A Practical Review and Update on the Management of Pruritus Sine Materia

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GOAL

To understand pruritus sine materia to better manage patients with the condition

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Describe the 4 categories of itch.
2. Differentiate between neuropathic and psychogenic pruritus.
3. Assess the utility of pharmacologic and nonpharmacologic therapies for treatment of neuropathic or psychogenic pruritus.

CME Test on page 201.

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Ms. Tuerk and Dr. Koo report no conflict of interest. The authors discuss off-label use of amitriptyline, anesthetic cream, capsaicin, carbamazepine, coal tar, doxepin, fluoxetine, gabapentin, lamotrigine, mirtazapine, olanzapine, oxcarbazepine, paroxetine, pimozide, sertraline, and thalidomide. Dr. Fisher reports no conflict of interest.

Pruritus can be divided into several categories: pruritoceptive, neurogenic, neuropathic, and psychogenic. Neuropathic itch is caused by lesions of afferent neural pathways. Psychogenic itch is secondary to primary psychiatric disorders. Both of these types of pruritus present with no evidence of primary cutaneous lesions. The presentation of both conditions can be confusing and patients with no primary cutaneous lesions can be prematurely diagnosed as having a psychiatric disorder. Treatment of neuropathic and psychogenic pruritus can be divided into pharmacologic and nonpharmacologic therapies. Medications used include topical capsaicin and anesthetic agents, antiepileptic agents, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs),

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and atypical antipsychotic agents. Nonpharmacologic therapies such as psychotherapy and hypnosis have been beneficial. Further studies are needed, as most reports of efficacy are not evidence based.

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Itch, also known as pruritus, is defined as "an unpleasant cutaneous sensation which provokes the desire to scratch."[1] Itch may be classified by its mechanisms. It is typically divided into one of several categories: pruritoceptive, neurogenic, neuropathic, and psychogenic.[2] Pruritoceptive itch originates in the skin, is mediated locally by molecules such as histamine, and is transmitted by C nerve fibers. Neurogenic itch is caused by circulating mediators acting centrally, such as opioid neuropeptides in cholestasis acting centrally on opioid receptors. Neuropathic itch is caused by peripheral or central nervous system (CNS) lesions along the afferent neural pathway leading from the skin to the brain. Finally, psychogenic itch is secondary to primary psychiatric disorders, such as delusions of parasitosis. It is possible to have pruritus of more than one type simultaneously. For example, a patient with psoriasis also may have generalized pruritus secondary to cholestasis.

When a pruritic patient is first seen by a physician, a thorough history and general physical examination are completed and the physician typically looks for primary cutaneous lesions that could provide clues to the etiology of the patient's complaint. If found, lesions likely would lead the physician to consider a differential diagnosis consisting mostly of pruritoceptive disorders. If no lesions are present, the condition is known as pruritus sine materia. The next logical step would be to evaluate the patient for an internal etiology for the itching sensation, such as uremia. Both pruritoceptive and neurogenic itch are mediated by identifiable organic causes.

Challenging cases arise when patients present with no primary cutaneous lesions and their extensive medical workup does not reveal any abnormalities. The physician may be tempted to conclude that the pruritus is secondary to some underlying psychiatric or supratentorial process and refer the patient to a mental health professional; however, this conclusion may be premature because neuropathic pruritus also is a possibility. If psychogenic pruritus is ultimately diagnosed, optimal care for patients results from a dermatologist working closely with a mental health professional. Therefore, it is beneficial for dermatologists to be updated on the management of these patients. This article reviews and updates diagnostic possibilities and available therapeutic options for patients with pruritus that exhibit no identifiable primary cutaneous lesions and have no apparent systemic medical condition accounting for their symptoms.

Neuropathic and Psychogenic Pruritus

To review the literature on pruritus sine materia, a MEDLINE/PubMed search was performed for English language articles and abstracts from 1960 to 2006 containing the keywords *neuropathic, psychogenic, pruritus, itch,* and *therapy*. Additional articles were obtained by reviewing the references cited in articles retrieved using the MEDLINE search.

Neuropathic Pruritus—The sensation of itch is carried by specialized C fibers that originate in the skin and carry information to the dorsal horn of the spinal cord.[2] These fibers are anatomically indistinct from fibers carrying pain signals. Itch impulses are transmitted via the spinothalamic tract to the thalamus and then to the somatosensory cortex.

Pruritus as a solitary or dominant symptom following CNS injury is rare but well-documented in the medical literature. Multiple CNS lesions have been implicated, including brain tumors, aneurysms, abscesses, multiple sclerosis, stroke, transverse myelitis, and spinal cord hemangioma, as well as postherpetic neuralgia.[3-9] The pruritus that results may be intermittent or constant and onset may or may not be immediate. The distribution often corresponds to a particular spinal segment but may be either bilateral or unilateral. Often a sensory deficit or an aberration in sensory perception such as allodynia (nonpainful stimuli evoke pain), allokinesis (sensation of itch produced by innocuous stimuli that would not ordinarily induce itch), or hyperpathia (evoked pain grossly out of proportion to painful stimuli) is present.

One example of neuropathic pruritus is brachioradial pruritus, which is characteristically localized to the dorsolateral aspect of the upper arm.[10] The etiology is unknown, but one study demonstrated cervical spine pathology on radiographs corresponding to the location of pruritus in 11 of 22 patients.[11] Notalgia paresthetica, characterized by pruritus on the back in a dermatomal distribution and occasionally associated with pain, paresthesia, or hyperesthesia, is thought to be attributable to neurologic pathology at the spinal level corresponding to the affected dermatomes.[12]

Because neuropathic pruritus is caused by neuronal damage anywhere along the afferent neural pathway, it can occur in a specific dermatomal pattern or in a more broad distribution. Therefore, a careful history and a high index of suspicion are

required for diagnosis in a patient with no evidence of pruritoceptive or neurogenic pruritus.

Psychogenic Pruritus—It is estimated that up to 75% of dermatology patients have a psychogenic component to their skin complaints.[13] Most psychogenic skin disorders have an underlying psychiatric component of depression, anxiety, obsessive-compulsive disorder (OCD), or psychosis.[14] Dermatologic diagnoses that are considered to have a primary psychogenic etiology include delusions of parasitosis, neurotic excoriations, and dermatitis artefacta. Some conditions, such as prurigo nodularis and lichen simplex chronicus, have both psychogenic and physiologic etiology; these disorders have an organic basis but also are strongly affected by psychologic factors. Because pruritus may be associated with one or more underlying psychiatric diagnoses, it is often difficult to determine if the psychiatric disorder is the cause of the patient's pruritus.

Depression is commonly associated with psychogenic pruritus.[15] These patients with psychogenic pruritus secondary to depression also may present with prominent anxiety and agitation. Careful pharmacologic management is essential, as use of anxiolytic agents with depressant effects (ie, older benzodiazepines such as diazepam and chlordiazepoxide) in the absence of antidepressant therapy may exacerbate the underlying depression.[16] Dopamine pathways in serious depression also have been implicated in the development of chronic tactile hallucinations that are manifested by sensations of itching, crawling, and burning in the absence of delusions.[17]

Patients with monosymptomatic hypochondriacal psychosis have a delusional preoccupation with a solitary hypochondriacal ideation (eg, an erroneous belief that one's skin is infested with parasites). Hallucinations experienced as formication, a sensation of crawling, biting, or stinging, frequently accompany the delusion. These patients typically do not have any other abnormal psychiatric function.[18] The primary etiology is a psychiatric disorder, but healthy skin may be secondarily damaged from manipulation by the patient. The delusion occasionally is experienced by the patient's spouse or a close relative or friend, as they come to believe in the delusion. Dopamine pathways have been implicated in hallucinations and delusions, as dopamine-blocking drugs are effective in treating these symptoms.[19]

Neurotic excoriations also have a primarily psychogenic etiology. Patients with neurotic excoriations are driven to pick, scratch, or rub healthy skin or skin with minor irregularities, such as minor blemishes. The lesions vary in size from a few millimeters in diameter to large craters and often are weeping, crusting, or scarring, with surrounding postinflammatory pigmentation changes.[20] Interestingly, pruritus is not always predominant in these patients. This behavior can lead to serious complications, such as chronic skin ulcers, extensive scarring, and abscesses. Neurotic excoriations often are associated with depression and OCD.[21,22] If associated with OCD, despite full awareness of their behavior and the potential consequences, patients find themselves unable to cease the destructive activity.

Dermatitis artefacta differs from neurotic excoriations in that the patients deny their participation in the development of the lesions and usually use more than just their fingernails (eg, sharp instruments, lighted cigarettes) to inflict damage on their skin. These patients typically are unable to give a reliable history regarding the evolution of the lesions. The lesions have varying morphology and may present as blisters, purpura, ulcers, erythema, edema, sinuses, or nodules, depending on how they were created by the patient.[23] In a study of patients with different forms of self-inflicted dermatoses, depressive illness was found in 46% (12/26).[24]

Treatment

Pharmacologic Therapy—Despite the different etiologies of neuropathic and psychogenic pruritus, similar classes of pharmacologic and adjunctive therapies are useful for both. A simple approach to therapy for these disorders is to divide treatment types, namely topical, supportive, and CNS-directed therapies.

Topical therapy consists of medications directed at the skin itself. Because the etiology of neuropathic and psychogenic pruritus is not primarily cutaneous, it seems unlikely that topical therapy would be helpful. However, topical therapy may be useful in patients with overlapping central and pruritoceptive pruritus. In addition, the empirical use of topical agents such as a eutectic mixture of local anesthetics, an anesthetic agent combining lidocaine 2.5% and prilocaine 2.5%, can help distinguish central from pruritoceptive pruritus. In addition, anesthetic cream has been effective in treating notalgia paresthetica.[25] Capsaicin, an alkaloid isolated from red pepper plants, relieves pruritus by depleting substance P from cutaneous nerve endings involved in pain and itch, resulting in the inhibition of itch signal transmission from the skin to the CNS.[26] Side effects include localized feelings of burning, stinging, and hyperalgesia. Pretreatment with topical anesthetic creams may reduce these side effects.[27] Capsaicin has been shown to be effective for

notalgia paresthetica,[28,29] brachioradial pruritus,[30] and prurigo nodularis.[31]

Supportive therapies combined with other therapeutic options augment overall management of these patients. Occlusion of pruritic areas with Unna boot, Duoderm, or nonlatex gloves may help the patient break the itch-scratch cycle.[13] If a patient has identifiable discrete lesions that are pruritic, such as prurigo nodularis or lichen simplex chronicus, intralesional steroid injections, laser therapy, or cryotherapy may control the pruritus associated with these lesions.[13,15,32-34] Occlusion alone or combined with topical and intralesional corticosteroid therapy is effective for notalgia paresthetica.[15] Goeckerman treatment, consisting of daily application of coal tar and UVB or psoralen plus UVA phototherapy, may provide benefit to patients with pruritus sine materia as well as prurigo nodularis and lichen simplex chronicus.[13,35,36]

Central nervous system–directed therapy in the treatment of neuropathic and psychogenic pruritus usually targets the suspected underlying etiology of the pruritus, such as depression and anxiety. Often, however, psychotropic agents are empirically used. Many of the same medications that show efficacy in the treatment of neuropathic pain also demonstrate therapeutic effect in neuropathic pruritus. Other than tricyclic antidepressants, there have been no controlled studies; therefore, the merits of most of these options are based on anecdotal reports. Carbamazepine, an antiepileptic agent, is beneficial in pruritus and dysesthesia in multiple sclerosis.[37] Aplastic anemia and agranulocytosis rarely have been reported. Even though there is a low incidence of these side effects, hematologic testing at baseline (pretreatment) as well as periodic monitoring is recommended. Oxcarbazepine, an analogue of carbamazepine, has efficacy in the treatment of brachioradial pruritus.[38] Oxcarbazepine lacks the hematologic risks associated with carbamazepine and does not require monitoring, but it does carry a risk of hyponatremia and Stevens-Johnson syndrome. Lamotrigine, another antiepileptic agent, is of benefit in brachioradial pruritus but also has been reported to cause Stevens-Johnson syndrome.[10] Therefore, oxcarbazepine and lamotrigine should be discontinued at the first sign of drug eruption. Gabapentin, a structural analogue of the neurotransmitter γ-aminobutyric acid, treats epilepsy and postherpetic neuralgia. It shows efficacy in the treatment of brachioradial pruritus, pruritus induced by multiple sclerosis, and pruritus of unknown origin.[39-42] Gabapentin should not be discontinued abruptly but rather should be tapered gradually to prevent withdrawal-related adverse events. Thalidomide, an immunomodulatory drug, has shown benefit in treating prurigo nodularis.[43-45] It is a powerful central depressant and has a sedative-related property. In addition, it inhibits C-fiber function and therefore may have a primary antipruritic effect. It also has anti-inflammatory action by which it inhibits synthesis of tumor necrosis factor α, a cytokine that may induce pruritus. The major adverse side effects of thalidomide are severe fatigue, peripheral neuropathy, and teratogenicity.

Antidepressants have demonstrated efficacy in reducing pruritus, presumably through neurotransmitter modulation. Tricyclic compounds, such as doxepin, and selective serotonin reuptake inhibitors (SSRIs) have been beneficial in psychogenic pruritus.

Tricyclic antidepressants have antihistaminic effects and inhibit the reuptake of norepinephrine and serotonin in the CNS and peripheral nervous system. Although the sedative and antihistaminic effects of these drugs occur promptly, the antidepressive effects can take 2 weeks or longer to manifest after reaching an adequate dose. However, the negative side-effect profile of tricyclic antidepressants, including cardiac conduction abnormalities, seizures, and drug interactions, limits their clinical utility. Amitriptyline is effective in the treatment of postherpetic neuralgia and brachioradial pruritus. Doxepin has shown benefit in the treatment of neurotic excoriations.[46] Doses of these agents should be more conservative in elderly patients.

Selective serotonin reuptake inhibitors specifically inhibit serotonin reuptake and increase serotonin synaptic activity. Examples of drugs in this class are fluoxetine, paroxetine, and sertraline. These drugs have fewer problems with the sedative or antihistaminic properties compared with the tricyclic antidepressants, which improves their safety profile, but their antidepressant effects also can take weeks to manifest. Selective serotonin reuptake inhibitors target many of the underlying psychopathologies in psychogenic pruritus, such as depression, anxiety, and OCD. There have been many reports of their efficacy in the treatment of neurotic excoriations.[21,47-56] Although these drugs are associated with fewer serious adverse events than tricyclic antidepressants, they can be associated with side effects that patients may find distressing, including nervousness, insomnia, fatigue, weight gain, and sexual dysfunction. Children or adolescents taking any of the SSRIs should be monitored closely for increased depression and suicidal ideation. In addition, if the medication is discontinued abruptly, a withdrawal syndrome can occur in rare cases, resulting in dizziness, tremor,

anxiety, and dysphoria, which may be minimized or avoided by gradually tapering the dose.

Mirtazapine is a noradrenergic and specific serotonergic antidepressant and antihistamine that has been used for the treatment of psychogenic pruritus. It facilitates norepinephrine neurotransmission and selectively increases serotonin neurotransmission. Compared with other antidepressants used for this purpose, mirtazapine has a more favorable side-effect profile, with fewer incidences of nausea and sexual dysfunction. However, as with SSRIs, children or adolescents taking mirtazapine should be monitored for rare occurrence of increased depression and suicidal ideation. Anecdotally, mirtazapine has been effective in reducing nocturnal itching in a case of chronic neurotic excoriation, with the onset of action within 2 weeks.[57] Discontinuation of mirtazapine resulted in recurrence of pruritus.

Pimozide is an antipsychotic medication that is useful in the treatment of delusions of parasitosis.[58] Its effect in reducing delusions is mediated primarily by its antidopaminergic effect. However, the antipruritic effect of pimozide may be attributed to its opiate-blocking effect.[59] As with other antipsychotic agents, there are many potential side effects, including prolongation of the QT interval; ventricular arrhythmias; neuroleptic malignant syndrome; and extrapyramidal side effects, such as restlessness, acute dystonic reactions, Parkinsonlike symptoms, and tardive dyskinesia. These effects usually are dependent on the dose and length of use and are not always reversible on discontinuation of the drug. The extrapyramidal side effects of pimozide may be minimized with the concurrent use of diphenhydramine.

Olanzapine, an atypical antipsychotic agent, has shown efficacy in treating neurotic excoriations in nonpsychotic patients.[60,61] Caution should be used when prescribing this drug in elderly patients, as the risk of cerebrovascular accidents and dementia-related psychosis is higher in this population. Other adverse side effects include hyperglycemia, diabetes mellitus, neuroleptic malignant syndrome, and tardive dyskinesia.

Nonpharmacologic Therapy—Some nonpharmacologic therapies have been anecdotally shown to benefit patients with pruritus of neurogenic and psychogenic etiology.

When the underlying psychiatric diagnosis is obvious to the physician, he/she must first consider if the patient should be confronted with the diagnosis. If the patient is unable to recognize his/her emotional distress, then early confrontation may produce anxiety and anger, resulting in loss of therapeutic rapport.[62] Rather, a strong physician-patient alliance is essential.[63] Once a trusting relationship has been established, psychotherapeutic options may be introduced. In dermatitis artefacta, a supportive and empathic approach is recommended, avoiding discussion of the self-inflicted nature of the lesions.[23,64-67] When a strong therapeutic relationship has been developed, a more insight-oriented psychotherapeutic approach may be helpful.[65,68]

Some patients with pruritus of a psychogenic etiology may have awareness of their participation in the development of skin lesions, such as patients with neurotic excoriations. Despite this awareness, a trusting physician-patient relationship should still be cultivated before broaching a discussion about participation in their disease.[69] Once a trusting physician-patient alliance is established, the underlying psychopathology may be openly discussed and treated, and nonpharmacologic psychocutaneous interventions may be discussed. The benefits of these interventions appear to result from stress reduction, the patient's increased sense of control of the illness, and normalization of the psychoneuroendocrine function.[70] More importantly, these therapeutic strategies do not cause the patient any harm and are likely to improve the patient's overall quality of life.

Cognitive behavior psychotherapy and behavior techniques coupled with biofeedback, minocycline, and sertraline were effective in reducing picking behavior in a young woman with acne excoriée.[70] Most reports of the effectiveness of psychotherapy are anecdotal. However, healing of neurotic excoriation lesions has been reported for up to 5 years after cessation of therapy in 17 of 20 patients who underwent psychotherapy with insight-oriented and behavior components.[71]

Hypnotic trance is defined as a heightened state of focus that can be helpful in reducing pruritus while simultaneously inducing favorable physiologic changes.[70] Direct suggestion while in the hypnotic state is the most commonly used method of decreasing pruritus.[72] In addition, retraining the subconscious through hypnosis to replace a destructive habit pattern with a more constructive one, called *symptom substitution*, can be helpful in patients with self-inflicted lesions.[73] There have been 2 reported cases of control of acne excoriée using posthypnotic suggestion.[74]

Comment

There is considerable overlap between neuropathic disorders and psychologic factors. As this review demonstrates, the presentation of neuropathic and

psychogenic pruritus can be similar. In addition, therapy that is effective for one disorder often can be effective for the other disorder. However, despite the variety of medications used to treat these disorders, it is an underdeveloped field. There is a paucity of controlled studies, and most reports of efficacy are based on anecdotal evidence. As a result, it is difficult to practice evidence-based medicine when treating patients with neuropathic and psychogenic pruritus.

Neuropathic and psychogenic pruritus constitutes an area of medicine in which expertise from specialists in the fields of dermatology, psychiatry, and neurology would be immensely helpful. Although a dermatologic approach to treating these conditions is effective, there also is benefit in therapies typically used in psychiatry and neurology. Therefore, interdisciplinary cooperation between these 3 fields will likely result in optimal treatment of patients with neurogenic and psychogenic pruritus. When approaching treatment of patients with these conditions, it may be beneficial to try a multimodality therapeutic approach, using agents from several medical disciplines.

Conclusion

The diagnosis and treatment of neurogenic and psychogenic pruritus were reviewed and updated. Evidence-based studies regarding therapies available for these conditions are sparse. Despite considerable overlap of dermatology, psychiatry, and neurology, pruritus sine materia is a neglected area of medicine, both clinically and scientifically. More interdisciplinary cooperation and studies are essential for further progress.

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