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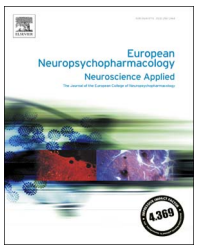

REVIEW

Antidepressants as antipruritic agents: A review

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Abstract
Pruritus is a concomitant symptom of various underlying disorders viz. dermatological, systemic and psychiatric disorders that provoke the person to scratch the skin. Many natural as well as, antipruritic therapies are usually practiced in the treatment of pruritus including general preventive measures, topical therapies such as cooling agents, antihistamines, anesthetics, capsaicin, corticosteroids, immunomodulators and; systemic therapies including administration of antihistamines, opioid antagonists/agonists, antiepileptic drugs/neuroleptics (e.g., gabapentin and pregabalin), antidepressants (e.g., doxepin, amitriptyline, paroxetine, fluvoxamine, sertraline, escitalopram and mirtazapine) (Patel and Yosipovitch, 2010; Reich et al., 2011; Martín and Padilla, 2015; Eskeland et al., 2016). Topical therapies are the mainstay of treatment of delicate and localized pruritus while other systemic drug therapies are used to treat stern and generalized pruritus. The reported antipruritic activity of some antidepressant drugs has intrigued this review to focus on the types of pruritus, pruritus mechanism, the antipruritic mechanism of antidepressants and to comprehend the role of antidepressants in the management of pruritus.

1. Introduction

Pruritus (or itching), the prevailing and distressing symptom of dermatological disorders as well as of systemic and psychiatric disorders, is defined as a nasty sensation that varies in intensity from a moderate to torturing leading to an urge to scrape the skin in order to transiently reduce itch. Scratching the skin causes more irritation which consecutively leads to pruritus. Although pruritus is an eternal symptom of dermatological, neurological, systemic and psychiatric diseases, notably a little and a few studies are there regarding the pervasiveness and extent of pruritus in specific diseases or diseased populations. The main reasons behind these are that patients suffering from acute itch do not consult physician taking it as a non-serious

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symptom, the specialists of non-dermatological diseases consider 'pruritus' symptom as a non-serious variable to assess, difficulty in the interpretation as well as comparison of available data on pruritus, and imperfect classification of pruritus so far (Weisshaar and Matterne, 2014). Pruritus is generally studied as acute and chronic pruritus. Acute pruritus is the one that lasts for a finite period of time i.e., less than six weeks (as a result of insect bite) whereas chronic pruritus which is perturbing and stubborn to the treatment. It is a prolonged itch that lasts for more than six weeks and is related to numerous diseased conditions such as atopic dermatitis, uremia, cholestatic liver diseases (Ständer et al., 2007; Reich et al., 2011). Every person experiences itch with the progression of age, which highly affects the quality of life such as sleep, sexual functioning, work quality. Therefore, in order to avoid an upsurge in other health problems related to pruritus an early treatment is necessary (Patel and Yosipovitch, 2010). As pruritus has numerous underlying etiologies, a detailed history and physical check-up of a patient while treating pruritus, therefore, is of paramount importance. Currently, numerous antipruritic drugs are used to manage/suppress itching when administered topically as well as systemically along with general preventive measures. The general preventive measures include wearing sheer and light clothes; avoiding alcohol, hot and peppering foods, contact with animal fur; maintaining proper moisture in the room, moisturizing the skin regularly with natural as well as mineral oils to avoid itching (Twycross et al., 2003).

Topical antipruritic drugs are the mainstay in suppressing/reducing itch particularly menthol, calamine, salicylic acid, antihistamines (e.g., mepyramine, diphenhydramine, doxepin), local anaesthetics (e.g., benzocaine, lidocaine, prilocaine, pramoxine, polidocanol), capsaicin, corticosteroids, immunomodulators/calcineurin inhibitors (e.g., tacrolimus, pimecrolimus) and endocannabinoids (e.g., anandamide, N-palmitoyl ethanolamine). Systemic therapies are given to the patients suffering from pruritus associated with systemic disorders. These encompass antihistamines (e.g., hydroxyzine, loratadine, desloratadine, cetrizine, levocetrizine, chlorphenamine, cimetidine), opioid antagonists/agonists (e.g., naltrexone, naloxone, nalmafene, butorphanol, nalfurafine, buprenorphine), antidepressants (e.g., doxepin, amitryptyline, fluoxetine, paroxetine, fluvoxamine, sertraline, mirtazapine), antiepileptic drugs/neuroleptics (e.g., gabapentin and pregabalin), serotonin 5-HT3 receptor antagonist (such as ondansetron), resin (e.g., cholestyramine), antiemetic drug/substance P antagonist (e.g.,aprepitant) and immunosupressants such as cyclosporine and azothioprine (Twycross et al., 2003; Patel and Yosipovitch, 2010; Reich et al., 2011; Martín and Padilla, 2015). Amongst these, antidepressants have been found to be eminently effective in reducing as well as suppressing itch where other drugs fail to treat the condition. Therefore, we mainly explore the reported antipruritic effect of antidepressants.

2. Classification of pruritus

According to International Forum for the Study of Itch (IFSI), individuals/patients suffering from chronic pruritus are categorized into three groups (Group I, Group II and Group III) that cover critical aspects to understand pruritus. It also classifies chronic pruritus into six categories viz. I) Pruritoceptive/cutaneous/dermatological pruritus, II) systemic pruritus, III) neurological pruritus (includes neuropathic and neurogenic), IV) somatoform/psychogenic pruritus, V) "mixed" pruritus and, VI) "others" pruritus on the basis of its origin. These aforementioned categories of individuals and pruritus help the physician to offer a better and improved treatment to pruritic patients. So, here we have tried to briefly explain these abovementioned categories.

(I) *Pruritoceptive/cutaneous/dermatological pruritus* arises from the skin disorders as a result of stimulation of specialized C-fibres's free nerve sensory endings by pruritogens. The underlying causes of this kind of itch are skin damage, dryness, inflammation. For instance, itch induced from eczema, atopic dermatitis, psoriasis, xerosis, urticaria, scabies and insect bite. More examples of this type of pruritus are explained elsewhere in the explanation of Group I patients. Numerous endogenous chemicals/inflammatory mediators such as proteases, amines, neuropeptides, eicosanoids, opioids, cytokines and growth factors cause local itching when injected into the skin. The mechanism by which these chemicals cause itching involves either sensitizing itch-specific C-fibres or causing the release of histamine from mast cells (Lerner, 1994; Hagermark, 1995).

(II) *Systemic pruritus* arises from the organ's disease rather than the skin's disease. For e.g. metabolic and endocrine diseases (which includes primary biliary cirrhosis, liver disease with or without cholestatis, hyperthyroidism, hypothyroidism, hyperparathyroidism, iron deficiency, chronic renal insufficiency blood), infectious diseases (such as HIV and AIDS, parasitosis including Helminthosis, parasitosis, haematological and lymphoproliferative disorders (such as iron deficiency, polycythaemia vera, myelodysplastic syndrome, Hodgkin's lymphoma, Non-Hodgkin's lymphoma, plasmocytoma), visceral neoplasms (such as tumours of the cervix, colon and prostate, carcinoid syndrome), pregnancy (pruritus gravidarum with and without cholestasis), and drug induced pruritus (e.g., ACE-inhibitors, opioids, allopurinol, simvastatin, amiodarone, hydrochlorthiazid, estrogens, hydroxyethyl starch) (Ständer et al., 2007; Weisshaar et al., 2012).

(III) *Neurological pruritus* occurs as a result of the central or peripheral systems diseases/disorders. For e.g., a nerve damage, a nerve compression, and a nerve irritation. Neurological pruritus comprises both neuropathic pruritus and neurogenic pruritus. *Neuropathic pruritus* arises at any point on the afferent pathway due to the damage to the nervous system, exemplified by itch in postherpetic neuralgia, hydroxyethyl infusion, multiple sclerosis, brachioradial pruritus, cerebral vascular events, notalgia paraesthetica, cheiralgia parasthetica, trigeminal trophic syndrome, HIV infection, abscess or thrombosis and cerebral tumour, vulvodynia, neoplasms (Liddell, 1974; Andreev and Petkov, 1975; King et al., 1982; Massey, 1984; Layton and Cotterill, 1991; Cockerall, 1994; Ständer et al.,

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