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Topical treatment in pain medicine: from ancient remedies to modern usage

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Abstract:

Over several millennia, substances have been applied to the skin for treatment of pain. Some ingredients are in current use; others have been discontinued. Mechanisms of action include interactions with nociceptive neural networks and inflammatory processes. Substances must penetrate the stratum corneum barrier and vehicles that enhance penetration have been developed. Topical drugs with links to the past include menthol, capsaicin, some opioids, local anaesthetic agents and non-steroidal anti-inflammatory drugs. Mandragora is also described as an example of a herbal remedy that has been discontinued due to its toxicity. The future for topical drugs is promising, with the advent of new drugs tailored for specific pain mechanisms and the development of both penetration enhancers and sterile preparation methods.

Key Words: Topical drugs, mechanisms, stratum corneum, antiquity, vehicles, receptors, current agents

Introduction

Over several millennia, substances have been applied externally for painful conditions but with variable success. In modern times, the mode of action of these ancient remedies has become clearer. Our Neolithic ancestors most probably used herbal remedies but records only appeared with the advent of cuneiform writing on clay tablets by the Sumerians (Third dynasty of Ur, c.3100 BCE)[1, 2], and later by the Egyptians writing on papyrus (Kahun c.1900 BCE and Ebers papyri c.1600 BCE).[3, 4] Pharmacopoeias of "bush medicines", including

analgesic applications may, however, have been in existence for much longer. Indigenous cultures have existed in Australia dating back at least 40,000 years.[5, 6] Recipes were initially passed on by oral tradition [7], but only appeared in the literature in recent times.[8] Similar ancient traditions of topical application for medicinal purposes can be found in Persian, Chinese, Indian, Central and South American cultures.[9] The use of herbal preparations continues to this day [10-12] and it is suggested that approximately 25% of modern medications are developed from plants. More than 85,000 plant species have been documented for medical use globally and many of them used topically.[13] This review will examine a number of substances, often with herbal ancestries, which have been applied topically over the past five thousand years. Some of these substances are still in use for the treatment of pain. Others, such as the topical application of Sciatica Cresses, listed in Culpepper's Herbal for the treatment of sciatica, are confined to history and, thankfully, are no longer in use.

"The leaves but especially the root, taken fresh in summer time, beaten or made into a poultice or salve with old hog's grease, and applied to the places pained with the sciatica, to continue thereon four hours if it be on a man, and two hours on a woman; the place afterwards bathed with wine and oil mixed together, and then wrapped with wool or skins, after they have sweat a little will assuredly cure not only the same disease in hips, huckle-bone, or other of the joints, as gout in the hands or feet, but all other old griefs of the head, (as inveterate rheums) and other parts of the body that are hard to be cured. And if of the former griefs any parts remain, the same medicine after twenty days, is to be applied again." [14]

Mechanisms for Topical Analgesia

Anatomy of nociception: A dense network of nerve fibres that runs along the dermal-epidermal junction, supplies strands that project through the epidermis almost to the skin surface. These nerve fibres are ideally positioned to detect potential sources of injury to the skin. When activated, they signal pain – often described as a sharp stabbing sensation or a burning ache. They also coordinate an inflammatory response, initiated by release of vasoactive neuropeptides from the nerve terminals in the skin. Below we describe effects of the local

environment on nociceptive signalling, both under normal conditions and in inflammatory states and neuropathic pain. We also suggest possible mechanisms of analgesia for topically applied drugs.

Illustration: Normal Human Skin

<u>Propagation of nociception</u>: Nociceptive sensations are detected by slowly-conducting unmyelinated C-fibres and faster-conducting myelinated A-fibres, ranging in size from thinly myelinated A-delta fibres through to thicker, more heavily myelinated A-beta fibres.[15] The faster-conducting A-fibres lose their myelin sheath in the dermis, terminating as free nerve endings.[16] These nerve endings are exquisitely sensitive to chemical and thermal disturbances in the surrounding extracellular fluid. The subsequent propagation of neural impulses involves sequential opening of voltage-gated ion channels that permit passage of sodium, potassium, chloride and calcium through the neural membrane. In addition, many other ligand-gated channels regulate neural excitability (such as acid-sensing ion channels, transient receptor potential channels, and hyperpolarization-activated cyclic nucleotide-gated channels).[17] These mechanisms make neurons particularly sensitive to minor perturbations in their local environment and also provide many targets for topical drug manipulation.

<u>The inflammatory milieu</u>: After injury to the skin, sensory transduction and signalling is modulated by a plethora of receptors that respond to substances released from the bloodstream, from injured tissue, from resident cells such as fibroblasts, keratinocytes, Langerhans cells and mast cells, and from immune cells recruited to the site of injury. Together, these substances produce a milieu containing, among other ingredients, hydrogen ions, prostaglandins, cytokines, growth factors, noradrenaline, glutamate, bradykinin, serotonin, histamine and adenosine.[18] This inflammatory *milieu* can both directly activate and sensitize nerve endings to stimulation by acting on ion channels (for example hydrogen ions that operate on acid-sensing ion channels) or by altering second-messenger systems (by acting on G-protein-coupled metabotropic receptors) such as α-adrenoceptors). Externally applied topical drugs that modify this *milieu* or its targets can therefore act directly to reduce pain and inflammation.

Signal transduction: Sensory afferents interact with cutaneous cells that not only provide physical and trophic support but also contribute to signal transduction. For example, keratinocytes produce many of the receptors and transmitters expressed by neurons and, by this means, can communicate with neurons in a paracrine manner.[19, 20] This is important after nerve and tissue injury. For example, after limb fracture, neuropeptides and noradrenaline released from nerve terminals in the skin activate receptors on the surface of keratinocytes which, in turn, secrete high levels of inflammatory cytokines and nerve growth factor.[21, 22] These agents degranulate mast cells and sensitize cutaneous nociceptive neurons, thereby contributing to pain.[23] Topical drugs that penetrate the stratum corneum can act directly on this keratinocyte layer, possibly modifying its function.

Receptor targets for analgesia: Some of the excitatory receptors expressed on peripheral nerve fibres provide useful targets for analgesia. For example, the capsaicin receptor (vanilloid receptor 1) is a member of the transient receptor potential (TRP) family of receptors and is expressed on polymodal nociceptors.[24] Occupancy of this receptor or activation by heat or hydrogen ions, triggers sodium and calcium ion influx, generates action potentials and results in burning pain. Excessive influx of calcium ions can, however, evoke desensitization, which potentially is useful in pain management. Another TRP receptor, TRPM8 (the menthol receptor), is expressed both on cold-specific A-delta fibres and on cold-sensitive nociceptors.[25, 26] Low concentrations of menthol appear to primarily activate cold-specific fibres whereas higher concentrations activate nociceptors as well.[27] Like the capsaicin receptor, excessive influx of calcium ions into these cold-sensitive nociceptors is associated with desensitization and analgesia.[28]

Although many receptors exert excitatory effects on neural activity, others inhibit neural excitability and discharge (for example, μ-opioid receptors).[29] Under normal conditions, the opioid receptors are separated from agents in the extracellular fluid by the perineurium, an impermeable sheath with tight cellular junctions that enclose bundles of nerve fibres. This sheath, however, becomes

porous during inflammation, thereby increasing access to protected receptors for endogenous and topically applied opioids.[30]

The effects of chronic inflammation: The receptor and ion-channel profile alters dramatically during chronic inflammation and on nerve fibres that survive peripheral nerve injury. For example, inflammation triggers an increase in expression of glutamate receptors on nociceptive fibres [31, 32], thereby providing a target for ketamine, a glutamate (N-methyl-D-aspartate: NMDA) receptor antagonist. Similarly, an up-regulation of purinergic (P2X$_3$) receptors after peripheral nerve injury profoundly influences neural excitability [33], in part via interaction with α_1-adrenoceptors.[34, 35] An increase in the expression of α_1-adrenoceptors on nerve fibres that survive partial nerve injury may also contribute to sympathetically maintained pain.[36, 37]

Ion channels as further targets for analgesia: Changes in the function or expression of ion channels in inflammatory and neuropathic pain conditions may also mediate pain. For example, an up-regulation of Na$_V$1.7 channels during inflammation and in rare hereditary pain disorders increases nociceptor excitability and impulse generation.[17] Local anaesthetic agents such as lidocaine inhibit pain and hyperalgesia partly by acting in a non-selective manner on voltage-gated sodium channels, including Na$_V$1.7.[38, 39]

Penetrating the Stratum Corneum

The stratum corneum, the outermost layer of the skin, provides a barrier to noxious chemicals, potential infective agents, physical insults and solar radiation from the outside world that is protective for the organism. The layer protects against water loss but also presents a physical barrier to the ingress of topical and transdermal drugs. The stratum consists of multiple layers of dead hydrated corneocytes arranged in interdigitating layers that are surrounded by a lipid matrix comprising approximately 20% by volume.[40] The microanatomy has been described as a "brick-and-mortar" structure.[41, 42] Illustration

It is not a perfectly uniform surface, varying in thickness at different parts of the body with the thickest layer on the soles of the feet. It is also perforated by hair follicles and sweat glands that can passively assist in the ingress of drugs from

the exterior. The skin is a complex structure as unwanted influences that cannot be physically kept on the exterior are subsequently neutralised and attacked by the immune system or degraded by enzymatic reactions.[40]

Various techniques are employed to improve the penetration of drugs through the outer layers of the skin. These include physical formulation and delivery methods. Physical methods include low frequency ultrasound, which disturbs the lipid matrix, radiofrequency energy formation of microchannels or electrophoretic assisted penetration. Even removal of the outer horny layer can be employed using chemical peels and dermabrasion.[43] Formulation techniques are the most commonly applied methods for enhanced penetration of drugs. The barrier to the ingress of drugs is reversibly reduced by agents, such as the lipid disrupting aprotic solvent dimethylsulphoxide (DMSO) [44] and the liposome, pleuronic lecithin organogel (PLO).[45, 46] Liposomes have been extensively studied since their discovery in the 1960s.[47] They comprise a lipid bilayer with the hydrophobic chains of the lipids forming the bilayer and the polar head groups of the lipids orientated towards the extra vesicular solution and the inner cavity.[48] Liposomes help localise topical drugs at their desired site of action or improve the penetration of transdermal drugs into the systemic circulation without causing skin irritation or harm.[49-52] Other proprietary liposomal preparations include Lipoderm® and Vanpen® that have the capacity to deliver multiple drug combinations through the skin.[53-55]

Despite the apparent harmless nature of topical applications, contact dermatitis can occur after the application of topical drugs or their vehicle components.[56] There can be irritant and allergic contact dermatitis or contact urticarial. Patch testing is used to ascertain the culprit allergen.[57]

At this point, the distinction between *topical* and *transdermal* should be emphasised. There are several effective *transdermal* preparations such as transdermal fentanyl and buprenorphine, whereby the active ingredient gains access to the systemic circulation but by the transdermal route. *Topical* applications, however, such as the application of a lidocaine patch for post herpetic neuralgia, reduce nociception by local skin mechanisms but achieve minimal systemic levels. Although neuropathic pain states can be improved by

achieving systemic levels of lidocaine, this is not the main aim of this topical application.

Historical Use of Topical Drugs

There have been a number of reviews of the use of topical agents, in particular in the management of neuropathic pain.[58-62] The size of this review precludes an exhaustive coverage of this topic. The reviews by Zur, Sawynok, Argoff and others [58-62] take a wider view of current topical agents than is possible in this paper. This review has included topical agents with historical links and current agents with a significant background literature. A few substances have ancient traditions and some of particular interest have been selected for discussion. Some agents have been employed over many centuries but have disappeared from clinical use, while others such as amitriptyline, clonidine and ketamine are the creation of modern times.

<u>Menthol</u>: The use of menthol stretches back into antiquity. It is a naturally occurring plant extract from several members of the plant genus *Mentha (Mint)* [63] but has been chemically synthesised in modern times. Menthol features in the Ebers papyrus (1550 BCE) as a remedy for stomach ailments [4] and there are claims of its cultivation for medicinal use in Japan over 2000 years ago.[63] Known in ancient Greece, the herb is named after the mythical beauty Minthe. The pungent sweet smelling mint was used in hospitality such as the fermented barley drink called the kykeon and in funerary rites.[64] Menthol is also included amongst a number of valuable herbs in the biblical indictment of the Pharisees (Luke 11:42). Peppermint appears in the London Pharmacopoeia in 1721 and menthol, the active ingredient, was first isolated as a compound by the Dutch botanist Gambius in 1771.[65]

Menthol (also known as mint camphor) is experiencing a renaissance as a topical analgesic agent. As well as providing a subjective cooling effect, it acts as a weak opioid agonist and weak sodium channel blocker.[66, 67] It is used in dermatology as an antipruritic agent, as a food additive in chewing gum and to flavour toothpaste and cigarette smoke. Menthol is a cyclic terpene alcohol acting on the transient receptor potential melastatin 8 receptor (TRPM8), a low

temperature sensing receptor in the skin and mucosa, (8-28°C) [68, 69] where it imparts a cool sensation. Capsaicin, in contradistinction, was the first of the transient receptor potential family to be identified. Menthol has several desirable qualities as well as its actions as a topical antipruritic agent, including antibacterial and antifungal activity.[70] It has been shown to enhance penetration of the stratum corneum in both animal and human models [71] possibly through disruption of the lipid layer of the stratum corneum.[72] Topical menthol has analgesic actions that make it a beneficial inclusion in over-the-counter pain relief applications. In low concentrations (<1%) menthol depresses cutaneous nociception and perhaps even desensitises nociceptive C fibres.[73] In high concentrations (>30% menthol can act as an irritant.[74, 75] As menthol acts on voltage-gated channels in neuronal structures, it also has a weak local anaesthetic effect.[76, 77] There are many possible uses for this topical agent, discussed in depth elsewhere.[78-81] Other substance acting on TRPM8 receptors include eucalyptol and the potent synthetic Icilin.[82]

Capsaicinoids: Capsaicin is the principal active component in hot chilli peppers of the plant genus *Capsicum*, which have their origin in the Americas. Chilli peppers were probably cultivated as a dietary condiment dating back over 6000 years.[83] Limited Mayan hieroglyphs (The Maya, circa 750BCE -1524 CE) have survived and have proved difficult to decipher as much written material was burnt in 1562. It is unknown if written descriptions of the medicinal use of chilli peppers exist from this period. Later, Aztec physicians in Central America may have used chilli pepper to treat painful conditions such as toothache.[84] Chilli pepper was probably transported to the Old World by Columbus and thence to Asia by Portuguese navigators in the 16th century.

Other capsaicinoids known to antiquity include euphorbium whose active ingredient is the potent capsaicinoid resinifratoxin, extracted from the latex of *Euphorbia resinifera*.[85] The physician Euphorbius may have used resinifratoxin-containing salves to treat the arthritic pains of the Emperor Augustus 63 BCE -14 CE, but it was probably in use well before this time.[85] Previously used as an emetic and violent purgative, euphorbium has been employed as a rubefacient for painful joints.[86, 87] It was listed in 1578 for

treating toothache and more recently for intractable bone pain.[86] Topical plant extracts containing capsaicinoids such as *Bhut jolokia*, indigenous to Northeast India, are still in use to treat arthritic pains.[87] Bhut jolokia is recorded as being 900.5 times as hot as Tabasco sauce.[88] One wonders what effect such a powerful capsaicinoid would have on the gastro-intestinal tract, if ingested. Capsaicin activates the transient receptor potential vanilloid receptor (TRPV1), an excitatory ion channel which is also activated by higher temperatures >43°C and is sensed as being hot.[24] Capsaicin has been extensively studied as a topical agent for the past three decades. As a low concentration, 0.025-0.075%, over-the-counter preparation (Zostrix), capsaicin has been prescribed for a number of conditions including post herpetic neuralgia. More recently it has also been marketed as an 8% patch (Qutenza) with effects lasting many weeks.[89] As a TRPV1 agonist, capsaicin induces a refractory period in nerve terminals expressing TRPV1 and in higher concentrations causes long term neuronal "defunctionalisation".[90, 91] A single application of capsaicin 8% to the skin can diminish skin hypersensitivity in neuropathic pain states for periods as long as three months, reducing the issue of poor patient compliance with the weaker preparations that require multiple applications.[89, 92] The application of the 8% patch can be intensely painful and is often applied under local anaesthesia. Targeting TRP channels on nociceptor neurons in the skin is an attractive strategy for pain control as it can modify the peripheral pain pathway.[93] The use of capsaicin preparations as a topical application for neuropathic pain states such as post herpetic neuralgia has been the subject of several Cochrane reviews of the supporting evidence. The author's concluded that repeated application of low dose (0.075%) capsaicin was without meaningful effect beyond placebo and that prior studies had not convincingly demonstrated efficacy. The use of low dose topical capsaicin commonly caused skin irritation leading to withdrawal.[94] The use of high dose capsaicin for neuropathic pain states including post herpetic neuralgia and HIV-neuropathy provided good relief of pain for about one patient in eight (NNT=8.8). It was also concluded that high dose capsaicin was probably less effective than gabapentin or pregabalin.[95]

Opioids: Opium obtained from *Papaver somniferum* was well known to the ancients and most probably was cultivated by the Sumerians (c. 3000 BCE) [96] and ancient Egyptians. Of particular historical interest is the use of transdermal patches of opioid in ancient Greece. Olympic victor's dark ointment (OVDO) mentioned by Galen (c. 129-200 CE), was an opium-based patch that was applied to the skin of athletes. It dried rapidly to cover a localised area and recent measurements of the transdermal transfer of morphine indicate a transfer comparable to 25% of modern transdermal patches.[97, 98] It may have, therefore, acted both systemically to reduce pain and by local effects, acting on inflammatory mechanisms. The Latin description for its use by Galen of Pergamum (130-200 CE) and its English translation states:

Facit ad maximos Dolores - useful for extreme pain

Nam ftatim liberat - providing relief immediately.[97]

Perhaps this was an early indicator for a more recent and disgraceful practice in sport.

The modern contemporary use of opioids as topical agents is somewhat marginal and is mainly confined to the management of skin and corneal ulceration, having some local anti-inflammatory actions.[99, 100] The increased expression of opioid receptors on nociceptors in inflammatory pain states provides a logical target for topically applied opioids. There are indications that topically applied opioids can ameliorate the pain of skin ulcers and post radiation mucositis [99, 101-103], but the numbers in various clinical trials have been low and further evidence is needed. Their usage is perhaps best seen in the palliative care field where they can relieve inflammatory pain without significant systemic side effects.[99] Topically applied morphine can be applied in gels and oral rinses prepared by pharmacies over a range from 0.1-2% concentration.[104, 105] Other opioids employed in topical applications include methadone [106], fentanyl [100], and oxycodone.[107]

Mandragora: Employed as a topical analgesic agent and central sedative that is no longer used due to its toxic effects, mandragora (mandrake) has an ancient and fascinating history. *Mandragora officinarum* is native to the eastern Mediterranean and contains the active ingredients scopolamine and

atropine.[108] It has even been termed the "Anesthetic of the Ancients".[109] It is mentioned in the Ebers papyrus as a sedative [4] and features in several hieroglyphic inscriptions.[109] Hannibal (247-182 BCE) used it to drug his opponents during the Battle of Carthage (200BCE).[110] Mentioned in the Bible, Genesis 30:14-24, mandrake subsequently achieved a reputation amongst medieval Christians for enhancing fertility. It was advocated in the writings of Flavius Josephus (c. 37-101) that a dog be employed to pull out the root, thus avoiding any lethal effects on humans from hearing the scream of the mandrake plant as it was pulled from the ground.[110] Mandrake also had demonic associations and was even used in the indictment of Joan of Arc in 1431 CE.[111] The use of mandrake most probably produced sufficient topical analgesia and sedation for the physician Hua Tuo (110-207 CE) to debride an arrow wound in General Guan Yu after the battle of Fan city but allowing him to continue playing chess, talk and laugh as if nothing had happened.[4] More recently, it featured in several of Shakespeare's works, such as *Cleopatra,* act 1, scene v: *"Give me to drink Mandragora-that I might sleep out this great gap of time. My Antony is away."* Mandragora was mixed with plant extracts such as opium and henbane (*Hyoscyamus niger,* another tropane alkaloid which can also be applied topically for "obstinate rheumatic pains"), to produce sedation for surgical procedures. It was evaporated into a sea sponge and the preparation known as *Spongia somnifera* was employed extensively until its use faded with the advent of general anaesthesia in the nineteen century CE.[109, 112] The potency and toxicity of this plant extract varied considerably depending on its mode of extraction. With no attempt at purification or precise dosing, *Spongia somnifera* could cause death from respiratory and circulatory depression.[113]

Cocaine: Topical local anaesthetic agents currently play a significant part in treating some neuropathic pain conditions. Cocaine derived from coca leaves, *Erythroxylum coca* was first used as a topical local anaesthetic agent on the cornea of a frog and then a human by Karl Koller in 1884, after discussions with his friend Sigmund Freud, who was interested in cocaine for its effects on his patient's mood.[114] The origins of coca are ancient, however, dating back to the pre-Moche period (100-750 CE) in Peru and the Eastern Andes. The coca leaf

was chewed or used to make tea to combat fatigue and altitude sickness. Traces of coca have been found in mummified human cadavers dating back 3000 years [115] and probably millennia before this. The French naturalist Joseph de Jussieu (1704-1779) introduced coca leaf into Europe, and cocaine was isolated from the mix of alkaloids from the coca plant by Gaedecke in 1855 who called it Erythroxyline and subsequently extracted and purified by Niemann in 1860. It became popular as a stimulant in the 19th century CE and was even included as an ingredient in early formulations of Coca-Cola until 1903 when it was withdrawn.[116] Cocaine's addictive qualities were recognised in the nineteenth century and it became a widely prohibited substance in the early 20th century CE. The use of unprocessed coca leaves is still lawful in some South American countries.

Local anaesthetic agents have become one of the mainstays of modern surgery. Topical local anaesthetic agents are also finding a place in the management of some pain states, in particular neuropathic pain. The use of a 5% lidocaine patch to treat neuropathic pain states, especially post herpetic neuralgia, has received particular attention and is the subject of several reviews.[117-119] The use of a lidocaine patch has also been the subject of a 2008 Cochrane review, which concluded that three studies into its efficacy had sufficient scientific rigour to be included but provided insufficient evidence to support its use as a first-line treatment of post herpetic neuralgia.[120] More recent reviews would suggest otherwise. For example, a review by Wolff et al. concluded that a 5% lidocaine topical patch is more effective than capsaicin and pregabalin.[119] Lidocaine has also been used as a topical spray for dressing changes, for pain associated with peripheral blood flow disorders, and post herpetic neuralgia.[121-123] Safety issues have been considered in a 2002 pharmacokinetic study that considered the 5% lidocaine patch to be safe, only causing mild skin erythema and low plasma lidocaine levels [124], but a single case report has concluded that lidocaine toxicity is possible when multiple forms of topical application are used.[125]

Topical non-steroidal anti-inflammatory drugs (NSAIDs): Extracts from willow trees and other salicylate containing plants also have their origins in

antiquity, possibly dating back to the Sumerians and ancient Egyptians in the treatment of fevers. The active ingredient, acetylsalicylic acid (aspirin) was synthesised by the Bayer Company in 1897.[126] Salicylates are largely administered orally but there has been some topical use of aspirin containing solutions of chloroform or ether in the treatment of post herpetic neuralgia.[127] Modern NSAID use commenced with the introduction of indomethacin in 1962.[128] Significant gastrointestinal adverse effects from the oral formulations of NSAIDs have been encountered and in an effort to reduce these effects, various topical preparations of NSAIDs have been developed. In a recent comprehensive review of these topical preparations, it was concluded that topical NSAIDs were superior to placebo and had similar outcomes to oral NSAIDs in the treatment of both acute and chronic musculoskeletal injuries.[129] Gastrointestinal side effects were less with the topical group but minor skin reactions were more frequent. Several formulations, discussion concerning penetration enhancers and guidelines for use have been published regarding this group of topical agents.[126, 130-132] Topical versus oral NSAIDs can be particularly advantageous in the elderly and have been recommended as a first-line treatment for osteoarthritis in this age group.[133]

Topical Agents of the Modern Era: amitriptyline, **clonidine and ketamine:** **Amitriptyline**, a tricyclic antidepressant, has a number of actions including its ability to inhibit the reuptake of noradrenaline and serotonin. It has been shown to block various voltage gated ion channels including Na^+, K^+ and Ca^{++} [134,135] and several receptors including α_2 adrenoceptor, cholinergic, NMDA and histamine [134-136] pointing to a use as a topical agent with peripheral nerve fibre effects.[137] Although not effective in every trial [138], amitriptyline at concentrations between 2-10%, along with some other antidepressant agents has been successfully used as a topical agent in a number of neuropathic pain states including complex regional pain syndrome (CRPS), multiple sclerosis and vulvodynia.[139-141] Amitriptyline has been employed as a sole agent or in combination with other topical agents such as ketamine and baclofen.[142-147] Although the topical application of antidepressant drugs can reduce their

unwanted central side effects, this form of administration can occasionally lead to adverse toxicity.[148]

Clonidine is an α2-adrenergic receptor agonist used in the treatment of hypertension. Side effects that include somnolence and hypotension have limited its use in treating neuropathic pain states. It has, however, been found to be antinociceptive if applied to the skin and successfully used in the reduction of hyperalgesia in patients with sympathetically maintained pain [149] and painful diabetic neuropathy.[150] Blood levels of clonidine in this later RCT were below the level of detection suggesting that the effects of this topical agent were peripherally mediated and probably a direct effect on epidermal nociceptors. Typically, it is applied as a patch ($30 mcg/cm^2/day$) or as a 0.1-0.2% solution.

Ketamine, which blocks glutamate *N*-methy*l*-$_D$-aspartate (NMDA) receptors on peripheral nerve fibres, can reduce nociceptive transmission.[151] It has been studied as a topical analgesic agent and has been the subject of many trials, case reports and reviews.[152-154] It can be used as a gel or cream with relative safety and apparent efficacy mainly for localised neuropathic pain states at concentrations up to 20%.[153] There have also been a number of reports of its use in combination with other agents such as amitriptyline, baclofen and gabapentin but with mixed results.[141, 142, 147] Long-term effects on the urinary tract [155] may be circumvented by the use of topically applied ketamine, which results in low plasma levels of the drug.[156] Nevertheless, as with some other topical drugs, inappropriate or excessive use can lead to significant toxicity.[157]

Combinations of drugs for topical application can be used for treatment of some pain states -for example: ketamine 10% with amitriptyline 4% in Vanpen® penetrant for post herpetic neuralgia or amitriptyline 2-4% combined with gabapentin 6-10% with oestradiol 0.01% for vulvodynia are used in clinical practice but the rationale for the selection of agents, their percentage composition and the vehicle used is not clear. A recent review by Zur 2014 considers such mixtures in depth.[62] Such tailored recipes are controversial and can attract the criticism of being entrepreneurial.

Conclusion and Future Perspectives

A number of substances have been applied to the skin and mucosa for painful conditions over thousands of years but without any understanding of their pharmacological actions. The inevitable toxic effects of some substances have led to their withdrawal from use. Others seen to have beneficial effects continue to be applied to this day, but with considerable refinement in their use and understanding of the mechanisms involved. As the knowledge of peripheral pain pathways has increased, so has the tailoring of drugs to act on these mechanisms of nociception. After penetration of the skin they are able to act directly on the initiating factors that lead to pain. Most advantageously, the use of topical drugs has reduced the adverse effects of many of these agents that are also administered systemically. This can be of great benefit to the frail and elderly. The future for the topical application of drugs is bright. In addition to improved targeting of specific pain mechanisms with new drugs or different formulations of existing ones, enhanced penetration agents will improve delivery of these agents. "Topicals" prepared in laminar flow facilities will allow application to areas of broken skin or mucosa without encouraging infection. Alternative routes for topical applications of drugs will be developed including the rectal mucosa, vulva and the oropharynx. Lastly, as best practice for topical drug application becomes clearer from a pharmacological perspective, so will the selection of suitable patients and pain states that are likely to respond.

Executive Summary:
- The topical application of drugs that act locally in the skin provides an attractive strategy for treating pain, reducing the potential systemic side effects of oral or parenteral administration.
- Some agents used since antiquity have been discontinued but others are used to this day.
- Mechanisms of action include effects on skin neural networks and inflammatory processes.
- The stratum corneum layer of the skin presents a significant barrier to the absorption of drugs. Penetration enhancers have evolved that improve this absorption.

- Menthol, used in ancient Egypt, is experiencing a renaissance. Acting on the TRPM8 receptor, it imparts a cool sensation to the skin and mucosa.

- Capsaicin, acting on the TRPV1 receptor, also has an ancient lineage being derived from chilli peppers. It imparts a sensation of heat to the skin and mucosa.

- Opioids, described for topical use for athletes in ancient Greece, have more recently been employed in the treatment of painful skin and corneal ulceration.

- Mandragora (Mandrake) is a topical plant extract with a long history of use that has been discontinued due to its unpredictable toxicity.

- Local anesthetic agents discovered in the nineteenth century, have their origin in cocaine from the Americas. The 5% lidocaine patch has some utility in treating neuropathic pain states such as post herpetic neuralgia.

- The use of topical NSAIDS follows in the footsteps of the application salicylate containing plants by ancient Sumerians and Egyptians. Topically applied NSAIDs show efficacy in the treatment of painful musculoskeletal structures comparable to oral ingestion but without the gastro-intestinal side effects.

- Topical amitriptyline, clonidine and ketamine are examples of modern topical agents, employed principally for neuropathic pain, that are supported by a significant literature.

- The future for topical drugs is encouraging, as the mechanisms of pain have become better understood. The development of new topical preparations, penetration enhancers and sterile techniques of preparation have all contributed to this expanding field.

References:

1. Magner LN: A history of medicine. Marcel Dekker, New York. (1992).
2. Porter R: The greatest benefit to mankind: A medical history of humanity from antiquity to the present. Fontana, London. (1999).
3. Aboelsoud NH: Herbal medicine in ancient Egypt. *J Med Plant Res.* 4(2), 082-086 (2010).
4. Majno G: The healing hand: man and wound in the ancient world. Harvard University Press, Cambridge, MA. (1975).
5. Barr A, Et Al: Traditional bush medicines: An aboriginal pharmacopoeia. Greenhouse Publications, Melbourne. (1988).

6. Pickrell J: Messages from Mungo. *Aust Geographic.* 123(Nov-Dec), 50-63 (2014).

7. Augustine SJ: *Oral histories and oral traditions.* In: *Aboriginal oral traditions: theory, practice, ethics*, Hulan R, Elgenbrod R (Eds.). Fernwood, Black Point, NSW 2-3 (2008).

8. Mills C, Carroll AR, Quinn RJ: Acutangulosides A-F, monodesmosidic saponins from the bark of Barringtonia acutangula. *J Nat Prod.* 68(3), 311-318 (2005).

9. Hamedi A, Zarshenas MM, Sohrabpour M, Zargaran A: Herbal medicinal oils in traditional Persian medicine. *Pharm Biol.* 51(9), 1208-1218 (2013).

10. Chen W, Luo YF, Liu JP: Topical herbal medicine for treatment of diabetic peripheral neuropathy: a systematic review of randomized controlled trials. *Forsch Komplementmed.* 18(3), 134-145 (2011).

11. De Silva V, El-Metwally A, Ernst E, Lewith G, Macfarlane GJ, Arthritis Research Uk Working Group on Complementary and Alternative Medicines: Evidence for the efficacy of complementary and alternative medicines in the management of osteoarthritis: a systematic review. *Rheumatology (Oxford).* 50(5), 11-20 (2011).

12. Gagnier JJ, Van Tulder MW, Berman B, Bombardier C: Herbal medicine for low back pain: a Cochrane review. *Spine.* 32(1), 82-92 (2007).

13. Liu Y, Wang MW: Botanical drugs: challenges and opportunities: contribution to Linnaeus Memorial Symposium 2007. *Life Sci.* 82(9-10), 445-449 (2008).

14. Culpepper N: Culpepper's herbal. J. Nicholson, Halifax, UK. (1824).

15. Djouhri L, Lawson SN: Abeta-fiber nociceptive primary afferent neurons: a review of incidence and properties in relation to other afferent A-fiber neurons in mammals. *Brain Res Brain Res Rev.* 46(2), 131-145 (2004).

16. Provitera V NM, Pagano a, Caporaso G, Stancanelli a, Santoro L.: Myelinated nerve endings in human skin. *Muscle Nerve.* 35(6), 767-775 (2007).

17. Waxman SG, Zamponi GW: Regulating excitability of peripheral afferents: emerging ion channel targets. *Nat Neurosci.* 17(2), 153-163 (2014).

18. Kessler W, Kirchhoff C, Reeh PW, Handwerker HO: Excitation of cutaneous afferent nerve endings in vitro by a combination of inflammatory mediators and conditioning effect of substance P. *Exp Brain Res.* 91(3), 467-476 (1992).

19. Boulais N, Misery L: The epidermis: a sensory tissue. *Eur J Dermatol.* 18(2), 119-127 (2008).

20. Lumpkin EA, Caterina MJ: Mechanisms of sensory transduction in the skin. *Nature.* 445(7130), 858-865 (2007).

21. Li W, Shi X, Wang L *et al.*: Epidermal adrenergic signaling contributes to inflammation and pain sensitization in a rat model of complex regional pain syndrome. *Pain.* 154(8), 1224-1236 (2013).

22. Li WW, Guo TZ, Li XQ, Kingery WS, Clark JD: Fracture induces keratinocyte activation, proliferation, and expression of pro-nociceptive inflammatory mediators. *Pain.* 151(3), 843-852 (2010).

23. Birklein F, Drummond PD, Li W *et al.*: Activation of cutaneous immune responses in complex regional pain syndrome. *J Pain.* 15(5), 485-495 (2015).

24. Premkumar LS, Abooj M: TRP channels and analgesia. *Life Sci.* 92(8-9), 415-424 (2013).
25. Takashima Y, Daniels RL, Knowlton W, Teng J, Liman ER, Mckemy DD: Diversity in the neural circuitry of cold sensing revealed by genetic axonal labeling of transient receptor potential melastatin 8 neurons. *J Neurosci.* 27(51), 14147-14157 (2007).
26. Wasner G, Schattschneider J, Binder A, Baron R: Topical menthol: a human model for cold pain by activation and sensitization of C nociceptors. *Brain.* 127(Pt 5), 1159-1171 (2004).
27. Proudfoot CJ, Garry EM, Cottrell DF *et al.*: Analgesia mediated by the TRPM8 cold receptor in chronic neuropathic pain. *Curr Biol.* 16(16), 1591-1605 (2006).
28. Abe J, Hosokawa H, Sawada Y, Matsumura K, Kobayashi S: Ca2+-dependent PKC activation mediates menthol-induced desensitization of transient receptor potential M8. *Neurosci Lett.* 397(1-2), 140-144 (2006).
29. Coggeshall RE, Zhou S, Carlton SM: Opioid receptors on peripheral sensory axons. *Brain Res.* 764(1-2), 126-132 (1997).
30. Antonijevic I, Mousa SA, Schäfer M, Stein C: Perineurial defect and peripheral opioid analgesia in inflammation. *J Neurosci.* 15(1 Pt 1), 165-172 (1995).
31. Carlton SM, Coggeshall RE: Inflammation-induced changes in peripheral glutamate receptor populations. *Brain Res.* 820(1-2), 63-70 (1999).
32. Du J, Zhou S, Coggeshall RE, Carlton SM: N-methyl-D-aspartate-induced excitation and sensitization of normal and inflamed nociceptors. *Neuroscience.* 118(2), 547-562 (2003).
33. Tsuzuki K, Kondo E, Fukuoka T *et al.*: Differential regulation of P2X(3) mRNA expression by peripheral nerve injury in intact and injured neurons in the rat sensory ganglia. *Pain.* 91(3), 351-360 (2001).
34. Maruo K, Yamamoto H, Yamamoto S *et al.*: Modulation of P2X receptors via adrenergic pathways in rat dorsal root ganglion neurons after sciatic nerve injury. *Pain.* 120(1-2), 106-112 (2006).
35. Meisner JG, Waldron JB, Sawynok J: Alpha1-adrenergic receptors augment P2X3 receptor-mediated nociceptive responses in the uninjured state. *J Pain.* 8(7), 556-562 (2007).
36. Drummond ES, Dawson LF, Finch PM, Bennett GJ, Drummond PD: Increased expression of cutaneous alpha1-adrenoceptors after chronic constriction injury in rats. *J Pain.* 15(2), 188-196 (2014).
37. Drummond PD, Drummond ES, Dawson LF *et al.*: Upregulation of α1-adrenoceptors on cutaneous nerve fibres after partial sciatic nerve ligation and in complex regional pain syndrome type II. *Pain.* 155(3), 606-616 (2014).
38. Liu M, Wood JN: The roles of sodium channels in nociception: implications for mechanisms of neuropathic pain. *Pain Med.* 12(Suppl 3), S93-S99 (2011).
39. Sheets PL, Jarecki BW, Cummins TR: Lidocaine reduces the transition to slow inactivation in Na(v)1.7 voltage-gated sodium channels. *Br J Pharmacol.* 164(2b), 19-30 (2011).
40. Baroli B: Penetration of nanoparticles and nanomaterials in the skin: fiction or reality? *J Pharm Sci.* 99(1), 21-50 (2010).

41. Elias PM: Epidermal lipids, barrier function, and desquamation. *J Invest Dermatol.* 80(1 Suppl), 44s-49s (1983).
42. Nemes Z, Steinert PM: Bricks and mortar of the epidermal barrier. *Exp Mol Med.* 31(1), 5-19 (1999).
43. Barry BW: Breaching the skin's barrier to drugs. *Nat Biotechnol.* 22(2), 165-167 (2004).
44. Loudon GM: Organic chemistry. (4th). Oxford University Press, New York. 317 (2002).
45. Jones M: The history of pluronic lecithin organogel: an interview with Marty Jones. *Int J Pharm Compd.* 7(3), 130-131 (2003).
46. Willimann H, Walde P, Luisi PL, Gazzaniga A, Stroppolo F: Lecithin organogel as matrix for transdermal transport of drugs. *J Pharm Sci.* 81(9), 871-874 (1992).
47. Bangham AD, Horne RW: Negative staining of phospholipids and their structural modification by surface-active agents as observed in the electron microscope. *J Mol Biol.* 8(5), 660-668 (1964).
48. Schmid MH, Kortin HC: Therapeutic progress with topical liposome drugs for skin disease. *Adv Drug Deliv Rev.* 18(3), 335-342 (1996).
49. Dreher F, Walde P, Luisi PL, Eisner P: Human skin irritation studies of a lecithin microemulsion gel and of lecithin liposomes. *Skin Pharmacol.* 9(2), 124-129 (1996).
50. El Maghraby GM, Barry BW, Williams AC: Liposomes and skin: from drug delivery to model membranes. *Eur J Pharm Sci.* 34(4-5), 203-222 (2008).
51. Jayachandra Babu R, Ravis WR, Duran SH *et al.*: Enhancement of transdermal delivery of phenylbutazone from liposomal gel formulations through deer skin. *J Vet Pharmacol Ther.* 32(4), 388-392 (2009).
52. Trommer H, Neubert RH: Overcoming the stratum corneum: the modulation of skin penetration: a review. *Skin Pharmacol Physiol.* 19(2), 106-121 (2006).
53. Anitescu M, Benzon HT, Argoff CE: Advances in topical analgesics. *Curr Opin Anaesthesiol.* 26(5), 555-561 (2013).
54. Bassani AS, Banov D, Klehman PA: Evaluation of the percutaneous absorption of promethazine hydrochloride, in vitro, using the human ex vivo skin model. *Int J Pharm Compd.* 12(3), 270-273 (2008).
55. Holt M: Evaluation of the in vitro human trunk skin percutaneous absorption of ketamine HCl, gabapentin, clonidine HCl and baclofen using the Franz skin finite dose model. *Presented at 4th International Science of Nutrition in Medicine Conference; Surfers Paradise, Queensland, Australia; May 3* (2014).
56. Goossens RA: Allergic contact dermatitis from the vehicle components of topical pharmaceutical products. *Immunol Allergy Clin North Am.* 34(3), 663-670 (2014).
57. Davis MD: Unusual patterns in contact dermatitis: medicaments. *Dermatol Clin.* 27(3), 289-297 (2009).
58. Argoff CE: Topical analgesics in the management of acute and chronic pain. *Mayo Clin Proc.* 88(2), 195-205 (2013).
59. Argoff CE: Topical analgesics in the management of acute and chronic pain: Introduction. *Postgrad Med.* 125(4 Suppl 1), 3-6 (2013).

60. De Leon-Casasola OA: Multimodal approaches to the management of neuropathic pain: the role of topical analgesia. *J Pain Symptom Manage.* 33(3), 356-364 (2007).
61. Sawynok J: Topical analgesics for neuropathic pain: preclinical exploration, clinical validation, future development. *Eur J Pain.* 18(4), 465-481 (2014).
62. Zur E: Topical treatment of neuropathic pain using compounded medications. *Clin J Pain.* 30(1), 73-91 (2014).
63. Lawrence BM: The story of India's mint oils and menthol. *Perfumer & Flavorist.* 38(1), 26-35 (2013).
64. Graves R: The Greek myths. (Revised). Penguin, London. 31d (p121); 31d note 6 (p124) (1960).
65. Kamatou GP, Vermaak I, Viljoen AM, Lawrence BM: Menthol: a simple monoterpene with remarkable biological properties. *Phytochemistry.* 96, 15-25 (2013).
66. Galeotti N, Di Cesare Mannelli L, Mazzanti G, Bartolini A, Ghelardini C: Menthol: a natural analgesic compound. *Neurosci Lett.* 322(3), 145-148 (2002).
67. Haeseler G, Maue D, Grosskreutz J *et al.*: Voltage-dependent block of neuronal and skeletal muscle sodium channels by thymol and menthol. *Eur J Anaesthesiol.* 19(8), 571-579 (2002).
68. Patel T, Ishiuji Y, Yosipovitch G: Menthol: a refreshing look at this ancient compound. *J Am Acad Dermatol.* 57(5), 873-878 (2007).
69. Yosipovitch G, Szolar C, Hui XY, Maibach H: Effect of topically applied menthol on thermal, pain and itch sensations and biophysical properties of the skin. *Arch Dermatol Res.* 288(5-6), 245-248 (1996).
70. Işcan G, Kirimer N, Kürkcüoğlu M, Başer KH, Demirci F: Antimicrobial screening of Mentha piperita essential oils. *J Agric Food Chem.* 50(14), 3943-3946 (2002).
71. Williams AC, Barry BW: Penetration enhancers. *Adv Drug Deliv Rev.* 56(5), 603-618 (2004).
72. Cornwell PA, Bary BW, Stoddart CP, Bouwstra JA: Wide-angle X-ray diffraction of human stratum corneum: effects of hydration and terpene enhancer treatment. *J Pharm Pharmacol.* 46(12), 938-950 (1994).
73. Cliff MA, Green BG: Sensory irritation and coolness produced by menthol: evidence for selective desensitization of irritation. *Physiol Behav.* 56(5), 1021-1029 (1994).
74. Binder A, Stengel M, Kiebe O, Wasner G, Baron R: Topical high-concentration (40%) menthol-somatosensory profile of a human surrogate pain model. *J Pain.* 12(7), 764-773 (2011).
75. Wasner G, Baron R: [Pain prevention allows patients with chronic pruritus to itch from central sensitivity for itching]. *Schmarz.* 19(4), 324-327 (2005).
76. Galeotti N, Ghelardini C, Mannelli L, Mazzanti G, Baghiroli L, Bartolini A: Local anaesthetic activity of (+)- and (-)-menthol. *Planta Med.* 67(2), 174-176 (2001).
77. Gaudioso C, Hao J, Martin-Eauclaire MF, Gabriac M, Delmas P: Menthol pain relief through cumulative inactivation of voltage-gated sodium channels. *Pain.* 153(2), 473-484 (2012).

78. Higashi Y, Kiuchi T, Furuta K: 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. *Clin Ther.* 32(1), 34-43 (2010).

79. Sundstrup E, Jakobsen MD, Brandt M *et al.*: Acute effect of topical menthol on chronic pain in slaughterhouse workers with carpal tunnel syndrome: triple-blind, randomized placebo-controlled trial. *Rehabil Res Pract.* 310913 (2014).

80. Topp R, Brosky JA, Pieschel D: The effect of either topical menthol or a placebo on functioning and knee pain among patients with knee OA. *J Geriatr Phys Ther.* 36(2), 92-99 (2013).

81. Topp R, Ledford ER, Jacks DE: Topical menthol, ice, peripheral blood flow, and perceived discomfort. *J Athl Train.* 48(2), 220-225 (2013).

82. Bharate SS, Bharate SB: Modulation of thermoreceptor TRPM8 by cooling compounds. *ACS Chem Neurosci.* 3(4), 248-267 (2012).

83. Perry L, Dickau R, Zarrillo S *et al.*: Starch fossils and the domestication and dispersal of chili peppers (Capsicum spp. L.) in the Americas. *Science.* 315(5814), 986-988 (2007).

84. Schumacher M, Pasvankas G: *Topical capsaicin formulations in the management of neuropathic pain*. In: *Capsaicin as a therapeutic molecule: Progress in drug research 68*, Abdel-Salam OME (Ed.), Springer, Basel 105-128 (2014).

85. Appendino G, Szallasi A: Euphorbium: modern research on its active principle, resiniferatoxin, revives an ancient medicine. *Life Sci.* 60(10), 681-696 (1997).

86. Geoffroy M: Traite de la matiere médicale, ou de l'histoire des vertus, du choix et de l'usage des remedes simples. Desaint & Saillant, Paris. (1757).

87. Sarwa KK, Das PJ, Mazumder B: A nanovesicle topical formulation of Bhut Jolokia (hottest capsicum): a potential anti-arthritic medicine. *Expert Opin Drug Deliv.* 11(5), 661-676 (2014).

88. Guiness World Records: Guinness world records 2007. Guinness World Records, New York. (2006).

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

90. Peppin JF, Pappagallo M: Capsaicinoids in the treatment of neuropathic pain: a review. *Ther Adv Neurol Disord.* 7(1), 22-32 (2014).

91. Smith H, Brooks JR: Capsaicin-based therapies for pain control. *Prog Drug Res.* 68, 129-146 (2014).

92. Bode AM, Dong Z: The two faces of capsaicin. *Cancer Res.* 71(8), 2809-2814 (2011).

93. Brederson JD, Kym PR, Szallasi A: Targeting TRP channels for pain relief. *Eur J Pharmacol.* 16(1-3), 61-76 (2013).

94. Derry S, Moore RA: Topical capsaicin (low concentration) for chronic neuropathic pain in adults. *Cochrane Database Syst Rev.* 9, CD010111 (2012).

95. Derry S, Sven-Rice A, Cole P, Tan T, Moore RA: Topical capsaicin (high concentration) for chronic neuropathic pain in adults. *Cochrane Database Syst Rev.* 2, CD007393 (2013).

96. El-Ansary MM: History of pain relief by ancient Egyptians. *Middle East J Anaesthesiol.* 10(2), 99-105 (1989).
97. Bartels EM, Swaddling J, Harrison AP: An ancient Greek pain remedy for athletes. *Pain Pract.* 6(3), 212-218 (2006).
98. Harrison AP, Hansen SH, Bartels EM: Transdermal opioid patches for pain treatment in ancient Greece. *Pain Pract.* 12(8), 620-625 (2012).
99. Graham T, Grocott P, Probst S, Wanklyn S, Dawson J, Gethin G: How are topical opioids used to manage painful cutaneous lesions in palliative care? A critical review. *Pain.* 154(10), 1920-1928 (2013).
100. Zöllner C, Mousa S, Klinger A, Förster M, Schäfer M: Topical fentanyl in a randomized, double-blind study in patients with corneal damage. *Clin J Pain.* 24(8), 690-698 (2008).
101. Farley P: Should topical opioid analgesics be regarded as effective and safe when applied to chronic cutaneous lesions? *J Pharm Pharmacol.* 63(6), 747-756 (2011).
102. Jacobsen J: Topical opioids for pain #185. *J Palliat Med.* 12(4), 380-381 (2009).
103. Twillman RK, Long TD, Cathers TA, Mueller DW: Treatment of painful skin ulcers with topical opioids. *J Pain Symptom Manage.* 17(4), 288-292 (1999).
104. Cerchietti LC, Navigante AH, Körte MW *et al.*: Potential utility of the peripheral analgesic properties of morphine in stomatitis-related pain: a pilot study. *Pain.* 105(1-2), 265-273 (2003).
105. Leppert W, Krajnik M, Wordliczek J: Delivery systems of opioid analgesics for pain relief: a review. *Curr Pharm Des.* 19(41), 7271-7293 (2013).
106. Gallagher RE, Arndt DR, Hunt KL: Analgesic effects of topical methadone: a report of four cases. *Clin J Pain.* 21(2), 190-192 (2005).
107. Ballas SK: Treatment of painful sickle cell leg ulcers with topical opioids. *Blood.* 99(3), 1096 (2002).
108. Muller JL: Love potions and the ointment of witches: historical aspects of the nightshade alkaloids. *J Toxicol Clin Toxicol.* 36(6), 617-627 (1998).
109. Chidiac EJ, Kaddoum RN, Fuleihan SF: Mandragora: anesthetic of the ancients. *Anesth Analg.* 115(6), 1437-1441 (2012).
110. Stewart A: Wicked plants: the weed that killed Lincoln's mother and other related botanical atrocities. Algonquin Books, Chapel Hill, NC. (2009).
111. Thompson CJS: The mystic mandrake. Rider, London. 146 (1934).
112. Aziz E, Nathan B, Mckeever J: Anesthetic and analgesic practices in Avicenna's Canon of Medicine. *Am J Chin Med.* 28(1), 147-151 (2000).
113. Lee MR: Solanaceae III: henbane, hags and Hawley Harvey Crippen. *J R Coll Physicians Edinb.* 36(4), 366-373 (2006).
114. Amm M, Holubar K: ["Coca-Koller" and his friends: on the 140th birthday of the Vienna Jewish trio: Carl Koller (1857-1944), Sigmund Lustgarten (1857-1911) and Sigmund Freud (1856-1939)]. *Wien Klin Wochenschr.* 109(5), 170-175 (1997).
115. Rivera MA, Aufderheide AC, Cartmell LW, Torres CM, Langsjoen O: Antiquity of coca-leaf chewing in the south central Andes: a 3,000 year archaeological record of coca-leaf chewing from northern Chile. *J Psychoactive Drugs.* 37(4), 455-458 (2005).

116. Prendergast M: For God, country and *Coca-Cola:* the unathorized history of the great American soft drink and the company that makes it. Pheonix, London. (1994).
117. Garnock-Jones KP, Keating GM: Lidocaine 5% medicated plaster: a review of its use in postherpetic neuralgia. *Drugs.* 69(15), 2149-2165 (2009).
118. Mick G, Correa-Illanes G: Topical pain management with the 5% lidocaine medicated plaster: a review. *Curr Med Res Opin.* 28(6), 937-951 (2012).
119. Wolff RF, Bala MM, Westwood M, Kessels AG, Kleijnen J: 5% lidocaine-medicated plaster vs other relevant interventions and placebo for post-herpetic neuralgia (PHN): a systematic review. *Acta Neurol Scand.* 123(5), 295-309 (2011).
120. Khaliq W, Alam S, Puri N: Topical lidocaine for the treatment of postherpetic neuralgia. *Cochrane Database Syst Rev.* 18(2), CD004846 (2007).
121. Desai C, Wood FM, Schug SA, Parsons RW, Fridlender C, Sunderland VB: Effectiveness of a topical local anaesthetic spray as analgesia for dressing changes: a double-blinded randomised pilot trial comparing an emulsion with an aqueous lidocaine formulation. *Burns.* 40(1), 106-112 (2014).
122. Kanai A, Kumaki C, Niki Y, Suzuki A, Tazawa T, Okamoto H: Efficacy of a metered-dose 8% lidocaine pump spray for patients with post-herpetic neuralgia. *Pan Med.* 10(5), 902-909 (2009).
123. Suzuki A, Kanai A: 8% Lidocaine pump spray relieves pain associated with peripheral blood flow disorders. *Clin J Pain.* 25(2), 107-110 (2009).
124. Gammaitoni AR, Alvarez NA, Galer BS: Pharmacokinetics and safety of continuously applied lidocaine patches 5%. *Am J Health Syst Pharm.* 59(22), 2215-2220 (2002).
125. Lutwak N, Howland MA, Gambetta R, Dill C: Even 'safe' medications need to be administered with care. *BMJ Case Rep.* (Jan 2), bcr2012006204 (2013).
126. Haroutiunian S, Drennan DA, Lipman AG: Topical NSAID therapy for musculoskeletal pain. *Pain Med.* 11(4), 535-549 (2010).
127. King RB: Topical aspirin in chloroform and the relief of pain due to herpes zoster and postherpetic neuralgia. *Arch Neurol.* 50(10), 1046-1053 (1993).
128. Rainsford KD: *Anti-inflammatory drugs in the 21st century*. In: *Inflammation in the pathogenesis of chronic diseases: the COX-2 controversy*, Harris RE (Ed.), Springer, New York 3-27 (2007).
129. Klinge SA, Sawyer GA: Effectiveness and safety of topical versus oral nonsteroidal anti-inflammatory drugs: a comprehensive review. *Phys Sportsmed.* 41(2), 64-74 (2013).
130. Balmaceda CM: Evolving guidelines in the use of topical nonsteroidal anti-inflammatory drugs in the treatment of osteoarthritis. *BMC Musculoskelet Disord.* 15, 27 (2014).
131. Herndon CM: Topical delivery of nonsteroidal anti-inflammatory drugs for osteoarthritis. *J Pain Palliat Care Pharmacother.* 26(1), 18-23 (2012).
132. Mcpherson ML, Cimino NM: Topical NSAID formulations. *Pain Med.* 13(Suppl 1), S35-39 (2013).
133. Arnstein PM: Evolution of topical NSAIDs in the guidelines for treatment of osteoarthritis in elderly patients. *Drugs Aging.* 29(7), 523-531 (2012).

134. Eisenach JC, Gebhart GF: Intrathecal amitriptyline acts as an N-methyl-D-aspartate receptor antagonist in the presence of inflammatory hyperalgesia in rats. *Anesthesiology.* 83(5), 1046-1054 (1995).

135. Gray AM, Pache DM, Sewell RD: Do alpha2-adrenoceptors play an integral role in the antinociceptive mechanism of action of antidepressant compounds? *Eur J Pharmacol.* 378(2), 161-168 (1999).

136. Traiffort E, Pollard H, Moreau J *et al.*: Pharmacological characterization and autoradiographic localization of histamine H2 receptors in human brain identified with [125I]iodoaminopotentidine. *J Neurochem.* 59(1), 290-299 (1992).

137. Duale C, Daveau J, Cardot JM, Boyer-Grand A, Schoeffler P, Dubray C: Cutaneous amitriptyline in human volunteers: differential effects on the components of sensory information. *Anesthesiology.* 108(4), 714-721 (2008).

138. Ho KY, Huh BK, White WD, Yeh CC, Miller EJ: Topical amitriptyline versus lidocaine in the treatment of neuropathic pain. *Clin J Pain.* 24(1), 51-55 (2006).

139. Kopsky DJ, Hesselink JM: High doses of topical amitriptyline in neuropathic pain: two cases and literature review. *Pain Pract.* 12(2), 148-153 (2012).

140. Kopsky DJ, Keppel Hesselink JM: Multimodal stepped care approach involving topical analgesics for severe intractable neuropathic pain in CRPS type 1: a case report. *Case Rep Med.* 319750 (2011).

141. Nyirjesy P, Lev-Sagie A, Mathew L, Culhane JF: Topical amitriptyline-baclofen cream for the treatment of provoked vestibulodynia. *J Low Genit Tract Dis.* 13(4), 230-236 (2009).

142. Lehman JS, Sciallis GF: Effective use of topical amitriptyline hydrochloride 2.5% and ketamine hydrochloride 0.5% for analgesia in refractory proctodynia. *J Drugs Dermatol.* 7(9), 887-889 (2008).

143. Lynch ME, Clark AJ, Sawynok J, Sullivan MJ: Topical 2% amitriptyline and 1% ketamine in neuropathic pain syndromes: a randomized, double-blind, placebo-controlled trial. *Amnesthesiology.* 103(1), 140-146 (2005).

144. Lynch ME, Clark AJ, Sawynok J, Sullivan MJ: Topical amitriptyline and ketamine in neuropathic pain syndromes: an open-label study. *J Pain.* 6(10), 644-649 (2005).

145. Mccleane G: 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. *Br J Clin Pharmacol.* 49(6), 574-579 (2000).

146. Poterucha TJ, Murphy SL, Rho RH *et al.*: Topical amitriptyline-ketamine for treatment of rectal, genital, and perineal pain and discomfort. *Pain Physician.* 15(6), 485-488 (2012).

147. Poterucha TJ, Weiss WT, Warndahl RA *et al.*: Topical amitriptyline combined with ketamine for the treatment of erythromelalgia: a retrospective study of 36 patients at Mayo Clinic. *J Drugs Dermatol.* 12(3), 308-310 (2013).

148. Zell-Kanter M, Toerne TS, Spiegel K, Negrusz A: Doxepin toxicity in a child following topical administration. *Ann Pharmacother.* 34(3), 328-329 (2000).

149. Davis KD, Treede RD, Raja SN, Meyer RA, Campbell JN: Topical application of clonidine relieves hyperalgesia in patients with sympathetically maintained pain. *Pain.* 47(3), 309-317 (1991).
150. Campbell CM, Kipnes MS, Stouch BC *et al.*: Randomized control trial of topical clonidine for treatment of painful diabetic neuropathy. *Pain.* 153(9), 1815-1823 (2012).
151. Lodge D: The history of the pharmacology and cloning of ionotropic glutamate receptors and the development of idiosyncratic nomenclature. *Neuropharmacology.* 56(1), 6 (2009).
152. Gammaitoni A, Gallagher RM, Weiz-Bosna M: Topical ketamine gel: possible role in treating neuropathic pain. *Pain Med.* 1(1), 97-100 (2000).
153. Kopsky DJ, Keppel Hesselink JM, Bhaskar A, Hariton G, Romanenko V, Casale R: Analgesic effects of topical ketamine. *Minerva Anestesiol.* 81(4), 440-449 (2015).
154. Sawynok J: Topical and peripheral ketamine as an analgesic. *Anesth Analg.* 119(1), 170-178 (2014).
155. Smith HS: Ketamine-induced urologic insult (KIUI). *Pain Physician.* 13(6), E343-E346 (2010).
156. Finch PM, Knudsen L, Drummond PD: Reduction of allodynia in patients with complex regional pain syndrome: A double-blind placebo-controlled trial of topical ketamine. *Pain.* 146(1-2), 18-25 (2009).
157. Sullivan RW, Ryzewski M, Holland MG, Marraffa JM: Compounded ointment results in severe toxicity in a pediatric patient. *Pediatr Emerg Care.* 29(11), 1220-1222 (2013).

References of Interest:

1. Zur E: Topical treatment of neuropathic pain using compounded medications. *Clin J Pain.* 30(1), 73-91 (2014). - An extensive review of compounded topical medications used in the treatment of neuropathic pain.
2. Trommer H, Neubert RH: Overcoming the stratum corneum: the modulation of skin penetration: a review. *Skin Pharmacol Physiol.* 19(2), 106-121 (2006). - A paper describing the structure of the stratum corneum and methods of skin penetration enhancement.
3. Sawynok J: Topical analgesics for neuropathic pain: preclinical exploration, clinical validation, future development. *Eur J Pain.* 18(4), 465-481 (2014). - A review of the mechanisms, evidence and use of current topical analgesic drugs.
4. Waxman SG, Zamponi GW: Regulating excitability of peripheral afferents: emerging ion channel targets. *Nat Neurosci.* 17(2), 153-163 (2014). - A description of the mechanisms regulating the excitability of peripheral afferents including ion channels.
5. Premkumar LS, Abooj M: TRP channels and analgesia. *Life Sci.* 92(8-9), 415-424 (2013). - A description of TRP channels and analgesia, especially with regard to capsaicin and menthol.
6. Mick G, Correa-Illanes G: Topical pain management with the 5% lidocaine medicated plaster: a review. *Curr Med Res Opin.* 28(6), 937-951 (2012). - A review of topical pain management with the 5% lidocaine patch.
7. Argoff CE: Topical analgesics in the management of acute and chronic pain. *Mayo*

Clin Proc. 88(2), 195-205 (2013). - A review of topical analgesic agents used in both acute and chronic pain.

1 **Illustration**

Stratum Corneum

Keratinocyte Layer

PGP 9.5 Pan neuronal
marker(green)
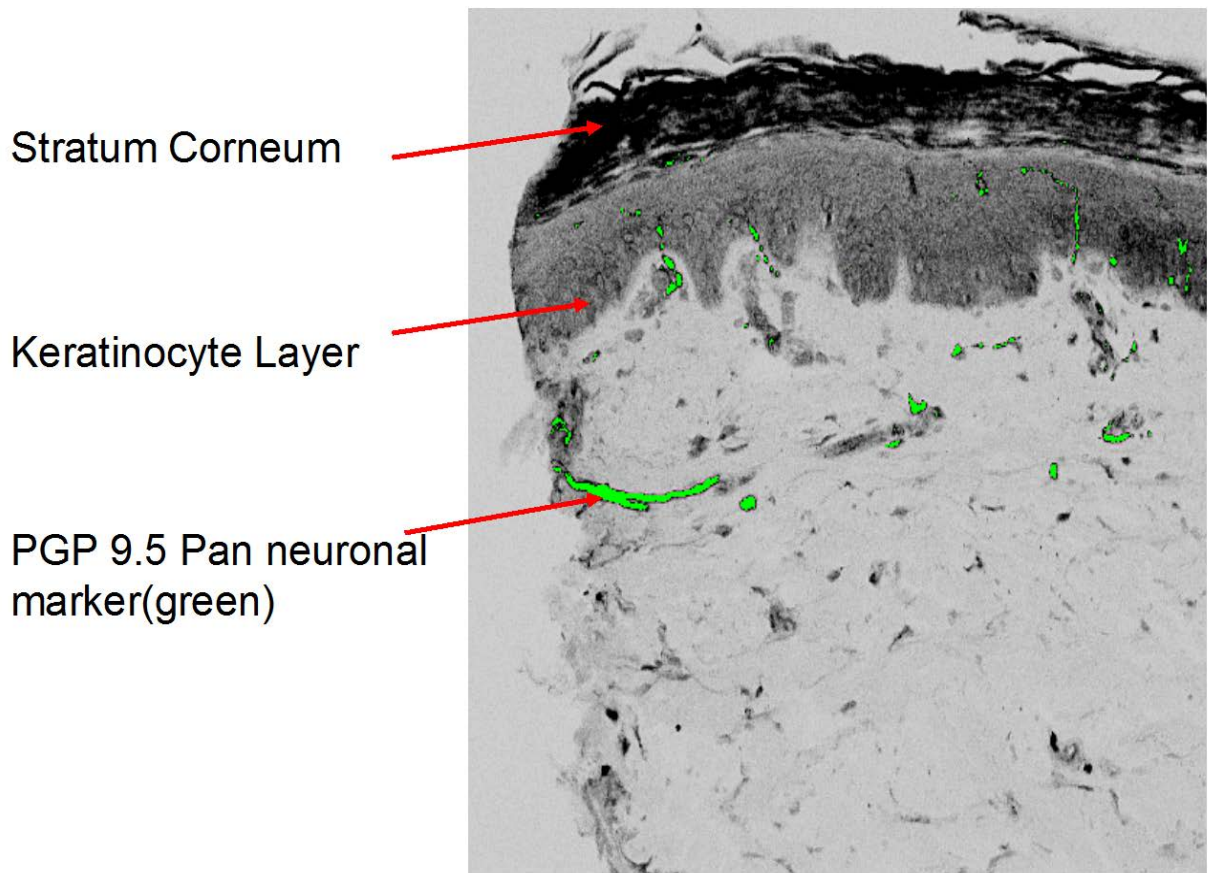
2
3

4 **Illustration:** Human Skin: A section of normal human skin demonstrating the

5 principal layers. Nerve fibres (green), including nociceptors have been stained by

6 PGP9.5, which is a pan neuronal immunohistochemical marker. (From

7 unpublished work by Finch P and Drummond D)