Diagnosis and Management of Chronic Pruritus: An Expert Consensus Review

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Abstract

The aim of this study is to formulate the best clinical practice in the diagnosis and management of chronic pruritus (CP). We searched PubMed, EMBASE, Scopus, Web of Science, and the WHO’s regional databases, for studies on “Diagnosis and management of chronic pruritus” from January 1, 2014, to July 31, 2015. We included programmatic reports and hand-searched references of published reviews and articles. Two independent reviewers screened articles and extracted data. We screened 87 of 95 studies that contained qualitative data. Avoid: Dry climate, heat, alcohol compress, ice packs, frequent bathing and washing, intake of very hot and spicy food, intake of alcohol, contact with irritant substances, excitement, strain and stress, and allergens. Using: Mild nonalkaline soaps, moisturizers, bathing oils, lukewarm water while bathing, soft cotton clothing and night creams/lotions, relaxation therapy, autogenic training, psychosocial education, educating patients to cope with itching and scratching, and educational programs. Especially use of moisturizers is considered important. In addition, symptomatic treatment options include systemic H1 antihistamines and topical corticosteroids. Symptomatic therapy directed toward the cause (hepatic, renal, atopic, polycythemia, etc.). If refractory or cause is unknown, consider capsaicin, calcineurin inhibitors for localized pruritus and naltrexone, pregabalin, ultraviolet therapy, Cyclosporine for generalized itching. CP is quite frequent finding associated with skin and systemic diseases in the overall population. It is known to significantly affect quality life score of an individual and also adds burden on the health-care cost. A specific recommendation for treatment of CP is difficult as a result of varied and diverse possibility of underlying diseases associated with CP.

Key Words: Chronic pruritus, Consensus, Management of Chronic pruritus

Introduction

Pruritus is an unpleasant sensation on the skin eliciting the desire to scratch. Chronic pruritus (CP) refers to daily/almost daily itching, lasting more than 6 weeks.[1] Clinically, pruritus has been described as the most frequent symptom in dermatological condition. It has demonstrated a significant impact on patient’s quality of life (QoL) that causes various problems related to sleep, anxiety, attention, and sexual function. Moreover, CP poses a significant burden on the society in terms of health-care cost and treatment challenges.[1] In addition, many systemic diseases are also known to be associated with pruritus and further incapacitating nature of this condition.[2] Insufficient data have been reported on the prevalence of CP. It has been suggested that there is an increase in the prevalence of CP with advancing age.[1] Moderate-to-severe pruritus is known to affect 60% of the elderly individuals (≥65 years of age).[4] Recent studies have suggested a point prevalence of CP to be approximately 13.5% in the general adult population and 16.8% in those undergoing cancer screening.[5,6] In addition, a German population-based cross-sectional study reported a 12-month prevalence and lifetime prevalence of CP to be approximately 16.4% and 22.0%, respectively.[5]

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Current Challenges in Management of Chronic Pruritus

In dermatologic practice, CP is the most troublesome symptom. It has a major impact on QoL score and also has severe psychological implications. Treatment of CP remains a challenge when it is not associated with a skin lesion or it is not of systemic origin. Anti-inflammatory agents including steroids and antihistamines help in managing pruritus in case of cutaneous inflammatory disorders and allergic disorders, respectively. Systemic disorders associated with pruritus include uremic pruritus, hepatobiliary pruritus, pruritus due to hematological causes such as polycythemia vera, leukemia, lymphomas (especially Hodgkin’s disease), multiple myeloma, pruritus due to endocrine disorders, and multiple sclerosis. In recent times, understanding the pathomechanism of pruritus of systemic origin has improved considerably. Clinicians must offer individualized therapy in the management of pruritus. However, lack of randomized controlled trials has been reported due to the diversity and complexity of the symptom, multifactorial etiologies, and lack of well-defined outcome measures. In addition, for documenting CP, no standardized method has been reported. There is lack of guidelines suggesting apt diagnostic modalities for the management of CP. This is suggestive of the dire need for comprehensive consensus discussing diagnosis and management of CP. Therefore, the current discussion will mainly focus on expert commentaries for the diagnosis and management of CP.

Methods

We screened 87 of 95 studies that contained qualitative data. We searched PubMed, EMBASE, Scopus, Web of Science, and the WHO’s regional databases, for studies on “Diagnosis and management of chronic pruritus” from January 1, 2014, to July 31, 2015. We included programmatic reports and hand-searched references of published reviews and articles. Two independent reviewers screened articles and extracted data.

Figure 1 depicts the clinical classification for the management of patients with CP. Pruritus and itch are considered to be synonymous. The term “pruritus of unknown origin” or “pruritus of undetermined origin” has been commonly specified in patients with no identified underlying disease. Although Groups I and II may already suggest a category, the classification of the patient is performed in the second step based on histological, laboratory, and radiological investigations. If no category fits or several diseases are found (green arrows), the patients are classified into “mixed” or “others.”

Table 1 shows etiological classification of CP.

Dermatological origin of chronic pruritus [Table 2]

- Pruritus due to dermatological diseases with/without primary skin lesions (rash)
  - Dermatoses induce pruritus locally or generalized and present with primary skin lesions.

Systemic origin of chronic pruritus [Table 3]

- Renal/uremic itch
  - Patients with uremia suffer from continuous itch while others experience it in episodes or exacerbations.

- Hepatic itch
  - Any liver disease with cholestasis can give rise to the development of pruritus which is generalized and without rash.

- Diabetes mellitus
  - Generalized pruritus has been documented in diabetics; however, its frequency is unknown. Localized pruritus along with infection (around anus, genitals) is more common in DM caused due to candidiasis.

Neuropathic

Figure 1: Clinical classification of patients with chronic pruritus
Table 1: Etiological classification of chronic pruritus

| Category               | Diseases                                                                                                                                 |
|------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Dermatological         | Arising from “diseases of the skin,” such as psoriasis, atopic dermatitis, dry skin, scabies, and urticarial                              |
| Systemic              | Arising from “diseases of organs” other than the skin, such as liver (e.g., primary biliary cirrhosis), kidney (e.g., chronic renal failure), blood (e.g., Hodgkin’s disease), and certain multifactorial (e.g., metabolic) states or drugs |
| Neurological[15]      | Arising from “diseases or disorders of the central or peripheral nervous system,” e.g., nerve damage, nerve compression and nerve irritation |
| Psychogenic/psychosomatic | Somatiform pruritus with comorbidity of "psychiatric and psychosomatic diseases"                                                        |
| Mixed                  | Overlapping and coexistence of several diseases                                                                                           |
| Others                 | Undetermined origin                                                                                                                       |

Table 2: Category 1 – Dermatological origin of chronic pruritus

| Dermatological diseases | Examples of diagnoses                                                                                     |
|------------------------|----------------------------------------------------------------------------------------------------------|
| Inflammatory dermatoses | Atopic dermatitis, psoriasis, contact dermatitis, dry skin, drug reactions, scars, “invisible dermatoses” |
| Infectious dermatoses   | Mycotic, bacterial and viral infections and folliculitis, scabies, pediculosis, arthropod reactions, insect bites |
| Autoimmune dermatoses   | Bullous dermatoses, especially dermatitis herpetiformis Duhring, bullous pemphigoid, dermatomyositis       |
| Genodermatoses          | Darier’s disease, Hailey–Hailey disease, ichthyoses, Sjögren–Larsson syndrome, epidermolysis bullosa pruriginosa |
| Dermatoses of pregnancy | Polymorphic eruption of pregnancy, pemphigoid gestation, prurigo gestation                              |
| Neoplasms               | Cutaneous T-cell-lymphoma (especially erythrodermic variants), cutaneous B-cell lymphoma, leukemic infiltrates of the skin |

Pruritus and malignancy

Generalized pruritus has been documented in cases of carcinoma of the lung, stomach, colon, prostate, breast, and pancreas. Surgical removal of the tumor and use of serotonin re-uptake inhibitors or serotonin antagonists in inoperable cases are usually the recommended treatments. Different forms of mastocytosis, i.e., solitary mastocytoma, urticaria pigmentosa, telangiectasia macularis eruptiva perstans, and systemic mastocytosis are also significantly associated with symptoms of pruritus. In addition, pruritus may be associated with flushing in patients with carcinoid syndrome. In such cases, serotonin, produced in the enterochromaffin cells of the tumor, is responsible for eliciting pruritus. The use of antiserotonin drugs is usually considered to alleviate this symptom. Frequently, brain tumors are reported to be associated with pruritus. Importantly, 50% of these cases have reported nasal pruritus. However, exact mechanism for this association has not been fully understood. It has been postulated that immunological mechanisms, toxic metabolites, iron deficiency, and dry skin may trigger pruritus in such patients. Commonly, antihistamines are not considered to be helpful for relieving itch. However, eradication of the tumor can help diminish or abolish itch. Unilateral pruritus over the scapular region has been documented in patients with multiple endocrine neoplasms syndrome and is reported to be associated with deposition of amyloid. Pruritus can also be caused due to drugs given for chemotherapy such as antimetabolites, alkylating agents, and irradiation.[16]

Hematologic diseases and pruritus

Several hematological diseases are linked to cause pruritus. Itching may appear following contact with water or after a hot bath in patients with polycythemia vera. Symptom of aquagenic pruritus may be reported before the development of polycythemia vera. The use of salicylates, photochemotherapy, or interferon-α can be considered for treating such cases. In addition, pruritus is often reported in patients with iron deficiency, even in absence of anemia. Iron supplementation often alleviates this symptom. Patients with hemochromatosis may also report pruritus where they demonstrate elevated levels of iron in blood and tissues. Itchiness is also reported in about 30% of patients with Hodgkin’s disease. Radiation therapy or chemotherapy improves the symptoms of pruritus in Hodgkin’s disease. Patients with...
host reactions after bone marrow transplantation may also report pruritus.[16]

**Pruritus in infectious diseases**
Pruritus may be reported in some generalized infections. Furthermore, pruritic papular eruption or eosinophilic folliculitis has been documented in patients infected with HIV.[19,20]

**Neurological and somatoform origin of chronic pruritus** (Table 4)

### Localized neuropathic pruritus
Neuropathic itch of the scalp has been reported in patients with herpes zoster. In addition, localized neuropathic pruritus suggesting a compression of peripheral or brachioradial pruritus is found in postzosteric pruritus, notalgia paresthetica, and brachioradial pruritus.[15,21]

### Systemic neurological pruritus
Such patients present with hypo/hyperesthesia with itching and have localized, dermatomal involvement.

**Syringomyelia**
The pruritus is characterized by chronic lichenoid rash secondary to scratching.[22]

**Neurofibromatosis**
Pruritus is commonly reported in patients with neurofibromatosis. Patients generally demonstrate widespread cutaneous phenomenon. Mast cells found in neurofibromas account for the release of histamine, which leads to itching. Furthermore, the presence of localized pruritus may aid for suspicion of an underlying spinal cord or central nervous tumor.[1]

**Transverse myelitis**
Transverse myelitis is seen mostly in the neurology or orthopedic inpatients. A case reported in 2003 stated the development of severe pruritus and hyperesthesia due to transverse myelitis. Usually, patients complain of pain in legs followed by severe pruritus and hyperesthesia. Patients with transverse myelitis may also show lichenoid plaques and excoriations over affected area. It is mostly treatable by surgical methods. Medically sedative antihistamines are helpful than nonsedative antihistamines.[23]

**Cerebral lesions**
Cerebrovascular accidents (CVA) may be responsible for neuropathic itch. Patients suffering from CVA have reported to develop poststroke pruritus in a few days or weeks. Patients with CVA may report excessive localized or generalized pruritus but primarily involves skin contralateral to the stroke lesion.[24]

**Notalgia paresthetica**
It is characterized by unilateral pruritus located medial or inferior to the scapula in the T2–T6 dermatomal region. It is commonly reported in middle-aged women and is known to last for months or years. It may also be associated with pain, paresthesias, numbness, or hypersensitivity.[25]

**Drug-induced pruritus**
Most of the medications including angiotensin-converting enzyme inhibitors, antibiotics, antidepressants, antidiabetics, and drugs are likely to cause generalized pruritus.[26] CP may develop due to drug-induced hepatotoxicity or cholestasis as well as drugs leading to xerosis or phototoxicity.[27] Hydroxyethyl starch used for restoration of fluids may be associated with generalized or localized pruritus.[28]

**Chronic pruritus in special population**

### Elderly patients
Pathological mechanism of pruritus in elderly patients is still unclear. However, associated etiological factors that
are known to contribute for developing pruritus may include pathophysiological changes of the aged skin, decreased function of the stratum corneum, xerosis cutis, comorbid conditions, and multiple-drug use.[29] Studies conducted in elderly patients reported pruritus as the most common symptom in 11.5% of 4099 patients.[30] Moreover, an American study and a Thailand study reported occurrence of pruritus as the common symptom among 29% and 41% elderly patients, respectively.[31,32] A prevalence of about 12.8% for pruritus was observed among patients aged >85 years.[30]

**Pregnant women**

Estimated occurrence of pruritus in pregnancy is 18%.[33] Polymorphic eruption of pregnancy, pemphigoid gestation, intrahepatic cholestasis of pregnancy (ICP), and atopic eruption of pregnancy are specific dermatoses associated with pruritus.[34-36] ICP is characterized by severe pruritus without any primary skin lesions, and it is more commonly reported in women of advanced maternal age, multiple gestations, history of cholestasis on oral contraceptives, and during winter months.[37-39] Recognizing ICP is important because it is associated with increased fetal mortality. The only recognizable sign would be pruritus.

**Children**

A Norwegian cross-sectional questionnaire-based population study in adolescents revealed a pruritus prevalence of 8.8%. In this study, mental distress, gender, sociodemographic factors, asthma, rhinoconjunctivitis, and eczema were associated with pruritus.[40] No evident epidemiological studies have been conducted for advocating the prevalence of CP in children.[33,41]

**Diagnostic criteria for chronic pruritus**

Figure 2 illustrates the diagnostic approach for CP.[10] Detailed history of the patient should be taken: Onset (drugs, winter itch), duration of itch, quality, time course (scabies), localization (notalgia paresthetica), preceding skin changes, relieving factors (atopic atokinesis occurs while changing clothes), exacerbating factors (scratching with brushes, combs, knitting needles), atopic diathesis, drug history, history of allergies, weight loss, fever, fatigue, emotional stress, and other symptoms indicating underlying disease have to be reviewed. Other important symptoms in diagnosing etiology of pruritus include history of infection in family members: Scabies and other parasites infection among family members. Pruritus during physical activity: Cholinergic pruritus, which is often reported to be atopic Aquagenic pruritus provoked by skin cooling/bathing, Nocturnal pruritus with chills, fatigue, sweating, weight loss reported in lymphoma, sleep disturbance are rare with psychogenic pruritus, whereas most types cause waking, seasonal variations cause asthmatoid/xerotic, atopic, solar urticarial and textile dermatitis.

**Clinical examination [Table 5]**[42]

i. Search for primary skin lesions: A thorough inspection of the entire skin including mucous membranes, scalp, hair, nails, and anogenital region. Look for lesions in the interscapular regions, nondominant hand site or areas not normally assessable to hand. The distribution of primary and secondary skin lesions should be recorded together with skin signs of systemic disease

ii. General physical examination should include palpation of the liver, kidneys, spleen, and lymph nodes

iii. A solely psychological cause of pruritus should not be diagnosed without psychiatric examination.

**Screening tests**

Fasting blood sugar, postprandial blood sugar, complete blood count, erythrocyte sedimentation rate, absolute eosinophil count, peripheral smear, serum IgE, urinalysis, stool routine and occult blood,
Table 5: Clinical classification of chronic pruritus as per skin changes

| Group | Clinical presentation and underlying disease | Diagnostics |
|-------|---------------------------------------------|-------------|
| Pruritus on primarily diseased, inflamed skin | Clinical picture: Skin disease | Skin biopsy, laboratory investigation if necessary (e.g., IgE, indirect immunofluorescence) |
| Pruritus on primarily normal, noninflamed skin | Clinical picture: Normal skin | Laboratory and radiological investigation, adapted to the patient’s history and preexisting diseases |
| Pruritus with chronic secondary scratch lesions | Clinical picture: Chronic secondary scratch lesions like prurigo nolus dularis | Skin biopsy, laboratory and radiological investigations, procedure adapted to the patients history and preexisting diseases |

Investigations

i. Baseline screening: Creatinine, aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase, bilirubin, TSH, complete blood count, glucose, chest X-ray and in case of genitoanal pruritus calcium (Ca), gamma-glutamyl transpeptidase (γ-GT), and Stool test for parasites in genitoanal pruritus

ii. Renal insufficiency: Creatinine (and urea for elderly), phosphate, parathyroid hormone (PTH), bicarbonate, urinalysis, urine protein concentration and sonography, computed tomography (CT) or magnetic resonance imaging (MRI) of the kidneys

iii. Liver diseases with or without cholestasis: γ-GT, arterial pressure (AP), bilirubin, AST, ALT (and hepatitis B- and hepatitis C-antibodies, if a risk-patient), lactate dehydrogenase (LDH), antimitochondrial antibodies (AMAs), antinuclear antibody, anti-hepatitis B core antibody, hepatitis B surface antigen, anti-hepatitis C virus-antibody, anti-smooth muscle antibody, anticitrullinated antibody, sonography of the liver, CT or MRT, magnetic resonance cholangiogram or endoscopic retrograde to rule out primary sclerosing cholangitis

iv. Hyperparathyroidism: PTH, calcium (only, if symptoms or signs of hyperparathyroidism (“stones, bones, and abdominal groans and psychiatric overtones”)), phosphate, Vitamin D (1,25-Vitamin D, 25-Vitamin D) and sonography of the parathyroid glands, scintigraphy, MRT

v. Hyper- and hypo-thyroidism: TSH, T3, T4, Human assay for microsomal thyroid antibodies (MakAs) and Human assay for thyrotropin receptor antibodies (TRAKs), sonography of the thyroid glands and iodine-scintigraphy

vi. Anemia: Complete blood count including mean corpuscular volume and mean corpuscular hemoglobin concentration, LDH, ferritin, transferrin saturation (TSAT) and bone marrow aspiration with iron staining

vii. Iron deficiency: Ferritin and TSAT

viii. Malabsorption: Serum protein, serum albumin, calcium, blood count, gliadin-antibody, Vitamin A (hyperkeratosis by Vitamin A deficiency), Vitamin B12 (neuropathy by Vitamin B deficiency) and endoscopy with biopsy

ix. Pruritus of the elderly: Serum creatinine, ALT, AST, alkaline phosphatase, bilirubin, TSH, full blood count and blood urea nitrogen (+estimated creatinine clearance)

x. Infective diseases: HIV-antibodies, Western blot

xi. Parasitoses including helminthesis, Giardia lamblia (rare): Stool culture and microscopic examination

xii. Hematological disorders: Polycythemia vera – Blood count, thrombocytes, sedimentation rate. To rule out secondary erythrocytosis: O₂ saturation, erythropoietin level (renal cell carcinoma or polycystic kidneys), bone marrow with chromosomal aberrations and sonography, CT or MRI of the spleen. Lymphoma – Blood count, blood smear, thrombocytes, sedimentation rate, bone marrow with chromosomal aberrations, sonography, CT or MRI of the abdomen, thorax and additional affected areas (positron emission tomography)

xiii. Neurological diseases: Multiple sclerosis – Cerebrospinal fluid analysis, electroencephalography (EEG), MRT and CT of the brain and functional tests. Brain tumors – Cerebrospinal fluid analysis with histopathology and EEG, MRT, CT of the brain. Notalgia paresthetica – MRI of the thoracic spine. Brachioradial pruritus – MRI of the thoracic and cervical spine

xiv. Psychiatric or psychosomatic diseases: Psychiatric and psychosomatic exploration, psychiatric short questionnaire for depressive and anxiety disorder

xv. Pregnancy with or without cholestasis: γ-GT, AP, bilirubin, ALT, AST, bile acids, hepatitis A, B, C, Epstein-Barr and cytomegalovirus, liver autoimmune screen for chronic, active hepatitis, and primary biliary cirrhosis (anti-smooth muscle and AMAs) and liver ultrasound

xvi. Drug-induced pruritus: γ-GT, AP, bilirubin, ALT, LDH, and skin biopsy in case of Hydroxy ethyl starch (HES) exposition.
Management of chronic pruritus

To improve the management of CP adherence following measures to be taken:

1. Develop a usable document or intake sheet
2. Form a decision tree
3. Prepare a list of basic investigations
4. Produce guidelines for usage of drugs
5. Prepare a patient education pamphlet.

Grading for the management of chronic pruritus

• No itch (Grade 0)
• Itch with no need to scratch (Grade 1)
• Itch with need to scratch (Grade 2)
• Itch with need to scratch requiring treatment (Grade 3).

General approach

Individualized treatment approach should be considered for patients with CP depending on their age, comorbid conditions, medications, quality, and intensity of pruritus. Medical care may extend for longer duration due to failure of previous therapies, psychological stress, and uncertainty of origin of pruritus. General measures for managing CP are shown in Table 1. Further, appropriate clinical and diagnostic evaluation may be required prior initiation of symptomatic treatment.

Stepwise approach to chronic pruritus

Overall stepwise approach for managing CP is shown in Figure 3.

Consensual Therapeutic Recommendations of Chronic Pruritus

Topical applications or treatments [Table 6]

Local anesthetics

These drugs are considered effective for short treatment of mixed pain, dysesthesia, and itch over localized areas.

Capsaicin

Similar to local anesthetics, it is used for managing CP, but it is not considered suitable for facial and periorificial skin. Further, capsaicin requires frequent reapplication. Moreover, its preparations with nonsteroidal anti-inflammatory drugs (NSAIDs) have demonstrated better tolerability (personal observation).

Topical corticosteroids

Topical corticosteroids are considered very effective, only in cases of inflammatory dermatoses.

Calcineurin inhibitors

These drugs are effective for medium to long-term treatment of localized pruritus of any etiology. These drugs have demonstrated good evidence mainly for all types of eczemas, Lichen sclerosus et atrophicus (LSA), Lupus erythematosus (LE). However, with its treatment, 25% patients may report initial itch and burning sensation.

Menthol, camphor, and zinc

Menthol, camphor, and zinc have demonstrated rapid onset of action and short duration of relief. These drugs can be applied on widespread areas with no significant risk of systemic toxicity.

Opioid agonists

Significant antipruritic activity has been demonstrated.

Table 6: General measures for managing chronic pruritus

| Interventions     | Agents                                                                 |
|-------------------|-------------------------------------------------------------------------|
| Avoid             | Dry climate                                                             |
|                   | Heat                                                                    |
|                   | Alcoholic compress                                                      |
|                   | Ice packs                                                               |
|                   | Frequent bathing and washing                                             |
|                   | Very hot and spicy food                                                 |
|                   | Alcohol                                                                 |
|                   | Contact with irritant substances such as chamomile, tea-tree oil, etc. |
|                   | Excitement, strain and stress                                           |
|                   | Allergens (house dust) as it aggravates pruritus in atopic patients     |
| Use               | Mild nonalkaline soaps, moisturizers, bathing oils                      |
|                   | Luke warm water while bathing, bathe for not >20 min                   |
|                   | Soft cotton clothing                                                    |
|                   | Night creams/lotions                                                    |
|                   | After contact with water, the skin should be dabbed dry without rubbing it, in patients with dermatoses |
| Relax             | Relaxation therapy, autogenic training                                 |
| Educate           | Psychosocial education                                                  |
|                   | Educating patients to cope with itching and scratching                 |
|                   | Educational training programs                                           |
by N-palmitoylethanolamine containing product among patients with atopic dermatitis (AD). Naltrexone\textsuperscript{51,52} is considered to be effective in cholestatic pruritus. It is also observed to be effective in renal itch.

**Systemic therapy [Tables 7 and 8]**

**Antihistamines\textsuperscript{71-74}**

H1-type antihistamines are the most clinically investigated drug for managing pruritus. Sedative first-generation antihistamines are considered to be highly effective where hydroxyzine is considered to be the most potent antihistamine in managing CP which has been demonstrated in vivo studies\textsuperscript{10}. Nonsedating second-generation antihistamines are long acting, less sedating, and have documented anti-inflammatory activity; however, they are considered to be less effective than sedative first-generation molecules for the relief from CP. Antihistamines have also been considered suitable for urticaria, mastocytosis, and allergic reactions. However, these are frequently administered and considered effective for itch of other etiologies. It is also not effective in standard doses for itch due to internal diseases. Antihistamines are the most commonly prescribed systemic antipruritic drug by the dermatologists. First-generation antihistamines such as hydroxyzine, chlorpheniramine, clemastine, cyproheptadine, diphenhydramine, and promethazine effectively bind to H1-receptors and also to muscarinic, α-receptors, dopamine, and serotonin receptors and demonstrate central sedative effect. Systemic H1-antihistamines are usually used to treat pruritus associated with AD. However, only sedative antihistamines have shown beneficial effects, mainly by improving sleep which is significantly affected leading to QoL impairments. Hydroxyzine in the dose of 75–100 mg/day and 1–2.5 mg/kg/day is recommended as an effective agent in the treatment of CP for adults and children, respectively. A controlled study reported that there was 750-fold increase in the dose of histamine that is required to elicit itch with the addition of hydroxyzine. Hydroxyzine was reported to be more efficacious in treating histamine-induced pruritus compared to neuroleptics such as thiothixene, chlorpromazine, and thioridazine. Antihistamines have demonstrated added efficacy when administered with leukotriene antagonists in physical and

| Table 7: Management of chronic pruritus due to renal causes |
|------------------------------------------------------------|
| **Antipruritic effects confirmed in controlled studies**   |
| Activated charcoal 6 g/day\textsuperscript{41}            |
| Gabapentin 300 mg three times/week postdialysis\textsuperscript{53} |
| Gamma-linolenic acid cream 3 applications/day\textsuperscript{48} |
| 0.025% capsaicin 3–5 applications/day\textsuperscript{44,45} |
| UVB phototherapy\textsuperscript{54}                     |
| Acupuncture\textsuperscript{56}                          |
| Thalidomide 100 mg/day\textsuperscript{54}               |
| UVB: Ultraviolet B, IV: Intravenous                      |

| **Equivocal effects in controlled studies**               |
|-----------------------------------------------------------|
| Naltrexone 50 mg/day\textsuperscript{51,52}             |
| Ondansetron 8 mg orally or IV\textsuperscript{57,58}     |

| **Antipruritic effects confirmed in case reports**       |
|----------------------------------------------------------|
| Cholestyramine 4 g TID before meals\textsuperscript{43} |
| 0.03% tacrolimus ointment 2 applications/day\textsuperscript{46,47} |
| Cream containing structured physiological lipids with endocannabinoids\textsuperscript{50} |
| Mirtazapine 15–30 mg OD\textsuperscript{49}             |
| 4% cromolyn sodium\textsuperscript{64} topical application |
| Erythropoietin 36 IU/kg 3 times/week\textsuperscript{60} |
| Lidocaine 200 mg IV/day\textsuperscript{43}             |
| Ketotifen 1–2 mg/day\textsuperscript{61}                |

| Table 8: Management of chronic pruritus due to hepatic cause |
|-------------------------------------------------------------|
| **Antipruritic effects confirmed in controlled studies**    |
| Cholestyramine 4–16 g/day (not in primarily biliary cirrhosis)\textsuperscript{62} |
| Ursodeoxycholic acid 13–15 mg/kg/day\textsuperscript{43}    |
| Sertraline 75–100 mg/day\textsuperscript{64}               |
| Rifampicin 300–600 mg/day\textsuperscript{65}              |
| Naltrexone 50 mg/day\textsuperscript{64,67}               |
| Naloxone 0.2 μg/kg/min\textsuperscript{46}                |
| Nalmefene 20 mg two times/day\textsuperscript{69}          |
| Thalidomide 100 mg/day\textsuperscript{69}                |

| **Equivocal effects in controlled studies**                |
|-----------------------------------------------------------|
| Ondansetron 4 mg or 8 mg IV or 8 mg orally\textsuperscript{71-74} |

| **Antipruritic effects confirmed in case reports**        |
|----------------------------------------------------------|
| Phenobarbital 2–5 mg/kg/day\textsuperscript{75}          |
| Stanozolol 5 mg/day\textsuperscript{76}                  |
| Phototherapy: UVA, UVB\textsuperscript{77}               |
| Bright light therapy (10.000 lux) reflected toward the eyes up to 60 min twice/day\textsuperscript{78} |
| Etanercept 25 mg SC. 2X/w\textsuperscript{79}            |
| Plasma perfusion\textsuperscript{77}                     |
| Extracorporeal albumin dialysis with MARS\textsuperscript{80-85} |
| Liver transplantation\textsuperscript{86}                |

UVB: Ultraviolet B, UVA: Ultraviolet A, MARS: Molecular Adsorbent Recirculating System
NSAID-aggravated urticarial. However, addition of H2 antagonists has shown poor.

**Gabapentin and pregabalin[72]**

Gabapentin and pregabalin are effective in all types of neuropathic itch and intractable itch of other etiologies as well. It can be a good evidence for renal and hepatic itch. Serotonin-specific reuptake inhibitors (SSRIs)[64] are considered effective for neurologic, psychogenic, or paraneoplastic itch. It can be considered as the second-line treatment for intractable itch of any type.

**Tricyclic antidepressants[75]**

It is similar to SSRIs and has also been considered in AD other than pruritus.

**Cyclosporine**

Cyclosporine is reported to be effective in managing pruritus associated with AD and its variants, such as chronic urticaria.

**Thalidomide[56,70]**

Thalidomide has reported its effectiveness in managing prurigo nodularis and pruritus associated with HIV infection.

**Ultraviolet rays[54,77]**

Narrow-band ultraviolet (UV) B, psoralen plus UV A, and UVA1 are considered to be effective in itch of primary dermatologic conditions. In addition, they have been observed to be effective in renal, hepatic, polycythemia vera, and paraneoplastic itch. Table 9 illustrates antipruritic agents using during pregnancy.[67]

**Summary**

CP is quite frequent finding associated with skin and systemic diseases in the overall population. It is known to significantly affect quality life score of an individual and also adds burden on the healthcare cost. Sedative H1 antihistamines are first-choice therapy in CP to improve night time sleep. Studies on application of higher doses are yet to be conducted. UV phototherapy is recommended for generalized pruritus, especially in the elderly pruritus patients or in case of contraindications for systemic therapy. Anticonvulsants/pain modulators are recommended in neuropathic pruritus. Antidepressants are recommended in forms of CP not responding to other therapies. Systemic glucocorticoids are not recommended for the treatment of CP except of very severe and desperate cases. Serotonin receptor antagonists and thalidomide are not recommended for treatment.

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There are no conflicts of interest.

**What is new?**

Chronic pruritus is quite frequent finding associated with skin and systemic diseases in the overall population. It is known to significantly affect quality life score of an individual and also adds burden on the healthcare cost. A specific recommendation for treatment of CP is difficult as a result of varied and diverse possibility of underlying diseases associated with CP. The recommendations in this guideline are offered with a view to reduce the burden on the physicians and assist in effective management of CP.

**References**

1. Patel T, Yosipovitch G. Therapy of pruritus. Expert Opin Pharmacother 2010;11:1673-82.
2. Tivoli YA, Rubenstein RM. Pruritus: An updated look at an old problem. J Clin Aesthet Dermatol 2009;2:30-6.
3. Rea JN, Newhouse ML, Halil T. Skin disease in Lambeth. A community study of prevalence and use of medical care. Br J Prev Soc Med 1976;30:107-14.
4. Zylicz Z, Twycross R, Jones EA. Pruritus in Advanced Disease. Oxford: Oxford University Press; 2004.
5. Mutterne U, Apfelbacher CJ, Loerbroks A, Schwarzer T, Büttner M, Ofenloch R, et al. Prevalence, correlates and characteristics of chronic pruritus: A population-based cross-sectional study. Acta Derm Venereol 2011;91:674-9.
6. Ständer S, Schäfer I, Phan NG, Blome C, Herberger K, Heigel H, et al. Prevalence of chronic pruritus in Germany: Results of a cross-sectional study in a sample working population of 11,730. Dermatology 2010;221:229-35.
7. Khopkar U, Pande S. Etiopathogenesis of pruritus due to systemic causes: Implications for treatment. Indian J Dermatol Venereol Leprol 2007;73:215-7.
8. Ständer S, Weisshaar E, Mettang T, Szepietowski JC, Carstens E, Ikoma A, et al. Clinical classification of itch: A position paper of the International Forum for the Study of Itch. Acta Derm
Veneroel 2007;87:291-4.

9. Boyd KP, Korf BR, Theos A. Neurofibromatosis type 1. J Am Acad Dermatol 2009;61:1-14.

10. Weisshaar E, Szepietowski JC, Darsow U, Misery L, Wallengren J, Mettang T, et al. European guideline on chronic pruritus. Acta Derm Venereol 2012;92:563-81.

11. Berger TG, Steinhoff M. Pruritus and renal failure. Semin Cutan Med Surg 2011;30:99-100.

12. Cacoumb P, Puyrard T, Ghillani P, Charlotte F, Olivi M, Piette JC, et al. Extrahepatic manifestations of chronic hepatitis C. Multidisciplinary group. Multidisciplinary group. Viral Hepatitis, Liver. Am J Gastroenterol 2007;52:2204-12.

13. Kremer AE, van Dijk R, Leckie P, Schaap FG, Kuiper EM, Mettang T, et al. Serum autotaxin is increased in pruritus of cholestasis, but not of other origin, and responds to therapeutic interventions. Hepatology 2012;56:1391-600.

14. Sreedevi C, Car N, Pavlic-Renar I. Dermatologic lesions in diabetes mellitus. Diabetol Croat 2002;31:147-59.

15. Bin Saif GA, Ericson ME, Yosipovitch G. The itchy scalp – Scratching for an explanation. Exp Dermatol 2011;20:959-68.

16. Yonova D. Pruritus in certain internal diseases. Hippokratia 2007;11:67-71.

17. Dahl MG. Premenstrual pruritus due to recurrent cholestasis. Trans St Johns Hosp Dermatol Soc 1970;56:11-3.

18. Stephens CJ, Black MM. Perimenstrual eruptions: Autoimmune progesterone dermatitis. Semin Dermatol 1989;8:26-9.

19. Gelfand JM, Rudikoff D. Evaluation and treatment of itching associated with diabetes mellitus. Diabetol Croat 2002;31:298-308.

20. Eisman S. Pruritic papular eruption in HIV. Dermatol Clin 2006;24:449-57, vi.

21. Marziniak M, Phan NQ, Raap U, Siepmann D, Schürmeyer-Horst F, Mettang T, et al. Bacterial papulopustules or chronic pruritus: A result of cervical spine pathology? The results of a magnetic resonance tomography study. J Am Acad Dermatol 2011;65:756-62.

22. Kinsella LJ, Carney-Godley K, Feldman E. Lichen simplex chronicus as the initial manifestation of intramedullary neoplasm and syringomyelia. Neurosurgery 1992;30:418-21.

23. Bond LD Jr., Keough GC. Neurogenic pruritus: A case of chronic pruritus induced by transverse myelitis. Br J Dermatol 1999;140:204-5.

24. Garibyan L, Chiou AS, Elmariah SB. Advanced aging skin care regimens in the elderly. Arch Dermatol 1987;123:1638-43.

25. Bergström K, Bergström S, Agnarsson I. The prevalence of skin diseases in the elderly: Analysis of 4099 geriatric patients. Int J Dermatol 2006;45:672-6.

26. Sheu L, Kuo Y, Chang S, et al. Topical capsaicin for treatment of chronic idiopathic pruritus. Arch Dermatol 2006;142:466-70.

27. Rosenblum SN. Pruritus in pregnancy and obstetric cholestasis. J Am Acad Dermatol 2006;54:395-404.

28. Giovannini M, et al. Serum levels of autotaxin are increased in pruritus of cholestasis, but not of other origin, and respond to therapeutic interventions. J Clin Pathol 2012;65:756-62.

29. Weisshaar E, Diepgen TL, Lugner DA, S€eberg E, Wittler R, St€ander S. Pruritus in pregnancy and childhood—Do we really consider all relevant differential diagnoses? Eur J Dermatol 2005;15:320-31.

30. Ambros-Rudolph CM, M€ullerger RR, Vaughan-Jones SA, Keri H, Black MM. The specific dermatomes of pregnancy revisited and reclassified: Results of a retrospective two-center study on 505 pregnant patients. J Am Acad Dermatol 2006;54:395-404.

31. Mettang T, et al. Serum autotaxin is increased in pruritus of cholestasis, but not of other origin, and responds to therapeutic interventions. J Clin Pathol 2012;65:756-62.
Gugeler N, et al. Naltrexone does not relieve uremic pruritus: Results of a randomized, double-blind, placebo-controlled crossover study. J Am Soc Nephrol 2000;11:514-9.

53. Guna AI, Ozalp G, Yoldas TK, Guna SY, Kirciman E, Celiker H. Gabapentin therapy for pruritus in haemodialysis patients: A randomized, placebo-controlled, double-blind trial. Nephrol Dial Transplant 2004;19:3137-9.

54. Gilchrest BA, Rowe JW, Brown RS, Steinnan TI, Arndt KA. Ultraviolet phototherapy of uremic pruritus. Long-term results and possible mechanism of action. Ann Intern Med 1979;91:17-21.

55. Che-Yi C, Wen CY, Min-Tsung K, Chiu-Ching H. Acupuncture in haemodialysis patients at the Quchi (LI11) acupoint for refractory uremic pruritus. Nephrol Dial Transplant 2005;20:1912-5.

56. Silva SR, Viana PC, Lugon NV, Hoette M, Ruzany F, Lugon JR. Thalidomide for the treatment of uremic pruritus: A crossover randomized double-blind trial. Nephron 1994;67:270-3.

57. Ashmore MD, Jones CH, Newstead CG, Daly MJ, Chrystyn H. Ondansetron therapy for uremic pruritus in hemodialysis patients. Am J Kidney Dis 2000;35:827-31.

58. Murphy M, Reachi D, Pai P, Finn P, Carmichael AJ. A randomized, placebo-controlled, double-blind trial of ondansetron in renal itch. Br J Dermatol 2003;148:314-7.

59. Davis MP, Frandsen JL, Walsh D, Andreus S, Taylor S. Mirtazapine for pruritus. J Pain Symptom Manage 2003;25:288-91.

60. De Marchi S, Cecchin E, Villalta D, Sepiaci G, Santini G, Bartoli E. Relief of pruritus and decreases in plasma histamine concentrations during erythropoietin therapy in patients with uremia. N Engl J Med 1992;326:969-74.

61. Francos GC, Kauh YC, Gittlen SD, Schulman ES, Besarab A, Buuren HR. Oral naltrexone treatment for cholestatic pruritus: A randomised controlled trial. Ann Intern Med 1995;123:161-7.

62. Bergasa NV, Mehlman JK, Jones EA. Pruritus and fatigue in primary biliary cirrhosis. Baillieres Best Pract Res Clin Gastroenterol 2000;14:643-55.

63. Goulis J, Leandro G, Burroughs AK. Randomised controlled trials of ursodeoxycholic-acid therapy for primary biliary cirrhosis: A meta-analysis. Lancet 1999;354:1053-60.

64. Mayo MJ, Handem I, Saldana S, Jacobe H, Getachew Y, Rush AJ. Sertraline as a first-line treatment for cholestatic pruritus. J Pain Symptom Manage 2003;25:555-60.

65. Connors GC, Kauh YC, Gittlen SD, Schulman ES, Besarab A, Goyal S, et al. Elevated plasma histamine in chronic uremia. Effects of ketotifen on pruritus. Int J Dermatol 1991;30:884-9.

66. Bergasa NV, Mehlman JK, Jones EA. Pruritus and fatigue in primary biliary cirrhosis. Baillieres Best Pract Res Clin Gastroenterol 2000;14:643-55.

67. Wolfhagen FH, Sternieri E, Hop WC, Vitale G, Bertolotti M, Van den Berghen HR. Oral naltrexone treatment for cholestatic pruritus: A double-blind, placebo-controlled study. Gastroenterology 1997;113:1264-9.

68. Terg R, Coronel E, Sordà J, Muñoz AE, Findor J. Efficacy and safety of oral naltrexone treatment for pruritus of cholestasis, a crossover, double-blind, placebo-controlled study. J Hepatol 2002;37:717-22.

69. Bergasa NV, Alling DW, Talbot TL, Swain MG, Yurdadyin C, Turner ML, et al. Effects of naloxone infusions in patients with the pruritus of cholestasis. A double-blind, randomized, controlled trial. Ann Intern Med 1995;123:161-7.

70. Shohrati M, Tajik A, Harandi AA, Davoodi SM, Akmasi M. Comparison of hydroxyzine and doxepin in treatment of pruritus due to sulfur mustard. Skinmed 2007;6:70-2.

71. Müllner C, Pongratz S, Pidlich J, Penner E, Kaider A, Schemper M, et al. Treatment of pruritus in chronic liver disease with the 5-hydroxytryptamine receptor type 3 antagonist ondansetron: A randomized, placebo-controlled, double-blind cross-over trial. Eur J Gastroenterol Hepatol 1998;10:865-70.

72. O'Donohue JW, Haigh C, Williams R. Ondansetron in the treatment of cholestasis: A randomised controlled trial. Gastroenterology 1997;112A1349.

73. McCormick PA, Scott F, Epstein O, Burroughs AK, Scheuer PJ, McIntyre N. Thalidomide as therapy for primary biliary cirrhosis: A double-blind placebo controlled pilot study. J Hepatol 1994;21:496-9.

74. Schwörer H, Ramadori G. Improvement of cholestatic pruritus by ondansetron. Lancet 1993;341:1277.

75. Raiford DS. Pruritus of chronic cholestasis. QJM 1995;88:603-7.

76. Walt RP, Daneshmend TK, Fellows IW, Toghill PJ. Effect of stanozolol on itching in primary biliary cirrhosis. Br Med J (Clin Res Ed) 1988;296:607.

77. Fleischer AB Jr. The Clinical Management of Itching. New York, London: Parthenon Publishing; 2000.

78. Bergasa NV, Link MJA, Keogh M, Yaroslavsky G, Rosenthal RN, McGee M. Pilot study of bright-light therapy reflected toward the eyes for the pruritus of chronic liver disease. Am J Gastroenterol 2001;96:1563-70.

79. Epstein MP, Kaplan MM. A pilot study of etanercept in the treatment of primary sclerosing cholangitis. Dig Dis Sci 2004;49:1-4.

80. Doria C, Mandalá L, Smith J, Vitale CH, Lauro A, Gruttadauria S, et al. Effect of molecular adsorbent recirculating system in hepatitis C virus-related intractable pruritus. Liver Transpl 2003;9:437-43.

81. Mullhaupt B, Kullak-Ublick GA, Ambühl PW, Stocker R, Benner EL. Successful use of the Molecular Adsorbent Recirculating System (MARS) in a patient with primary biliary cirrhosis (PBC) and treatment refractory pruritus. Hepatol Res 2003;25:442-6.

82. Bellmann R, Graziaidei IW, Feistritzer C, Schwaghofer H, Stellard F, Sturm E, et al. Treatment of refractory cholestatic pruritus after liver transplantation with albumin dialysis. Liver Transpl 2004;10:107-14.

83. Bellmann R, Feistritzer C, Zoller H, Graziaidei IW, Schwaghofer H, Prost A, et al. Treatment of intractable pruritus in drug induced cholestasis with albumin dialysis: A report of two cases. ASAIO J 2004;50:387-91.

84. Acevedo Ribó M, Moreno Planas JM, Sanz Moreno C, Rubio González EE, Rubio González E, Boullosa Graña E, et al. Therapy of intractable pruritus with MARS. Transplant Proc 2005;37:1480-1.

85. Montero JL, Pozo JC, Barrera P, Fraga E, Costán G, Domínguez JL, et al. Treatment of refractory cholestatic pruritus with molecular adsorbent recirculating system (MARS). Transplant Proc 2006;38:2511-3.

86. Neuberger J. Liver transplantation for cholestatic liver disease. Transplant Proc 2006;38:2511-3.

87. Neuberger J. Liver transplantation for cholestatic liver disease. Transplant Proc 2006;38:2511-3.

88. Neuberger J. Liver transplantation for cholestatic liver disease. Transplant Proc 2006;38:2511-3.

89. Neuberger J. Liver transplantation for cholestatic liver disease. Transplant Proc 2006;38:2511-3.