

Pruritus: still a challenge *

Prurido: ainda um desafio

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Abstract: Prurido é um sintoma que pode estar associado a uma gama ampla de patologias, sejam elas cutâneas, sistêmicas ou mesmo sem causa definida. Conforme sua intensidade e evolução pode comprometer de forma significativa a qualidade de vida dos pacientes. Novas abordagens terapêuticas estão sendo descritas para o controle do prurido, onde a liberação da histamina não é o fator principal. Assim, baseando-se na origem de seus mediadores, faz-se uma revisão desses recursos e ressalta-se que, embora de grande importância no arsenal terapêutico, os anti-histamínicos não são a panacéia para todos os tipos de prurido.

Palavras-chave: Antipruriginosos; Diagnóstico; Prurido; Resultado de tratamento

Resumo: Pruritus is a symptom that may be associated with a wide array of diseases - skin diseases, systemic diseases or even those without a defined cause. According to its severity and evolution, it may compromise the patients' quality of life in a significant way. New therapeutic approaches, in which histamine release is not the main event, are being described for pruritus control. Therefore, taking into account the origin of the mediators of pruritus, we conducted a review of the available resources emphasizing that, although very important, anti-histamines are not the answer for every kind of pruritus.

Keywords: Antipruritics; Diagnosis; Pruritus; Treatment outcome

INTRODUCTION

Pruritus is a symptom that essentially manifests itself in the skin and/or mucous membranes and can range from mild to intense (fierce pruritus), localized to generalized and intermittent to persistent (chronic pruritus). Treatment of intense and persistent pruritus is challenging because knowledge of the mechanisms involved is required to help the clinician establish a therapeutic approach that provides the patient with relief and comfort. Based on evidence from the most recent studies on this topic, this paper aims at establishing practical therapeutic approaches to deal with difficult cases of pruritus.

DEFINITION OF PRURITUS

Unpleasant sensation in the skin that provokes the act of or desire to scratch.^{1,2}

PATHOPHYSIOLOGY OF PRURITUS

Slow-conducting unmyelinated C fibers, histamine-responsiveness and non-mechanosensitivity were discovered as transmitters of pruritus in humans in the 1990s.³ Recent advances in our knowledge of the neurobiology of pruritus, at both the peripheral and central levels, have shown that these specific fibers do not appear to play an important role in the modulation of chronic pruritus because patients with systemic diseases and pruritus do not respond to anti-histamine treatment, despite the use of high doses.⁴ Since the 1950s, it has been suggested that non-histaminergic pathways also contribute to the conduction of pruriginous impulses. Over the past 3 years, researchers have identified a distinct group of type C nerve fibers in monkeys and humans through which these impulses might be conducted. These impulses are

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triggered by mechanical stimuli and are unresponsive to histamine. The identification of these dual and independent pathways suggests the potential existence of other unknown paths of transmission, which are expected to be detected and described in future research.^{5,6} Pruritus can also be triggered by chemical stimuli, such as cytokines, proteases, serotonin, prostaglandins, neuropeptides, endogenous opioids and substance P. Serotonin and endogenous opioids play an important role in systemic pruritus.⁷

Physical stimuli, such as electricity, pressure and temperature, can also trigger pruritus.⁸

The impulses travel through C fibers, the spinal dorsal horn and the thalamus, ending at the cerebral cortex, where pruriginous perception occurs leading to the desire to scratch. At the level of the spinal cord and brain, central sensitization of pruritus contributes to the abnormal modulation of chronic pruritus, which is similar to the one observed in chronic pain, as seen in post-herpetic neuralgia.⁹ The act of scratching stimulates A-delta myelinated sensory fibers and temporarily blocks the pruriginous sensation.¹⁰

CLASSIFICATION OF PRURITUS

A. PRIMARY OR IDIOPATHIC: Pruritus for which no causal factor can be identified following extensive investigation. Data from the literature show that up to 70% of cases can be included in this category; however, they also show that at least 20% of these cases, when thoroughly investigated, are shown to have a systemic cause.¹¹

B. SECONDARY: In this category, pruritus accompanies an underlying pathology and can be associated with the following diseases:

1. SKIN DISEASES: contact dermatitis, eczema, atopy, xerosis, hives, prurigo, lichen planus, dermatitis herpetiformis, bullous pemphigoid, pityriasis rosea, psoriasis, mastocytosis, scabies and pediculosis, among others.

2. SYSTEMIC DISEASES: cholestatic and non-cholestatic liver diseases, chronic renal failure/hemodialysis, diabetes mellitus, diabetes insipidus, hyper and hypothyroidism, parathyroid diseases, iron-deficiency anemia, polycythemia vera, drug reactions, carcinoid syndrome, paraneoplastic syndrome, lymphomas (Hodgkin and non-Hodgkin), multiple sclerosis, stroke, tabes dorsalis, notalgia and meralgia paresthetica, herpes zoster and brain tumors.

INVESTIGATION OF PRURITUS

Oftentimes dermatologists are required to evaluate and give their opinion about these cases. Anamnesis and a detailed physical examination are mandatory, in addition to complementary laboratory exams, such as CBC, glycemia, bilirubin test, liver, kid-

ney and thyroid functions tests, routine urine examination, fecal examination, skin biopsy and image diagnosis, when necessary.

MEDIATORS OF PRURITUS

A. HISTAMINE RECEPTORS: Four types of histamine receptors have been described. The HR1 receptor is the major responsible for histamine release, whereas HR2 stimulates gastric secretion and maintains prolonged vasodilatation.^{12,13,14} The HR4 receptor, found in inflammatory and immune cells, participates in the modulation of pruritus as it was noticed that experimentally induced pruritus can be inhibited by anti-HR4 treatment. Animal models have shown that HR3, found in the central nervous system (CNS) and peripheral nervous system (PNS), also appears to be involved in this type of modulation. Antihistamine receptors have little effect in the treatment of systemic pruritus.

B. PROTEINASES: The proteinase-activated receptor-2 (PAR-2) is located in the terminals of C fibers and appears to play an important role in the modulation of pruritus; however, its role in systemic diseases has not yet been established.¹⁵

C. VANILLOID RECEPTORS: Transient receptor potential vanilloid subtype 1 (TRPV1) is a capsaicin receptor expressed in nociceptive primary afferent neurons, keratinocytes, dendritic cells and dermal mast cells.¹⁶

TRPV3 is associated with the development of pruritus in rats and may play an important role in the modulation of chronic pruritus.

D. GASTRIN-RELEASING PEPTIDE RECEPTOR (GRPR): Together with the gastrin-releasing peptide (GRP), GRPR has been shown to modulate pruritus through different stimuli in the spinal cord of rats.¹⁷

E. ENDOGENOUS OPIOIDS: Two types of opioid receptors are associated with pruritus. When stimulated, the *mu*-receptor promotes pruritus and the *kappa*-receptor inhibits it.¹⁸ Intense and generalized pruritus is one of the most common adverse effects of analgesic therapy with exogenous *mu*-opioid receptor agonists. Endogenous opioids play an important role in the pathogenesis of pruritus and are related to its presence in systemic diseases, as observed in cases of cholestasis (e.g., primary biliary cirrhosis) and chronic renal failure/hemodialysis. The role of pruritus in lymphomas has not been well established. However, the use of *kappa*-agonists and *mu*-antagonists in some cases of non-Hodgkin lymphoma has been found to be effective in controlling pruritus.

F. INTERLEUKINS: Interleukins are cytokines, also known as lymphokines. Structurally, they are polypeptides primarily produced by T lymphocytes, but they can also be synthesized by macrophages,

monocytes and other cells, such as epithelial cells. Interleukins mediate immune and inflammatory responses by promoting communication between lymphocytes, attracting macrophages, stimulating the phagocytosis of foreign microorganisms and promoting erythropoiesis.^{19,20} Interleukins are identified by numbers, e.g., IL-1 and IL-2, and over 30 types have already been described. Interleukin-2 promotes pruritus in atopic dermatitis and other inflammatory diseases of the skin; however, its association with systemic diseases is unclear. Recent findings have shown that IL-31 (produced by Th2 cells) is capable of triggering pruritus in atopic patients and in cases of nodular prurigo, indicating a potential role for this cytokine in the modulation of pruritus. The antibody anti-IL-31 has been experimentally shown to effectively reduce itching in an animal model of atopy, demonstrating a potential future therapeutic approach in the treatment of this form of chronic pruritus. Other cytokines that may modulate pruritus are IL-6 and TNF-alpha, although new inhibitors (immunobiologicals) of TNF-alpha appear not to have antipruritic effect. However, thalidomide, a TNF-alpha inhibitor, does exert antipruritic effects.

G. SEROTONIN RECEPTORS: Serotonin, or 5-hydroxytryptamine (5-HT), is a neurotransmitter derived from tryptophan that is involved in the communication between neurons and regulation of the circadian rhythm, sleep rhythms and appetite.²¹ Ecstasy and LSD mimic some of the effects of serotonin in specific target cells. Initially, ecstasy promotes a massive release of serotonin, followed by a subsequent depletion. Drugs that control the activity of serotonin through the 5-HT₂ and 5-HT₃ receptors are used to treat disorders such as anxiety, depression, obesity, migraines and schizophrenia. Studies have demonstrated an involvement of serotonin in the genesis of chronic pruritus, particularly of systemic origin.

H. OTHER FACTORS: Exogenous or endogenous cannabinoids are known for their hallucinogenic and analgesic effects, and the existence of cannabinoid receptors (CB1 and CB2) in cutaneous sensory nerve fibers, mast cells and keratinocytes has been recently proven.^{22,23} Cannabinoid agonists, such as palmitoyl ethanolamine (PEA), can suppress histamine-triggered pruritus, although the mechanism responsible for this effect remains unknown. Gamma-aminobutyric acid (GABA) and its receptors are also involved in the modulation of pruritus, particularly of neuropathic origin. However, few studies have examined the relationship between the cannabinoid system, GABA and its receptors in the modulation of chronic pruritus. Substance P is a neuropeptide that belongs to the family of tachykinins and regulates numerous biological functions via its receptor, neurokinin-1

(NK-1R). This substance is released at nociceptive neuronal terminals and modulates pruritus by promoting vasodilation and histamine release. Kallikrein is a proteolytic polypeptide that affects the modulation of pruritus through its significant direct and indirect vasodilating properties. Kallikrein activity results in the breakdown of bradykinogen, which generates the potent vasodilators bradykinin and kallidin.

THERAPEUTIC RESOURCES

To date, there is no specific antipruritic treatment. Current treatments aim to reduce the intensity of pruritus by blocking the afferent impulse via peripheral and central neural mechanisms, specifically acting on the receptors involved, whenever possible. Few evidence-based studies have evaluated the efficacy of these agents. Most of the available data are based on isolated case reports or small case series (Chart 1).

A. ANTIHISTAMINES: Antihistamines primarily block H1 receptors.²⁴ In addition to the H1 receptor's main function of releasing histamine, it is also responsible for immediate vasodilatation. The H2 receptor, which is responsible for gastric secretion, is also responsible for prolonged vasodilation. Therefore, the combination of anti-H1 and anti-H2 agents can be beneficial in the treatment of some cases of hives.

Anti-H1 antihistamines are classified as 1st and 2nd generation.

1. 1st GENERATION ANTI-H1: These agents are liposoluble, have low molecular weight, can cross the blood-brain barrier, are fast acting, are quickly metabolized (4-6 hrs), are sedative due to their high affinity for H1 receptors in the CNS and have muscarinic effects (dry mouth, urinary retention, sinus tachycardia). The following compounds are classified as part of this group: dexchlorpheniramine, diphenhydramine, hydroxyzine, clemastine, cyproheptadine and ketotifen.

2. 2nd GENERATION ANTI-H1: These agents have low liposolubility, do not cross the blood-brain barrier, have a prolonged action (12-24 hrs), are more potent and have little sedation and few muscarinic effects. The following compounds are classified as part of this group: cetirizine, loratadine, ebastine, fexofenadine, desloratadine, levocetirizine and rupatadine.

The anti-H2 anti-histamines cimetidine and ranitidine are most commonly used in the treatment of gastric dyspepsia. However, because they control prolonged vasodilatation, they may be combined with anti-H1 antihistamines for better control in some cases of hives.

DOXEPIN: Doxepin is a tricyclic antidepressant belonging to the amitriptyline family. It exhibits marked sedative properties and inhibits the reuptake of

CHART 1: Therapeutic options for pruritus

HEPATIC PRURITUS	1st OPTION: CHOLESTYRAMINE* (Maximum dose 16gr/day) – 1-4gr/1-4x/day-2hs before meals 2nd OPTION: RIFAMPICIN**; 300-600mg/day or 10mg/kg/day 3rd OPTION: Receptor <i>mu</i> -opioid antagonist or receptor <i>Kappa</i> -opioid agonist
RENAL PRURITUS	1st OPTION: BAA§ low doses 2nd OPTION: AST§§ 3rd OPTION: Phototherapy- UV rays 4th OPTION: BAA + AST 5th OPTION: Receptor <i>Kappa</i> opioid agonist
LYMPHOMA	1st OPTION: AST or BAA 2nd OPTION: AST + BAA 3rd OPTION: Receptor <i>Kappa</i> opioid agonist 4th OPTION: Oral corticosteroid short course- 1-2mg/kg/d Prednisone.

CHOLESTYRAMINE*: a bile acid sequestrant which binds bile in the gastrointestinal tract to prevent its reabsorption (strong ion exchange resin)

It not always relieves pruritus.

RIFAMPICIN**: antibiotic with properties not fully understood in the treatment of cholestatic pruritus, perhaps due to hepatic enzyme induction or intestinal flora exchange.

BAA§: Brain antiarrhythmics

AST§§: Anti-Serotonins

Adapted source: Wang H, et al. 2010 ¹¹

noradrenaline. In addition to anticholinergic and serotonergic effects, doxepin displays an antihistamine effect and, consequently, an antipruritic effect through the blockage of H1 receptors. ²⁵ It is well absorbed in the gastrointestinal tract and metabolized in the liver to produce the active metabolite desmethyldoxepin, which is eliminated by the kidneys following glucuronidation. Doxepin is widely distributed through the tissues, including the CNS, because it is able to cross the blood-brain barrier. It also crosses the placenta and is excreted in breast milk, with a half-life ranging from 11 to 23 hrs. In dermatology, this drug can be used as treatment for mild pruritus both parenterally (25-50 mg-VO-3x/day – elderly: 10-50 mg/day) and topically as a 5% cream (2-4x/day) to help relieve localized pruritus. This substance can also be administered intravenously (IV) and intramuscularly (IM). The adverse effects of doxepin treatment include drowsiness, dryness of mucous membranes, headaches, fatigue, dizziness, nausea and fever. Contraindications include narrow angle glaucoma, prostatic hyperplasia, pregnancy and lactation. Doxepin should not be prescribed to patients under 12 years of age. Due to increase of QT interval, before the treatment, patients over 40 years must undergo an ECG. Not to be prescribed in cases of cardiac deficiency, arrhythmia, A-V block or recent myocardial infarction.

B. ANTI-SEROTONINS: Anti-serotonins are primarily indicated for systemic pruritus of metabolic origin (liver diseases, renal failure/hemodialysis, thy-

roid diseases) and neoplastic and paraneoplastic pruritus, which are primarily mediated by serotonin. ²⁶ These compounds act primarily by blocking the 5-HT2 and 5-HT3 receptors. The main agents used include the following:

1. **MIRTAZAPINE:** Mirtazapine is a tricyclic antidepressant with anti-5-HT2, anti-5-HT3 and anti-H1 effects. ²⁷ The dosage varies between 7.5-15 mg-VO at night and may reach 30 mg/day. The main adverse effects of mirtazapine treatment are drowsiness (57%), increased appetite (17%) and increased weight (12%). It has little anticholinergic activity. Use of mirtazapine is not recommended for children; no alcoholic beverages should be ingested during treatment, and there can be no concurrent use of benzodiazepines or MAO inhibitors. Due to its pleiotropic cytochrome metabolism, mirtazapine may be combined with other drugs with relative safety.

2. **PAROXETINE:** Paroxetine, an antidepressant derived from piperidine, is a potent serotonin reuptake inhibitor. ²⁸ The dosage varies from 5-20 mg-VO in the morning. It has a lesser sedative effect than mirtazapine and may be used in combination with this drug. Paroxetine has anticholinergic effects and is not recommended for children. No alcoholic beverages should be ingested during treatment, and it should not be used in combination with MAO inhibitors.

3. **ONDANSETRON:** Ondansetron is a potent anti-emetic drug used as an adjuvant in anticancer chemotherapy. ²⁹ This drug has a highly selective anti-5-HT3 effect and is used at a dosage of 4 mg-VO-3-

4x/day. It is a well-tolerated drug and has few adverse effects, including constipation, dizziness and headaches. It is metabolized by the cytochrome p450 system and shows little interaction with other drugs.

C. OPIOID ANTAGONISTS AND AGONISTS:

These agents are used in situations in which endogenous opioids are released in addition to serotonin, such as cholestatic pruritus.³⁰ Exogenous opioids (morphine) administered via the spinal cord as a palliative for pain in cancer patients also trigger pruritus through agonist effects on *mu*-receptors. The main agents include the following:

1. **NALTREXONE:** Naltrexone, a synthetic analog of oxymorphone and a *mu*-receptor antagonist, is used as an anti-opioid. Dosages start at 25 mg/day-VO and can reach 50 mg/day-VO if necessary.³⁰

2. **NALOXONE:** Naloxone, a synthetic opiate similar to morphine, is used to reverse coma and respiratory depression due to opiate poisoning.^{31,32} It also has a *mu*-receptor antagonist effect. It is used at IV-400-2000 micrograms/dose and may be repeated at intervals of 4-8 minutes. A maximum dose of 10 mg can be reached.

NOTE: Although the use of *mu*-receptor antagonists may control pruritus, it may also cause pain, which may result in greater discomfort for the patient. These drugs can be very useful in the treatment of chronic cholestasis, though they may increase suffering in patients with chronic renal failure.

3. **NALFURAFINE (TRK-820):** Nalfurafine is a *kappa*-receptor agonist specifically developed for use in uremic pruritus of patients subjected to hemodialysis.^{33,34,35} It is commercially available as Remitch (nalfurafine hydrochloride) in 2.5- μ g capsules. The dosage is 1 capsule (2.5 μ g-VO-1x/day) after dinner or before bed, not to exceed 5 μ g/day.

4. **BUTORPHANOL:** Butorphanol is an opioid *mu*-receptor antagonist and *kappa*-receptor agonist.³⁶ It has been proven effective in the treatment of refractory pruritus in lymphoma, primary biliary cirrhosis and other systemic diseases. It is available as a nasal spray, and the recommended dosage is 3-4 mg/day; each application provides 1 mg of the drug.

D. BRAIN ANTIARRHYTHMICS or ANTICONVULSANTS: These agents are indicated for the treatment of neuropathic pruritus, i.e., when the lesion is in the neural tissue and destabilizes the electrical conduction activity at a peripheral and central level, as observed in the following situations: notalgia and meralgia paresthetica, tabes dorsalis, stroke, herpes zoster, brain tumors and lumbosacral radiculopathy (anal itching).³⁷ In these cases, the best results are observed for drugs that act on the metabolism of GABA.

1. **PREGABALIN:** Pregabalin is an anticonvulsant

and GABA analog with the same indications as gabapentin; however, the onset of action of pregabalin is quicker (5-7 days), and the adverse effects are less severe.^{26,38} The dosage is 75-150 mg-VO-3x/day.

2. **GABAPENTIN:** Gabapentin, an anticonvulsant GABA analog, is occasionally used for the treatment of pain and pruritus of neuropathic origin.^{39,40,41} It may cause drowsiness, fatigue and dizziness. This drug presents few drug interactions, and treatment should not be abruptly interrupted. Onset of action occurs after 10-14 days of use. The dosage is 400-600 mg-VO-3x/day.

E. NON-HORMONAL ANTI-INFLAMMATORY (NHAI) AGENTS: The goal of these agents is an anti-prostaglandin effect, especially in pruritus associated with AIDS, in which the release of prostanoids enhances the effect of histamine.^{7,8} In most of these cases, antihistamines are unable to relieve the symptoms. The following agents can be used: diclofenac, indomethacin, piroxicam, ibuprofen, naproxen and phenylbutazone. Protection of the gastric mucosa with anti-H2 or proton pump inhibitors may be necessary.

F. PHOTOTHERAPY – TREATMENT WITH UV

RAYS: Phototherapy is indicated for cases of severe and/or refractory pruritus, which can occur in the following situations: severe atopy, chronic eczema, chronic renal failure/hemodialysis, cholestatic liver diseases, lymphomas and AIDS, among others.⁴² Narrow-band UVB (311-312 nm) without psoralens is normally used. Treatment begins with sessions 2-3x/week for up to 3 months or until symptoms improve, and treatment is maintained with sessions 1-2x/month. Pruritus may worsen during the first two weeks of treatment, and improvement only occurs after the first month of treatment. Treatment exceeding 160 applications, on average, should be avoided due to the risk of predisposing the patient to skin cancer, particularly squamous cell carcinoma (SCC) and melanoma. Phototherapy has the following properties:

1. **Anti-inflammatory/Immunosuppressor property:** decreases the production of proinflammatory interleukins and T lymphocyte activity.

2. **Anti-proliferative property:** decreases DNA synthesis and, consequently, cell proliferation and induces apoptosis (programmed cell death) of keratinocytes.

G. TOPICAL THERAPY: Hydration, lubrication and restoration of the skin barrier with creams, lotions or emollients are important primary and adjuvant approaches because these diseases often present asteatosis. Thus, patients must be advised to avoid hot long baths as well as the excessive use of soap. In localized areas, pruritus can be treated with some specific creams and ointments.

1. **CAPSAICIN:** Capsaicin is a natural neuropep-

tide derived from red pepper (chili) that depletes substance P, which is the main nociceptive transmitter from the PNS to the CNS. It is applied in the form of a cream (0.025% and 0.075%) or lotion (0.025%), with 3-4 applications per day.⁷ Skin irritation and burning sensations occur with the first few applications and disappear with continued treatment. This treatment is not for facial use; care must be taken with the eyes, and hands should be thoroughly washed after each application.

2. **DOXEPIN:** Doxepin is a tricyclic antidepressant with anti-H1 activity that is used topically for the treatment of mild to moderate localized skin pruritus.²⁵ It is formulated as a 5% cream and should be applied 4x/day, with intervals of at least 3-4 hrs between applications. Its use is contra-indicated during pregnancy and lactation. Alcoholic beverages should not be ingested during treatment. Sun exposure should be avoided, and the medication should be protected from light.

3. **TACROLIMUS:** Tacrolimus, formulated as 0.03% and 0.1% creams, has been found to have no effect beyond that of the vehicle control.⁴³

4. **STRUCTURED LIPIDS CONTAINING ENDOCANNABINOIDS:** Structured lipid emollients have been shown to be effective in controlling asteatosis and improving uremic pruritus.⁴⁴

H. **PSYCHOSOMATIC THERAPY:** Relaxation and behavioral therapy techniques have proven useful as auxiliary resources in controlling pruritus and the scratching compulsion.⁴⁵

IMPORTANT CONSIDERATIONS

General measures of coexisting factors, especially skin xerosis, should not be overlooked, and the patient's skin should be kept properly hydrated and lubricated. Detailed instructions should be provided on the type of care to be taken in the shower. In most cases, these types of behaviors, while not fully resolvent, aid in alleviating symptoms and avoid the need for more aggressive therapeutic approaches, which are subject to intolerance and undesirable adverse effects. Dietary counseling with a nutritionist, if possible, is also of great importance in certain cases, such as in uremic pruritus, in which protein intake must be planned, and in cholestatic pruritus, in which the ingestion of polyunsaturated fatty acids should be encouraged. Moreover, it has been demonstrated that high permeability hemodialysis is significantly more effective than conventional hemodialysis in terminal patients with chronic renal failure and is associated with much lower rates of pruritus.^{46, 47}

CONCLUSION

Studies conducted over the past few decades have uncovered greater details about the complex pathophysiology associated with pruritus related to systemic diseases, cancer and paraneoplastic conditions. This evidence, observed in the fields of neurobiology, immunology, molecular biology and pharmacology, introduces further and improved knowledge of the main pathologies that present significant concurrent pruritus, enabling the development of new and more effective protocols for the clinical approach to the treatment of these patients. However, it is clear that pruritus remains a puzzle with unknown pieces. □

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