

# Review of management of pruritus in palliative care

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## ABSTRACT

Pruritus or itch is an uncommon symptom observed in palliative care, even more uncommon in cancer patients. However, if a patient experiences pruritus, the 'itch-scratch' cycle can damage the skin integrity and can increase the susceptibility of patients to infection owing to their frail immune system. The outcome can be very distressing, dramatically impacting the quality-of-life of the patient. Moreover, since severe pruritus seen in patients with advanced disease can be associated with failure of different organ systems, pruritus must be assessed based on the underlying organ systems and the pathophysiology involved. Regardless of the cause of pruritus, general skin care is important. Depending on the origin of pruritus, specific approach and medications must be considered. Caution must be taken during management of pruritus since most cancer patients take pain medications that interact with some antipruritic medications. In addition to the complex and unclear nature of cutaneous and central pathogenesis of pruritus, treatment of pruritus is challenging.

**Keywords:** Clinical manifestation, itch, pain, palliative care, pathophysiology, pruritus

## INTRODUCTION

Pruritus or itch is a sensation of the skin or mucous membranes with free nerve endings, which causes the desire to scratch the affected area and consequently causing breaks in the skin, inflammation, infection and/or bleeding.<sup>[1,2]</sup>

Pruritus is a rare symptom observed in palliative care of cancer patients, projected to have a frequency rate of 6% for general palliative care setting and between 5% and 24% occurrence for patients with 'incurable' cancer diagnoses. Manifestation of pruritus in patients during palliation can be one major factor that contributes to difficulties in the daily activities of the patients. In addition to the mood disorders, social unacceptability

and lack of sleep alter the patients quality-of-life (QOL) detrimentally. Pruritus is not simply a skin disorder but rather a systemic problem from multiple causes. Moreover, depending on the cause(s) of pruritus, the best fit approach for certain clinical manifestations might not necessarily work for the others and vice versa.<sup>[1,2]</sup>

This article presents the different pathophysiological processes and clinical manifestations of pruritus in palliative care patients, and it further describes the different therapeutic options of pruritus.

## PATHOPHYSIOLOGY OF PRURITUS

Pruritus has a complex and unclear nature of cutaneous and central pathogenesis. It is important to be aware of the risk factors and causes of pruritus, and the best available means of effective therapy. Pathophysiologically, pruritus can be classified as prurioreceptive (within the skin), neuropathic (damage to the afferent pathway),

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#### DOI:

10.4103/1658-600X.173844

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**How to cite this article:** Alshammary SA, Duraisamy BP, Alsu hail A. Review of management of pruritus in palliative care. *J Health Spec* 2016;4:17-23.

neurogenic, (cerebrally induced) and psychogenic pruritus (related to psychiatric disorder).<sup>[1,2]</sup> It is difficult to isolate these categories from each other entirely; therefore, may presumably overlap one another to some extent.

### Prurioreceptive pruritus

This occurs when the itch is initiated within the skin (e.g., inflammation of the skin, adverse insect bite reactions), which opens up the neuronal pathway in the free nerve endings of the skin that is similar to the response of the body to pain. This is then received by the brain through the transmission by the dedicated unmyelinated C fibres along the dorsal horn and relayed to the contralateral spinothalamic tract, where it is identified as an itch. It in turn blocks the perception of the feeling of irritation by stimulating the A $\delta$  sensory fibres through scratching, which is directed by our motor reflexes.<sup>[1,2]</sup> This is known as the Melzak-Wall 'gate theory'. Though both pain and itch have the same chemical messengers that excite these C fibres, a subset of these fibres responds specifically to pruritus-inducing stimuli and peripheral mediators, and these include histamine, serotonin, prostaglandin, acetylcholine, cytokines, opioids and neuropeptides.

### Neuropathic pruritus

It happens along the neurological pathway where the damage to the nervous system is known to have occurred. It is frequently associated with symptoms of tingling and numbness.<sup>[1,2]</sup> This type of itch is usually seen after shingles, post-stroke, burn injury and nostalgia paraesthesia (an area of itching, usually at the back), often treated with non-narcotic analgesics and capsaicin.

### Neurogenic pruritus

It is brought about and mediated by the opioid and serotonin receptors, and for that reason, it is unresponsive to antihistamines. It fundamentally affects the central inhibitory circuits.<sup>[1,2]</sup> It can be commonly observed in patients with chronic liver and kidney disease and in response to opioid neuropeptides. Narcotic and non-narcotic analgesics are used for the treatment.

### Psychogenic pruritus

It is commonly linked to psychiatric disorders<sup>[1,2]</sup> such as depression and delusional parasitosis. It is in response to altered norepinephrine and serotonin in the brain, which is also associated with chronic stress. The choices of treatment medications for this are antidepressants and antipsychotics.

## CAUSES OF PRURITUS

Similar to pathogenesis, the disease processes causing pruritus are also of different kinds, such as cholestasis, uraemia, opioid-induced, malignancies, infection and drug-induced (reaction) pruritus.

### Cholestasis

This is the most prevalent source of pruritus, occurring in 20 - 25% of the patients with end-stage liver disease. Cholestasis occurs in 100% of the patients with primary biliary cirrhosis. It not only relies on the accumulation of bile acids but it is also believed to be associated with breakdown of endogenous opioids; hence, the use of opioid antagonist medications will also be advantageous. The pathogenesis of cholestasis is still unknown, but one supposed mechanism is in the increased release of serotonin hormones, in which serotonin modulators can be prescribed. On the other hand, histamines may also be related but to a lesser extent; therefore, the use of antihistamine in most cases is ineffective.<sup>[1,2]</sup>

### Uraemia

Also known as renal itch, uraemia affects patients with chronic renal failure. This can happen to both dialysed and non-dialysed patients with no significant difference in the probability of occurrence, even with the absence of primary skin disease and/or psychological dysfunction. Manifestation of uraemic pruritus can be continuous or intermittent. In end-stage renal disease (ESRD), the extent of pruritus reaches up to 55 - 80%.<sup>[3]</sup>

### Malignancy

Pruritus in malignancies can be attributed to multiple factors, i.e., cancer-causing cells that produce the itching sensation, side-effect of cancer medication, medications used in pain management (i.e. opioids) and complications from the malignancy such as renal failure and cholestasis.<sup>[1]</sup> Malignancy can be categorised as either solid tumours or haematologic disorders.

Pruritus in solid tumours is believed to signify disease progression. However, it could be due to an immunologic reaction to the tumour-specific antigens though the pathophysiology is not fully clear. Itch can be localised or generalised as perianal itch in colorectal cancer, vulvar itch in cervical cancer or scrotal itch in prostate cancer. It can also be caused by biliary obstruction, for example, in pancreatic cancers, in which biliary drainage by stenting is a very potent therapy.<sup>[1,2]</sup>

Haematologic disorders such as leukaemia and lymphoma also present with itching; more frequently experienced

than in solid tumours due to the direct infiltration of the skin in chronic myeloid leukaemia, lymphoma and polycythaemia vera. Pruritus is associated in about 30% of the patients with Hodgkin disease. About 30 - 50% of the patients with polycythaemia vera experience itching after taking a shower.<sup>[1,2]</sup>

### Opioid-induced pruritus

It is normally encountered with spinal administration of opioids with 20 - 90% incidence as compared to systemic opioids (<1%). The specific mechanism of the opioid-induction is still unknown. It is centrally mediated through  $\mu$ -opioid receptors and prevented by  $\kappa$ -opioid receptors.<sup>[2,4]</sup>

### Infection

Infection is another probable cause of itching. Genital pruritus can be associated to genital infections such as sexually transmitted disease and acquired immunodeficiency syndrome (AIDS) that are triggered by human immunodeficiency virus (HIV). Varicella-zoster virus, which is responsible for chicken pox, can cause rash, blisters and itching.

### Drug-induced (reaction) pruritus

Apart from the above-mentioned clinical conditions that can cause itching, drug administration can result in acute or chronic itching, as reaction, depending on the body's response. One of the common medications that have adverse pruritus effect are the highly active antiretroviral therapy drugs, which are used for the treatment of AIDS. Some antibiotics can cause urticarial rashes and systemic reactions as well.<sup>[4]</sup>

## MANAGEMENT OF PRURITUS

Regardless of the origin of pruritus, general skin measures play a big role in preventing and managing pruritus. Although it is not completely effective, in some cases, topical creams and ointments are helpful for patients who experience both acute and chronic itching as well as dry skin. Moisturisers (containing glycerol acetate, urea, petroleum, mineral oil and glyceryl stearate), corticosteroids, Vitamin D analogues, topical anaesthetics, capsaicin and menthol are some of the widely used topical treatments for pruritus.<sup>[5]</sup> Regular application of these emollients helps keep the skin moist and lubricated. Topical anaesthetics such as 2.5% lidocaine cream can be applied to the localised area of itch to anaesthetise nerve endings. Applying menthol or phenol to affected areas can also help by substituting itch with a cooling sensation. Moreover, applying agents such as capsaicin that block pruritus mediators can relieve itching. In the presence of inflammations, corticosteroids might be of

help.<sup>[5]</sup> Bathing with lukewarm water and unscented soap are helpful in patients experiencing dry and bad skin reaction. Table 1 enumerates the different general measures and different topical remedies for the management of pruritus.<sup>[1,2,4]</sup>

**Table 1: General measures and topical remedies of pruritus management**

General measures	Topical remedies
Prevent boredom and anxiety	Emollients and moisturisers
Stay away from heat	1-2% menthol or phenol
Stay in a cool, humidified environment	0.025-0.5% capsaicin
Wear loose, nonirritating clothing	2.5% lidocaine cream
Avoid fragrant topical agents	Corticosteroids
Avoid intake of caffeine	
Trim fingernails and wear cotton gloves if scratching is uncontrolled or occurs during sleep	
Treat skin infections appropriately	
Discontinue drugs that may cause pruritus	
Eliminate common skin allergens	
Apply cold application	
Provide medicated baths	
Apply topical medications	

Systemic medications for the management of pruritus include antihistamines, opioid antagonists, serotonin modulators, antiepileptics, rifampicin, cholestyramine, thalidomide, nalfurafine, leukotriene antagonists, charcoal and oral cromolyn sodium, [Table 2].

### Antihistamines

Also known as H1 receptor antagonists, antihistamines such as hydroxyzine and diphenhydramine act by blocking the histamines that are produced during itching. In addition, antihistamines have a sedating effect that can assist sleep, but on the other hand, may also result in some adverse anticholinergic effects such as dry mouth, nausea and headache. Due to these unwanted side-effects, low-sedating antihistamines such as loratadine and cetirizine are commonly used. However, because majority of the causes of pruritus in palliative care is not from histamines, administration of antihistamines is considered ineffective for pruritus management in palliative care. Since histamine is not a contributing factor in uraemia, this drug is ineffective in management of uraemic pruritus as well. Moreover, since histamine is involved in cholestatic pruritus only to a lesser extent, it is ineffective in cholestasis as well.<sup>[1,2]</sup>

### Opioid antagonists

Opioid-induced pruritus (OIP) is an adverse side-effect of therapeutic use of opioid medications. Pure opioid antagonists such as naltrexone and naloxone have been used for the management of OIP, as  $\mu$ -opioid receptor antagonists are central mediators of pruritus.<sup>[1,2,4]</sup> Studies

**Table 2: Pharmacologic treatments for pruritus**

Pruritus clinical background	Treatment	Mechanism of action	Advantage/s	Disadvantage/s
Allergy	Antihistamine	H1 receptor antagonist	Inexpensive	Sedation for some, rarely effective for severe case
Cholestasis	Paroxetine	5-HT3 reuptake inhibition	Effects seen within 24 - 48 h	N/A
	Mirtazapine	5-HT2, 5-HT3 and H1 receptor antagonist	Effective	Sedation
	Sertraline	5-HT reuptake inhibitor	Effective	N/A
	Ondansetron	5-HT3 receptor antagonist	N/A	Expensive, constipation
	Naloxene or naltrexone	μ-opioid receptor antagonists	N/A	Reverses analgesia, expensive
	Rifampicin	Bile acid uptake inhibitor	Effective	Constipation
	Cholestyramine	Bile acid sequestrant	Effective, inexpensive	Acidosis
Uraemia	Paroxetine	5-HT3 reuptake inhibition	Effects seen within 24 - 48 h	N/A
	Mirtazapine	5-HT2, 5-HT3 and H1 receptor antagonist	Effective	Sedation
	Ondansetron	5-HT3 receptor antagonist	N/A	Expensive, constipation
	Naloxene or naltrexone	μ-opioid receptor antagonists	N/A	Reverses analgesia, expensive
	Gabapentin or pregabalin	Impedes transmission of nociceptive sensations to brain	Effective with low-dose	N/A
	Thalidomide	Immunomodulation	Effective	Sedation
	Nalfurafine	κ-opioid receptor antagonist	Effective	Insomnia
	Montelukast	CysLT1 leukotriene receptor antagonist	Effective	Expensive
	EPO	γ-linolenic acid	Effective	N/A
	Oral activated charcoal	Unknown	Effective, inexpensive	N/A
Opioid-induced	Paroxetine	5-HT3 reuptake inhibition	Effects seen within 24 - 48 h	N/A
	Mirtazapine	5-HT2, 5-HT3 and H1 receptor antagonist	Effective	Sedation
	Naloxene or Naltrexone	μ-opioid receptor antagonists	N/A	Reverses analgesia, expensive
Malignancy (solid tumours and haematologic disorders)	Paroxetine	5-HT3 reuptake inhibition	Effects seen within 24-48 h	N/A
	Mirtazapine	5-HT2, 5-HT3 and H1 receptor antagonist	Effective	Sedation
Infection	Indomethacin	Prostaglandin production inhibitor	Effective	N/A

EPO: Evening primrose oil, N/A: Not available

have shown that intake of pure opioid antagonists at a dosage of 50 mg/day, by patients not requiring opioids for pain control, to be particularly effective in the treatment of uraemic and cholestatic pruritus.<sup>[6-9]</sup> However, these drugs are often unsuitable for the palliative patient population since most of these patients are using opioids for pain management. Opioid antagonists could reverse analgesia or lead to withdrawal symptoms. For OIP secondary to systemic opioids, the initial approach is to switch to a different opioid. Spinal opioids are frequently given with bupivacaine that reduces itch as well.<sup>[2]</sup>

### Serotonin modulators

Serotonin reuptake inhibitors, referred to more simply as serotonin modulators, help in pruritus management by blocking reuptake of serotonin into presynaptic vesicles, hence significantly increasing the concentration of serotonin in the central nervous system. Different case reports have acknowledged the antipruritic role of centrally released serotonin. Below are the most common serotonin modulators used:

- Ondansetron (Zofran) is a serotonin 5-HT3 receptor antagonist, which is used for managing pruritus associated with uraemia, opioids and cholestasis. Compared to other antipruritic medicines, it is rather

expensive and can result in constipation, in which palliative patients are often distressed.<sup>[1,2]</sup> In addition to these disadvantages, ondansetron reported no advantage over placebo, concluding no significant effectiveness for the management of pruritus<sup>[10]</sup>

- Mirtazapine is primarily used to treat depression and post-traumatic stress disorder. However, with its 5-HT2, 5-HT3 and H1 receptor antagonist properties, it can also be used for the management of uraemic, cholestatic and malignant pruritus. Treatment usually begins with a 15 mg dose nightly, but a lower dose of 7.5 mg to begin is also effective. It can have some sedating effect and can cause weight gain<sup>[11]</sup>
- Paroxetine is a serotonin reuptake inhibitor, and it can be administered to patients having pruritus associated with cholestasis, uraemia and opioids. Furthermore, paroxetine shows evidence of efficacy with management of pruritus secondary to malignant disease. Preferably, patients must start with small doses of 5 - 10 mg nightly to have fewer side-effects. Effects can usually be observed within 24 - 48 h<sup>[1,2,12]</sup>
- Sertraline, an antidepressant of the serotonin reuptake inhibitors class, is considered the first-line treatment for cholestatic pruritus. Usage of sertraline shows effectiveness at the 25 mg dosage and tolerance level

of patients to this medicine is high. A retrospective study shows that low-dose sertraline is effective for the management of antihistamine-refractory pruritus in patients with ESRD.<sup>[13]</sup>

### Antiepileptic

Gabapentin and pregabalin which are commonly used as anticonvulsant or antiepileptic drugs have the capabilities of managing symptoms of pruritus by blocking neuropathic pathway. Gabapentin is approved by US Food and Drug Authority for the treatment of partial seizures and post-herpetic neuralgia. When used, patients tolerate it well, and there is no need for routine clinical laboratory monitoring. It does not have drug interactions due to its pharmacokinetics.<sup>[14]</sup> It is proven to be effective for the management of uraemic pruritus with low-dose administration of 300 - 400 mg after dialysis 3 times a week,<sup>[15,16]</sup> but not for cholestatic pruritus.<sup>[17]</sup> Pregabalin, which is another anticonvulsant medicine, presented equal effectiveness as gabapentin based on a study wherein a randomised trial on 17 patients were given 75 mg of pregabalin and 300 mg of gabapentin after dialysis. Patients showed comparable level of tolerance toward the two medications.<sup>[18]</sup>

### Rifampicin

Rifampicin inhibits the uptake of bile acids by hepatocytes, and evidence suggests that it is second line of treatment for cholestatic pruritus, although the usage of this medication is unsatisfactory for most patients due to gastrointestinal side-effects such as constipation.<sup>[19-21]</sup> Rifampicin is also consumed as an ansamycin antibiotic at the dosage of 300 - 600 mg/day, which exhibits antibacterial properties. A study has shown significant changes during a 14-day treatment period.<sup>[21]</sup>

### Cholestyramine

Cholestyramine is more commonly known as a safe cholesterol-lowering agent being a bile acid sequestrant. Although cholestyramine has shown a level of efficacy for the management of cholestatic pruritus to some extent;<sup>[22,23]</sup> because there is no correlation between the level of bile acids and the degree of pruritus, usage of cholestyramine is often ineffective. This drug is not effective for uraemic pruritus in addition to the adverse side-effects such as acidosis. Because of its low-cost, it is recommended to try this medication first before considering more expensive treatments. The usual administration of cholestyramine is 4 mg or 5 mg BID.

### Thalidomide

As an immunomodulatory drug, thalidomide is the main treatment for multiple myelomas and leprosy

complications. A common side-effect of this drug is sedation. A study has shown 81% mean reduction in pruritus scores of 29 haemodialysis case patients experiencing uraemic pruritus after administration of thalidomide at bedtime for 7 days.<sup>[24]</sup>

### Nalfurafine ( $\kappa$ -opioid receptor antagonist)

From a  $\kappa$ -opioid receptor antagonist, nalfurafine just as thalidomide is used and found effective for the treatment of uraemic pruritus for haemodialysis patients.<sup>[25,26]</sup> The activation of  $\kappa$ -opioid receptors is known to control the signals activated through micro-opioid receptors, hence reducing pruritus in patients undergoing haemodialysis. The most common side-effect is insomnia.

### Montelukast

This CysLT1 leukotriene receptor antagonist is commonly used for maintenance treatment of asthma and to relieve symptoms of seasonal allergies. With administration of 10 mg/day, montelukast suggests effectiveness for the management of uraemic pruritus.<sup>[27]</sup>

### Evening primrose oil

Evening primrose oil is rich in essential fatty acids such as  $\gamma$ -linolenic acid that aids the body in reducing inflammation and is found effective for the treatment of uraemic pruritus.<sup>[28]</sup>

### Oral activated charcoal (6 g/d)

Although charcoal's mechanism of action in pruritus is unknown, a study had shown effectiveness of activated powdered charcoal in patients with uraemic pruritus when administered with 6 g/day dosage. Few advantages are safety, low-cost and effective.<sup>[29]</sup>

### Oral cromolyn sodium (135 mg TID)

This acts by inhibiting the release of histamine and leukotrienes from the mast cell. A study had shown its effectiveness in the management of haemodialysis patients with uraemic pruritus with the administration of cromolyn sodium.<sup>[30]</sup>

### Indomethacin

Patients with HIV can develop pruritus from different factors, i.e., xerosis, drug and photo eruptions, follicular and papular eruptions, and infections by a variety of organisms. A study compared four different regimes of treatment for pruritus caused by infection and showed that indomethacin provided relief more consistently and more effectively to the patients.<sup>[31]</sup>

### Nonpharmacologic approaches

Aside from the above-mentioned medications, a number of non-pharmacologic approaches of treatment are

available for patients experiencing severe pruritus. Surgery is also of benefit for gastric and pancreatic tumours to relieve the obstruction. On the other hand, stenting for bile duct obstruction can be considered in pancreatic cancer patients.<sup>[4]</sup> These procedures are particularly important in avoiding adverse side-effects from certain drugs. Ultraviolet B therapy, although exact mechanism is unknown, can be attempted for the management of cholestatic and uraemic pruritus and malignant skin infiltrations. It is done 3 times a week, but for patients who are toward their end of life, this is considered an impractical approach.<sup>[1,2]</sup>

## CONCLUSION

Pathogenesis of pruritus is complex and to some extent is uncertain, and hence trying to understand its behaviour is challenging. Through different clinical trials, some medications and non-pharmacological procedures are found to be effective in the management strategy of certain types of pruritus. The suitability of medication mainly depends on the mechanism of action involved in the pruritus and of the medication itself; essentially the two should have reversing actions. If pruritus is not managed accordingly, this can adversely affect the QOL of the patients. General skin measures play a big role in preventing and managing pruritus.

## Financial support and sponsorship

Nil.

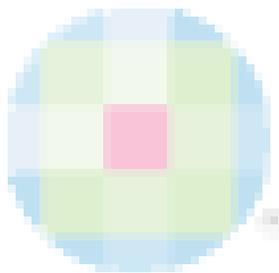
## Conflicts of interest

There are no conflicts of interest.

## REFERENCES

- Anand S. Gabapentin for pruritus in palliative care. *Am J Hosp Palliat Med* 2012;30:192-6.
- Seccareccia D, Gebara N. Pruritus in palliative care: Getting up to scratch. *Can Fam Physician* 2011;57:1010-3, e316-9.
- Razeghi E, Eskandari D, Ganji MR, Meysamie AP, Togha M, Khashayar P. Gabapentin and uremic pruritus in hemodialysis patients. *Ren Fail* 2009;31:85-90.
- Braithwaite D, Jochim J. *Dermatology*. In: Downing GM, Wainwright W, editors. *Medical Care of Dying*. 4<sup>th</sup> Edition. Victoria British Columbia, Canada: Victoria Hospice Society Learning Centre for Palliative care, 2006. p. 502-04.
- Elmariah SB, Lerner EA. Topical therapies for pruritus. *Semin Cutan Med Surg* 2011;30:118-26.
- Peer G, Kivity S, Agami O, Fireman E, Silverberg D, Blum M, et al. Randomised crossover trial of naltrexone in uraemic pruritus. *Lancet* 1996;348:1552-4.
- Legroux Crespel E, Clèdes J, Misery L. A comparative study on the effects of naltrexone and loratadine on uremic pruritus. *Dermatology* 2004;208:326-30.
- Wolfhagen FH, Sternieri E, Hop WC, Vitale G, Bertolotti M, Van Buuren HR. Oral naltrexone treatment for cholestatic pruritus: A double blind, placebo controlled study. *Gastroenterology* 1997;113:1264-9.
- Terg R, Coronel E, Sord CJ, Muronel E, 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.
- Siemens W, Xander C, Meerpohl JJ, Antes G, Becker G. Drug treatments for pruritus in adult palliative care. *Dtsch Arztebl Int* 2014;111:863-70.
- Davis MP, Frandsen JL, Walsh D, Andresen S, Taylor S. Mirtazapine for pruritus. *J Pain Symptom Manage* 2003;25:288-91.
- Zylicz Z, Krajnik M, Sorge AA, Costantini M. Paroxetine in the treatment of severe non dermatological pruritus: A randomized, controlled trial. *J Pain Symptom Manage* 2003;26:1105-12.
- Chan KY, Li CW, Wong H, Yip T, Chan ML, Cheng HW, et al. Use of sertraline for antihistamine refractory uremic pruritus in renal palliative care patients. *J Palliat Med* 2013;16:966-70.
- Namaka M, Gramlich CR, Ruhlen D, Melanson M, Sutton I, Major J. A treatment algorithm for neuropathic pain. *Clin Ther* 2004;26:951-79.
- Gunal AI, Ozalp G, Yoldas TK, Gunal 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.
- Naini AE, Harandi AA, Khanbabapour S, Shahidi S, Seirafiyani S, Mohseni M. Gabapentin: A promising drug for the treatment of uremic pruritus. *Saudi J Kidney Dis Transpl* 2007;18:378-81.
- Bergasa NV, McGee M, Ginsburg IH, Engler D. Gabapentin in patients with the pruritus of cholestasis: A double blind, randomized, placebo controlled trial. *Hepatology* 2006;44:1317-23.
- Solak Y, Biyik Z, Atalay H, Gaipov A, Guney F, Turk S, et al. Pregabalin versus gabapentin in the treatment of neuropathic pruritus in maintenance haemodialysis patients: A prospective, crossover study. *Nephrology (Carlton)* 2012;17:710-7.
- Bachs L, Parès A, Elena M, Piera C, Rodés J. Comparison of rifampicin with phenobarbitone for treatment of pruritus in biliary cirrhosis. *Lancet* 1989;1:574-6.
- Podesta A, Lopez P, Terg R, Villamil F, Flores D, Mastai R, et al. Treatment of pruritus of primary biliary cirrhosis with rifampin. *Dig Dis Sci* 1991;36:216-20.
- Ghent CN, Carruthers SG. Treatment of pruritus in primary biliary cirrhosis with rifampin. Results of a double blind, crossover, randomized trial. *Gastroenterology* 1988;94:488-93.
- Duncan JS, Kennedy HJ, Triger DR. Treatment of pruritus due to chronic obstructive liver disease. *Br Med J (Clin Res Ed)* 1984;289:22.
- Silverberg DS, Iaina A, Reisin E, Rotzak R, Eliahou HE. Cholestyramine in uraemic pruritus. *Br Med J* 1977;1:752-3.
- 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.
- Wikström B, Gellert R, Ladefoged SD, Danda Y, Akai M, Ide K, et al. Kappa opioid system in uremic pruritus: Multicenter, randomized, double blind, placebo controlled clinical studies. *J Am Soc Nephrol* 2005;16:3742-7.
- Kumagai H, Ebata T, Takamori K, Muramatsu T, Nakamoto H, Suzuki H. Effect of a novel kappa receptor agonist, nalfurafine

- hydrochloride, on severe itch in 337 haemodialysis patients: A Phase III, randomized, double blind, placebo controlled study. *Nephrol Dial Transplant* 2010;25:1251-7.
27. Nasrollahi AR, Miladipour A, Ghanei E, Yavari P, Haghverdi F. Montelukast for treatment of refractory pruritus in patients on hemodialysis. *Iran J Kidney Dis* 2007;1:73-7.
28. Mettang T, Pauli-Magnus C, Alscher DM. Uraemic pruritus – New perspectives and insights from recent trials. *Nephrol Dial Transplant* 2002;17:1558-63.
29. Pederson JA, Matter BJ, Czerwinski AW, Llach F. Relief of idiopathic generalized pruritus in dialysis patients treated with activated oral charcoal. *Ann Intern Med* 1980;93:446-8.
30. Vessal G, Sagheb MM, Shilian S, Jafari P, Samani SM. Effect of oral cromolyn sodium on CKD-associated pruritus and serum tryptase level: A double-blind placebo-controlled study. *Nephrol Dial Transplant* 2010;25:1541-7.
31. Smith KJ, Skelton HG, Yeager J, Lee RB, Wagner KF. Pruritus in HIV-1 disease: Therapy with drugs which may modulate the pattern of immune dysregulation. *Dermatology* 1997;195:353-8.



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