in the pathogenesis of migraine. *Headache: The Journal of Head and Face Pain*, 3(3), 86-92.

Silberstein, S. D. (2004). Migraine pathophysiology and its clinical implications. *Cephalalgia*, 24(2 suppl), 2-7.

Siu, A., & Drachtman, R. (2007). Dextromethorphan: A Review of N-methyl-d-aspartate Receptor Antagonist in the Management of Pain. *CNS Drug Reviews*, 13(1), 96-106.

Simpson, D. M., Brown, S., & Tobias, J. (2008). Controlled trial of high-concentration capsaicin patch for treatment of painful HIV neuropathy. *Neurology*, 70(24), 2305-2313.

Simpson, D. M., Gazda, S., Brown, S., Webster, L. R., Lu, S. P., Tobias, J. K., ... & NGX-4010 C118 Study Group. (2010). Long-term safety of NGX-4010, a high-concentration capsaicin patch, in patients with peripheral neuropathic pain. *Journal of Pain and Symptom Management*, 39(6), 1053-1064.

Simpson, D. M., Brown, S., Tobias, J. K., Vanhove, G. F., & NGX-4010 C107 Study Group. (2014). NGX-4010, a capsaicin 8% dermal patch, for the treatment of painful HIV-associated distal sensory polyneuropathy: results of a 52-week open-label study. *The Clinical Journal of Pain*, 30(2), 134-142.

Skoutakis, V. A., Carter, C. A., Mickle, T. R., Smith, V. H., Arkin, C. R., Alissandratos, J., & Petty, D. E. (1988). Review of diclofenac and evaluation of its place in therapy as a nonsteroidal antiinflammatory agent. *Drug Intelligence & Clinical Pharmacy*, 22(11), 850-859.

Sluka, K. A., Winter, O. C., & Wemmie, J. A. (2009). Acid-sensing ion channels: A new target for pain and CNS diseases. *Current Opinion in Drug Discovery & Development*, 12(5), 693.

Smith, G. A., Strausbaugh, S. D., Harbeck-Weber, C., Shields, B. J., Powers, J. D., & Hackenberg, D. (1996). Comparison of topical anesthetics without cocaine to tetracaine-adrenaline-cocaine and lidocaine infiltration during repair of lacerations: bupivacaine-norepinephrine is an effective new topical anesthetic agent. *Pediatrics*, 97(3), 301-307.

Smith, H. S., & Sang, C. N. (2002). The evolving nature of neuropathic pain: individualizing treatment. *European Journal of Pain*, 6(SB), 13-18.

Smith, H. S. (2008). Peripherally-acting opioids. *Pain Physician*, 11(2 Suppl), S121-32.

Smith, H. S., & Argoff, C. E. (2011). Pharmacological treatment of diabetic neuropathic pain. *Drugs*, 71(5), 557-589.

Stanos, S. P. (2007). Topical agents for the management of musculoskeletal pain. *Journal of Pain and Symptom Management*, 33(3), 342-355.

Stanos, S. P. (2013). Osteoarthritis guidelines: a progressive role for topical nonsteroidal anti-inflammatory drugs. *Journal of Multidisciplinary Healthcare*, 6, 133.

Stanos, S. P., & Galluzzi, K. E. (2013). Topical therapies in the management of chronic pain. *Postgraduate Medicin*e, 125(4 Suppl 1), 25-33.

Staud, R., Price, D. D., Robinson, M. E., Mauderli, A. P., & Vierck, C. J. (2004). Maintenance of windup of second pain requires less frequent stimulation in fibromyalgia patients compared to normal controls. *Pain*, 110(3), 689-696.

Staud, R. (2010). Is it all central sensitization? Role of peripheral tissue nociception in chronic musculoskeletal pain. *Current Rheumatology Reports*, 12(6), 448-454.

Staud, R. (2011). Peripheral pain mechanisms in chronic widespread pain. *Best Practice & Research Clinical Rheumatology*, 25(2), 155-164.

Stein, C., Clark, J. D., Oh, U., Vasko, M. R., Wilcox, G. L., Overland, A. C., ... & Spencer, R. H. (2009). Peripheral mechanisms of pain and analgesia. *Brain Research Reviews*, 60(1), 90-113.

Sudoh, Y., Cahoon, E. E., Gerner, P., & Wang, G. K. (2003). Tricyclic antidepressants as long-acting local anesthetics. *Pain*, 103(1), 49-55.

Suzuki, M. (2009). Role of N-methyl-D-aspartate receptor antagonists in postoperative pain management. *Current Opinion in Anesthesiology*, 22(5), 618-622.

Sweitzer, S. M., Schubert, P., & DeLeo, J. A. (2001). Propentofylline, a glial modulating agent, exhibits antiallodynic properties in a rat model of neuropathic pain. *Journal of Pharmacology and Experimental Therapeutics*, 297(3), 1210-1217.

Tawfik, V. L., Regan, M. R., Haenggeli, C., LaCroix-Fralish, M. L., Nutile-McMenemy, N., Perez, N., ... & DeLeo, J. A. (2008). Propentofylline-induced astrocyte modulation leads to alterations in glial glutamate promoter activation following spinal nerve transection. *Neuroscience*, 152(4), 1086-1092.

Taylor, C. P. (2009). Mechanisms of analgesia by gabapentin and pregabalin-Calcium channel α 2-δ [Cav α 2-δ] ligands. *Pain*, 142(1-2), 13-16.

Telci, L., Esen, F., Akcora, D., Erden, T., Canbolat, A. T., & Akpir, K. (2002). Evaluation of effects of magnesium sulphate in reducing intraoperative anaesthetic requirements. *British Journal of Anaesthesia*, 89(4), 594-598.

Thomas, S. J., & Grossberg, G. T. (2009). Memantine: a review of studies into its safety and efficacy in treating Alzheimer's disease and other dementias. *Clinical Interventions in Aging*, 4, 367.

Thorpe, A. J., & Offord, J. (2010). The α2-δ protein: an auxiliary subunit of voltage-dependent calcium channels as a recognized drug target. *Current Opinion in Investigational Drugs* (London, England: 2000), 11(7), 761-770.

Todorovic, S. M., & Jevtovic-Todorovic, V. (2011). T-type voltage-gated calcium channels as targets for the development of novel pain therapies. *British Journal of Pharmacology*, 163(3), 484-495.

Tominaga, M., Numazaki, M., Iida, T., Moriyama, T., Togashi, K., Higashi, T., ... & Tominaga, T. (2004). Regulation mechanisms of vanilloid receptors. Pathological Pain: *From Molecular to Clinical Aspects*, 4.

Treede, R. D., Wagner, T., Kern, K. U., Husstedt, I. W., Arendt, G., Birklein, F., ... & Baron, R. (2013). Mechanism-and experience-based strategies to optimize treatment response to the capsaicin 8% cutaneous patch in patients with localized neuropathic pain. *Current Medical Research & Opinion*, 29(5), 527-538.

Tremont-Lukats, I. W., Megeff, C., & Backonja, M. M. (2000). Anticonvulsants for neuropathic pain syndromes. *Drugs*, 60(5), 1029-1052.

Truong, W., Cheng, C., Xu, Q. G., Li, X. Q., & Zochodne, D. W. (2003). μ Opioid receptors and analgesia at the site of a peripheral nerve injury. *Annals of Neurology*, 53(3), 366-375.

Vane, J. R. (1971). Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nature: New Biology*, (231), 232-5.

Vane, J. R., Mitchell, J. A., Appleton, I., Tomlinson, A., Bishop-Bailey, D., Croxtall, J., & Willoughby, D. A. (1994). Inducible isoforms of cyclooxygenase and nitric-oxide synthase in inflammation. *Proceedings of the National Academy of Sciences*, 91(6), 2046-2050.

Vardanyan, A., Wang, R., Vanderah, T. W., Ossipov, M. H., Lai, J., Porreca, F., & King, T. (2009). TRPV1 receptor in expression of opioid-induced hyperalgesia. *The Journal of Pain*, 10(3), 243-252.

Verma, V., Singh, N., & Jaggi, A. S. (2014). Pregabalin in neuropathic pain: evidences and possible mechanisms. *Current Neuropharmacology*, 12(1), 44.

von Hehn, C. A., Baron, R., & Woolf, C. J. (2012). Deconstructing the neuropathic pain phenotype to reveal neural mechanisms. *Neuron*, 73(4), 638-652.

Vranken, J. H., Dijkgraaf, M. G. W., Kruis, M. R., Van Dasselaar, N. T., & Van der Vegt, M. H. (2005). Iontophoretic administration of S (+)-ketamine in patients with intractable central pain: a placebo-controlled trial. *Pain*, 118(1), 224-231.

Vranken, J. H. (2009). Mechanisms and treatment of neuropathic pain. *Central Nervous System Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Central Nervous System Agents)*, 9(1), 71-78.

Vranken, J. H. (2012). Elucidation of pathophysiology and treatment of neuropathic pain. *Central Nervous System Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Central Nervous System Agents)*, 12(4), 304-314.

Walker, K., Reeve, A., Bowes, M., Winter, J., Wotherspoon, G., Davis, A., ... & Urban, L. (2001). mGlu5 receptors and nociceptive function II. mGlu5 receptors functionally expressed on peripheral sensory neurons mediate inflammatory hyperalgesia. *Neuropharmacology*, 40(1), 10-19.

Wallace, J. M. (2002). Nutritional and botanical modulation of the inflammatory cascade—eicosanoids, cyclooxygenases, and lipoxygenases—as an adjunct in cancer therapy. *Integrative Cancer Therapies*, 1(1), 7-37.

Wang, R., King, T., De Felice, M., Guo, W., Ossipov, M. H., & Porreca, F. (2013). Descending facilitation maintains long-term spontaneous neuropathic pain. *The Journal of Pain*, 14(8), 845-853.

Wasner, G., Naleschinski, D., Binder, A., Schattschneider, J., McLachlan, E. M., & Baron, R. (2008). The effect of menthol on cold allodynia in patients with neuropathic pain. *Pain Medicine*, 9(3), 354-358.

Watson, C. P. N., Gilron, I., & Sawynok, J. (2010). A qualitative systematic review of head-to-head randomized controlled trials of oral analgesics in neuropathic pain. P*ain Research & Management: The Journal of the Canadian Pain Society*, 15(3), 147.

Wei, T., Sabsovich, I., Guo, T. Z., Shi, X., Zhao, R., Li, W., ... & Clark, D. J. (2009). Pentoxifylline attenuates nociceptive sensitization and cytokine expression in a tibia fracture rat model of complex regional pain syndrome. *European Journal of Pain*, 13(3), 253-262.

Winkelstein, B. A. (2004). Mechanisms of central sensitization, neuroimmunology & injury biomechanics in persistent pain: implications for musculoskeletal disorders. *Journal of Klectromyography and Kinesiology*, 14(1), 87-93.

Wood, J. N., Abrahamsen, B., Baker, M. D., Boorman, J. D., Donier, E., Drew, L. J., ... & Zhao, J. (2004, August). Ion channel activities implicated in pathological pain. *Novartis Foundation. Symposium* (Vol. 261, pp. 32-40).

Wood, P. B. (2008). Role of central dopamine in pain and analgesia. *Expert Review of Neurotherapeutics*, 8(5), 781-797R

Wood, P. L. (2005). The NMDA receptor complex: a long and winding road to therapeutics. *IDrugs: the Investigational Drugs Journal*, 8(3), 229-235.

Woolf, C. J. (2011). Central sensitization: implications for the diagnosis and treatment of pain. *Pain*, 152(3), S2-S15.

Xia, R., Dekermendjian, K., Lullau, E., & Dekker, N. (2011). TRPV1: a therapy target that attracts the pharmaceutical interests. *Transient Receptor Potential Channels* (pp. 637-665). Springer Netherlands.

Xu, Z. Z., Zhang, L., Liu, T., Park, J. Y., Berta, T., Yang, R., ... & Ji, R. R. (2010). Resolvins RvE1 and RvD1 attenuate inflammatory pain via central and peripheral actions. *Nature Medicine*, 16(5), 592-597.

Yagi, A., Harada, N., Yamada, H., Iwadare, S., & Nishioka, I. (1982). Antibradykinin active material in Aloe saponaria. *Journal of Pharmaceutical Sciences*, 71(10), 1172-1174.

Yan, J., Edelmayer, R. M., Wei, X., De Felice, M., Porreca, F., & Dussor, G. (2011). Dural afferents express acid-sensing ion channels: a role for decreased meningeal pH in migraine headache. *Pain*, 152(1), 106-113.

Yan, J., Wei, X., Bischoff, C., Edelmayer, R. M., & Dussor, G. (2013). pH-Evoked Dural Afferent Signaling Is Mediated by ASIC3 and Is Sensitized by Mast Cell Mediators. *Headache: The Journal of Head and Face Pain*, 53(8), 1250-1261.

Yarnitsky, D., Goor-Aryeh, I., Bajwa, Z. H., Ransil, B. I., Cutrer, F. M., Sottile, A., & Burstein, R. (2003). 2003 Wolff Award: possible parasympathetic contributions to peripheral and central sensitization during migraine. *Headache: The Journal of Head and Face Pain*, 43(7), 704-714.

Yoshimura, M., Furue, H., Nakatsuka, T., Matayoshi, T., & Katafuchi, T. (2004). Functional reorganization of the spinal pain pathways in developmental and pathological conditions. *Pathological Pain: From Molecular to Clinical Aspects*, 148, 116.

Zhang, W., Doherty, M., Leeb, B. F., Alekseeva, L., Arden, N. K., Bijlsma, J. W., ... & Zimmermann-Górska, I. (2007). EULAR evidence based recommendations for the management of hand osteoarthritis: report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Annals of the Rheumatic Diseases*, 66(3), 377-388.

Zeilhofer, H. U., Benke, D., & Yevenes, G. E. (2012). Chronic pain states: pharmacological strategies to restore diminished inhibitory spinal pain control. *Annual Review of Pharmacology and Toxicology,* 52, 111-133.

Zhou, H. Y., Chen, S. R., & Pan, H. L. (2011). Targeting N-methyl-D-aspartate receptors for treatment of neuropathic pain. *Expert Review Clinical Pharmacology,* 4(3): 379-388.

Zhuo, M. (2004, August). Central plasticity in pathological pain. *In Novartis Foundation Symposium,* 261, 132-145.

Zin, M. C. S., Nissen, L. M., Smith, M. T., O'Callaghan, J. P., & Moore, B. J. (2008). An update on the pharmacological management of post-herpetic neuralgia and painful diabetic neuropathy. *CNS Drugs,* 22(5), 417-442.

TRANSDERMAL® THERAPEUTICS

We've Got Pain Covered.

Transdermal Therapeutics, Inc.
211 Summit Parkway, Suite 124
Birmingham, AL 35209

transdermaltherapeutics.com

Physician Prescription Line:
Ph: **1.877.581.5444**
Fax: **1.877.495.5445**