Update for nurse anesthetists

Itching, the “little” big problem as an orphan symptom

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The phenomenon of itching has received surprisingly little scientific scrutiny despite its commonality—hence its designation as a kind of neglected, “orphan symptom.” Recent research and clinical understanding has shed light on itching, helping to illuminate its previously shaded landscape. This course reviews the nature of itching, its physiology, major triggers of particular interest to anesthetists (especially when using neuraxial agents), and interventions directed at its resolution.

A variety of chemical mediators and modulators have important roles in the genesis and experience of itching. Although many medical comorbidities can cause itch, the ubiquitous use of neuraxial opioids in the perioperative care of patients has been attended by a dramatic increase in the number of patients experiencing, and complaining of, itching as a consequence of our management.

Patient satisfaction inventories have placed the sensation of refractory itch among the most distressing, non–life-threatening complications that are experienced. Intractable itch can be so incapacitating that it deserves the same degree of clinical attention as pain.

Key words: Complications, neuraxial opiates, pruritis.

Objectives:
At completion of this course, the reader should be able to:

1. Understand the physiology of itch.
2. Differentiate between common variants of itch, including neurogenic, neuropathic, senile, and psychogenic.
3. Describe the various endogenous mediators of itch.
4. Recognize common characteristics of neuraxial opioid–induced itch.
5. Discuss common treatment modalities for itch.

Introduction
Visiting the website of the International Forum for the Study of Itch, one encounters 5 short films illustrating the devastating impact that chronic itching has on the quality of life of the afflicted.1 The films reveal the complexity fascinating intersection of pain and pleasure and the overwhelming compulsion to scratch. Itching is a phenomenon we have all experienced at one time or another—consider the mosquito bite or that poison ivy rash around your ankles that seemed to torment you relentlessly.

Normally, we are not cognizant of our skin. You might put on your clothes in the morning, noticing the feel or texture of the fabric, perhaps even its weight. Yet within moments, the brain dispenses of the sensation, busying itself with other, more important sensory input. Yet, if an itch is provoked for any of a dozen (hundred?) reasons, a kind of neural super-highway linking skin, spinal cord, and brain opens up with the sensation suddenly prioritized seemingly in the same way it might be if we inadvertently placed our hand on a hot stove.

The phenomenon of itching has received surprisingly little scientific scrutiny despite its commonality—hence its designation as a kind of neglected, “orphan symptom.” Recent research and clinical understanding has shed light on itching, helping to illuminate its previously shaded landscape. This course reviews the nature of itching, its physiology, major triggers of particular interest to anesthetists, and interventions directed at its resolution. Emphasis will be placed on neuraxial applied agents.

The physiology of itch
A pruritogen is a mechanical or chemical stimulus initiating the cascade of events that result in the sensation of itch (pruritis). Itch has a protective (or warn-
ing) role and can vary from a temporary nuisance to a phenomenon that literally becomes overwhelming. Itch may be highly localized to a particular point (eg, the raised wheal of a mosquito bite) or it may be generalized. A cutaneous stimulus can arise from a variety of external (eg, light touch, chemical irritant) sources transmitted by specialized C fibers in the skin. Although the neural pathway is shared with pain fibers, the C fibers transmitting itch are distinct from those of afferent pain fibers and were first described in 1997.2 These fibers tend to have particularly thin axons and conspicuously diffuse terminal branching. Although the most common type of C fiber is the polymodal nociceptor (mechanical and heat nociceptor), about 5% of the afferent C fiber pool mediates itch.3 Itch afferent impulses reach the thalamus via the spinal dorsal horn and spinothalamic tract. Subsequent to thalamic input, the postcentral cingulate gyrus of the somatosensory cortex is stimulated, resulting in the sensation of itch (Figure 1).

Although cutaneously provoked itch is the most common form encountered, the sensation of itch can manifest in other ways as well. For example, the squamous epithelium of the eyes’ conjunctiva and that of the oral and nasal cavities, throat, trachea, and anogenital area can experience itch. A variety of endogenous chemicals are pruritogenic, including opioids, neuropeptides, amines, proteases, growth factors, eicosanoids, and cytokines.

Because they share a common neural pathway, there is considerable overlap between the mediation and modulation of itching and pain. The perception of itch and pain can undergo neuromodulation at the level of the central nervous system. Similarly, pain-related allodynia (ie, pain induced by a nonnoxious stimulus) has its parallel in itch-related “alloknesis” (ie, itching evoked by innocuous mechanical stimulation). Investigations into these parallels ultimately resulted in the clinical observation that centrally acting opioid antagonists (eg, naltrexone) and peripherally acting H1-receptor antagonists (eg, cetirizine) diminished the itch sensation provoked by intradermal injection of histamine.4

Neuropathic itch is yet another variant that also is explained by the commonality of the itch and pain pathways. As with neuropathic pain, neuropathic itch can be triggered as a result of trauma at any point on the afferent pathway. Classic examples are the localized pruritis seen with peripheral nerve lesions in patients with postherpetic neuralgia, in certain nerve entrapment lesions, and even in cerebral diseases such as tumors and abscesses.5-7

Neurogenic itch is induced centrally but does not involve trauma or damage to a nerve pathway (neuropathic itch). This is a common form of itch seen by anesthetists in the wake of neuraxial injection of an opiate, parenteral injection of an opiate, in states of accumulation of endogenous opiates, and in cholestasis.8,9 Psychogenic itch also is an itch of apparent central origin and is associated with a variety of psychiatric disorders. Senile itch is a general rubric for the common finding (>50% of people older than 70 years experience “itchy skin”) attributed to the lower water content in the skin of elderly people and the subsequent inducement of pruritogenic mediators in the skin.10

A variety of chemical mediators and modulators have important roles in the genesis and experience of itching. These are listed and briefly reviewed in Table 1.

**Clinical manifestations of particular anesthetic relevance**

The mechanism of pruritis after neuraxial administration of opioids is not fully understood. Pruritis occurs in 1% of patients receiving oral opioids, but there is a 10% to 90% occurrence with intrathecally administered opioid analgesics.22,23 The incidence of pruritis depends on the specific opioid used and whether tolerance has developed in the patient. Intrathecally administered morphine has demonstrated the highest incidence of pruritis.14

Specific areas of the face are particularly vulnerable to the pruritic effects of neuraxial opioids. These areas include the distribution of the trigeminal nerve, especially its maxillary and ophthalmic divisions. These afferent tracts innervate the nose and upper portions of the face.24,25 The trigeminal nucleus is an elongated structure spanning down into the cervical region of the brainstem. The subnucleus caudalis, an anatomical region of the trigeminal nucleus, contains an

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**Figure 1. Cutaneously originated pruritis**

Itch afferent impulses reach the thalamus via the spinal dorsal horn and spinothalamic tract. Subsequent to thalamic input, the postcentral cingulate gyrus of the somatosensory cortex is stimulated, resulting in the sensation of itch.
arrangement of cells responsible for sensations from the face (Figure 2). It is here that the postulated “itch receptors” reside. Following neuraxial administration, opioids ascend cephalad toward the subnucleus caudalis, where they interact with these receptors, giving the characteristic symptoms of an itchy nose or face. The trigeminal nucleus is an elongated structure spanning down into the cervical region of the brainstem. The subnucleus caudalis, an anatomical region of the trigeminal nucleus, contains an arrangement of cells responsible for pain sensations from the face. Following neuraxial administration, opioids ascend cephalad toward the subnucleus caudalis, where they interact with these receptors, giving the characteristic symptoms of an itchy nose or face.

### Table 1. Itch-related endogenous mediators/transmitters

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Action</th>
<th>Notes</th>
<th>References</th>
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<tbody>
<tr>
<td>Histamine</td>
<td>Direct stimulation of H1 receptors on itch-specific C fibers</td>
<td>Dermal mast cell primary source</td>
<td>11-13</td>
</tr>
<tr>
<td></td>
<td>Intradermal injection produces itch, wheal, and flare</td>
<td>H1 and H2 receptors have a role</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mediator for urticaria, insect bite, drug rash, mastocytosis</td>
<td>Intravenous histamine does not usually cause itch</td>
<td></td>
</tr>
<tr>
<td>Serotonin (5-HT)</td>
<td>Peripherally releases histamine</td>
<td>Ondansetron relieves itch associated with exogenous opiates</td>
<td>14, 15</td>
</tr>
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<td></td>
<td>Centrally involves the opioid neurotransmitter system</td>
<td></td>
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<tr>
<td>Prostaglandins</td>
<td>Not pruritogenic but potentiate histamine’s pruritogenicity</td>
<td>Prostaglandin inhibitors of little value in neuraxial opioid itch treatment but may reduce peripheral histamine-mediated itch</td>
<td>16, 17</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>Stimulates histamine-sensitive and histamine-insensitive C fibers in healthy people but causes itch in atopic persons</td>
<td>Intradermally causes pain</td>
<td>18</td>
</tr>
<tr>
<td>Cytokines</td>
<td>Interleukin-2 given intradermally or intravenously causes severe itch</td>
<td>Relevance to elderly people and in people with HIV</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Dry skin and immune system dysfunction alter cytokines and may result in significant itch</td>
<td></td>
<td></td>
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<tr>
<td>Neuropeptides</td>
<td>Substance P and CGRP peptides potentiate itch; injected forms variably result in itch</td>
<td>Capsaicin depletes substance P and destroys superficial C fibers; relieves itch in some</td>
<td>20, 21</td>
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CGRP indicates calcitonin gene related peptide; HIV, human immunodeficiency virus.

**Figure 2. Trigeminal nerve: subnucleus caudalis**

The trigeminal nucleus is an elongated structure spanning down into the cervical region of the brainstem. The subnucleus caudalis, an anatomical region of the trigeminal nucleus, contains an arrangement of cells responsible for pain sensations from the face. Following neuraxial administration, opioids ascend cephalad toward the subnucleus caudalis, where they interact with these receptors, giving the characteristic symptoms of an itchy nose or face.

Interventions
- **Antihistamines.** Mast cells are distributed throughout the body, predominantly within connective tissues. They are highly concentrated in the skin around peripheral nerves and adjacent to blood vessels. The great majority of histamine receptors located in the skin are of the H1 specific subtype, with H2 receptors making up only about 15% of the total. Combinations of H1 and H2 blockers often are used in the management of pruritis.
Unlike intravenously administered opioids, histamine release is not associated with neuraxial opioids and does not seem to be a cause of pruritis in this setting. However, the sedative effect of antihistamines can be quite helpful in allowing the needed sleep that people with intense itch often lack.

- **Nonsteroidal anti-inflammatory drugs.** It has been postulated that prostaglandins (specifically PGE₁ and PGE₂) have a role in causing pruritis. It is recognized that prostaglandins enhance the C fiber itch neuron transmission, which consequently modulates the itch sensation. This occurs more specifically in the presence of histamine. Nonsteroidal anti-inflammatory drugs block cyclooxygenase and, in turn, inhibit prostaglandin production. Colbert et al studied the efficacy of 100 mg of rectal diclofenac and found a 25% reduction in pruritis 30 minutes after administration and a 98% reduction after 24 hours. Similarly, 20 mg of intravenous tenoxicam demonstrated a decrease in the incidence, intensity, and duration of pruritis.

- **Propofol.** Propofol depresses posterior horn nerve transmission within the spinal cord in a dose-dependent manner. Several studies have demonstrated that subhypnotic doses of propofol can specifically depress the sensation of pruritis. Torn et al demonstrated that a 10-mg bolus followed by subhypnotic infusion decreased the incidence of itch by 40%. Borgeat et al demonstrated an 84% success rate in propofol-treated patients. In addition, a significant number of initial treatment failures were managed successfully with supplemental dosing. Although propofol has demonstrated effectiveness in the treatment of pruritis, it is important to consider the risks of this powerful hypnotic. Vigilant monitoring is essential to prevent catastrophic outcomes.

- **Serotonin (5-HT₃) receptor antagonists.** The trigeminal nucleus within the medulla contains a high density of 5-HT₃ receptors. Injection of morphine into this anatomical site produces a dose-dependent, naloxone-reversible pruritis on the face. A randomized, placebo-controlled study demonstrated a 70% success rate in the reduction of pruritis with the administration of ondansetron, a 5-HT₃ receptor antagonist. Several studies have demonstrated the effectiveness of ondansetron in blocking opioid-induced pruritis in various general, orthopedic, and pediatric populations. Others have demonstrated no reduction in pruritis following a mixed neuraxial opioid treatment using sufentanil and morphine. This effect may be explained by the high lipid solubility of sufentanil, resulting in activation of 5-HT₃ receptors before they were blocked by ondansetron.

- **Droperidol.** Droperidol, a butyrophenone derivative, is well recognized as an antiemetic. Horta and Horta and Horta et al found a dose-dependent reduction in neuraxial-mediated pruritis following intravenous administration of droperidol. An intravenous dose of 2.5 mg has been shown to be effective at reducing pruritis, but at higher doses (5 mg), the benefit was lost. Systemic administration of droperidol is associated with many undesirable side effects, including somnolence, dysphoria, and some concerns of arrhythmogenicity, resulting in a black box warning by the US Food and Drug Administration. Epidural administration, on the other hand, has demonstrated much lower systemic concentrations and a reduction in the side effect of somnolence. Although the mechanism is not completely understood, it is postulated that extradural droperidol diffuses across the dura and is carried cephalad to the

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<th>Treatment</th>
<th>Notes</th>
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<tr>
<td>Antihistamines</td>
<td>Beneficial for peripherally mediated itch; H₁ and H₂ antagonist combinations demonstrate greater efficacy than either one alone.</td>
<td>14, 31, 32</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
<td>Attenuate prostaglandin-enhanced C fiber transmission; also have analgesic properties</td>
<td>33, 34</td>
</tr>
<tr>
<td>Propofol</td>
<td>Depresses posterior horn transmission within the spinal cord, blunting itch transmission along the spinthalamic tract</td>
<td>28, 29, 36</td>
</tr>
<tr>
<td>Serotonin (5-HT₃) antagonists</td>
<td>Block 5HT₃ receptors responsible for pruritis located within the trigeminal nucleus of the medulla</td>
<td>25, 27, 37, 38</td>
</tr>
<tr>
<td>Droperidol</td>
<td>Unknown mechanism of action for relief of pruritis; possible interaction with itch receptors located in the medulla; conflicting reports of efficacy</td>
<td>39, 40, 41</td>
</tr>
<tr>
<td>Opioid antagonists</td>
<td>Block opioid receptors responsible for producing pruritis; nalbuphine possibly more beneficial to patients due to κ-receptor agonism–mediated analgesia</td>
<td>32, 46</td>
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“scratch center” within the medulla, where it interacts with the receptors responsible for pruritus. However, in a study of 97 patients who received epidural morphine after cesarean section, no significant relief of pruritus was identified using the epidural route for droperidol. Several authors have found no effect of intravenous or epidural droperidol. The effectiveness of this route has demonstrated inconsistent results, and further studies are needed.

• Opioid antagonists. Opioid antagonists are known to decrease neuraxial opioid–dependent pruritus. Nalbuphine, a mixed µ-opioid receptor antagonist and κ-receptor agonist, has been a standard treatment of opioid-induced pruritus. Some believe nalbuphine to be more advantageous than naloxone, a pure µ-opioid antagonist. Nalbuphine has the effect of suppressing opioid-mediated itch while maintaining analgesia. The mechanism of this may be that activation of the κ-opioid receptor averts the responsiveness and processing of the µ-opioid–mediated itch response.

A summary of interventions relevant to anesthetists is provided in Table 2.

Conclusions and a look to the future
Although many medical comorbidities can cause itch, the virtually ubiquitous use of neuraxial opioids in the perioperative care of patients has been attended by a dramatic increase in the number of patients experiencing, and complaining of, itching as a consequence of our management. Patient satisfaction inventories have placed the sensation of refractory itch among the most distressing, non-life-threatening sensations that are experienced. Intractable itch can be so incapacitating that it deserves the same degree of clinical attention as pain. Although research and clinical work are being leveled aggressively at itching, much remains unknown, and highly effective preventive and treatment interventions are still far from ideal. Itching may be the most recently appreciated “little” big problem that anesthetists face.

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