

Antidepressants in chronic idiopathic urticaria

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ABSTRACT

Chronic idiopathic urticaria (CIU) is a common disease estimated to affect 0.1% of the population and can be very difficult to treat. Many psychotropic medications have been reported to be successful in treating refractory CIU. The purpose of this article was to discuss the pathophysiology of chronic urticaria and provide practicing allergists and dermatologists alternative treatment options in the management of refractory CIU, especially in those who have concurrent psychiatric comorbidity. A review was performed of pertinent literature pertaining to the pathophysiology of CIU and the many psychotropic medications reportedly successful in disease management. Although more research is needed, this article serves to broaden the mind of the physician treating CIU.

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Chronic idiopathic urticaria (CIU) presents with recurrent pruritic wheals persisting for >6 weeks.¹ Chronic urticaria has a prevalence of 0.5–3% in the general population, is rare in children, and usually persists for months or years.² Forty percent of patients have symptomatic hives 10 years after diagnosis. CIU results in significant patient disability, impacting patient health status with limitations on daily life activities, physical well-being, and emotional functioning.³ In some patients, there is evidence that chronic urticaria has an autoimmune origin caused by autoantibodies to FcεR1 or to IgE itself, although the presence of autoantibodies does not have any consistent predictive effect of response to any alternative agent.⁴ The psychophysiological component of this disorder includes triggers such as emotional stress.⁵ The use of psychotropic medications in the management of chronic urticaria has not been well characterized. Conversely, psychotropic treatments of other disease entities with a similar pruritus component have been published. The purpose of this study was to describe the neurological and psychotropic components of CIU pathophysiology and associated potential treatment options.

PSYCHIATRIC COMORBIDITY

Patients with CIU frequently exhibit psychiatric comorbidity. The prevalence of psychiatric disorders among patients with chronic physical diseases varies between 29 and 40% compared with 10 and 20% general population prevalence. Moreover, psychiatric di-

agnoses, most frequently depression, affect 60% of CIU patients. Depression in CIU results in lower quality-of-life scores. Alternatively, CIU patients without depression (no comorbid Axis I or Axis II psychiatric disorders) had a quality of life similar to that of healthy controls.⁶ Psychiatric comorbidity also results in 56% of working patients missing at least 1 day of work per month. Cost analysis of direct and indirect medical costs for CIU in the United States total nearly a quarter billion dollars a year.⁷ Disease impact is comparable with that of patients with severe coronary artery disease.⁸ However, the relationship between treatment of psychiatric comorbidity and CIU disease control still has to be defined by large clinical studies.

PATHOPHYSIOLOGY

CIU is characterized by pruritus classically described as a distinct sensation that evokes a desire to scratch. Transmitted by C fibers at the dermoepidermal junction, these fibers synapse in a specific class of dorsal horn neurons and ascend up the spinal cord in the lateral spinothalamic tract. Supraspinal processing of the itching sensation is attributed to the activation of the anterior cingulate cortex, supplementary motor area, and inferior parietal lobe in the brain with left hemisphere predominance.⁹

Whether psychological ailments are associated with or simply the result of chronic urticaria remains to be resolved. Current hypotheses indicate the etiology of many organic diseases such as CIU is complex. The molecular signaling involved in the relationship between psychiatric disease and CIU involves several potential factors. Vasodilatation and its autoregulation associated with emotions have been hypothesized as one etiology of urticarial lesions.¹⁰ The central nervous system responds to stress, reflecting a unique immune profile focused on humoral (T-helper type 2 cell) responses. Subjected to stress, the hypothalamus releases hormones including cortisol, resulting in increased hu-

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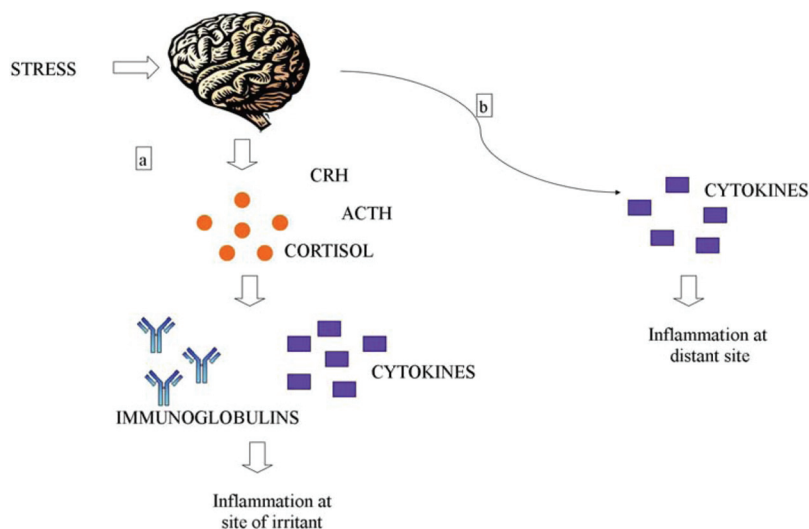


Figure 1. (a) Stress causes release of hormones from the hypothalamus resulting in increased humoral production of immunoglobulins and up-regulated cytokine expression worsening inflammation. (b) Neurogenic switching consists of rerouting of sensory activation via the central nervous system, causing neurogenic inflammation at a second location.

moral production of immunoglobulins and up-regulated cytokine expression. Associated illnesses such as atopic dermatitis have been linked to similar cytokine overexpression and IgE production. Alternatively, elevated inflammatory cytokine states are linked to major depression.¹¹ (Fig. 1) Hence, the dynamic interactions between neurological, immune, vascular, and psychological pathways are intricately intertwined.

The peripheral nervous system may also contribute to the pathophysiology of CIU. Specific neuropeptides in CIU are elevated and associated polymodal and chemosensitive small cutaneous nerve fibers are known to participate in skin inflammation.¹² Neurogenic switching is proposed to result when a sensory impulse from a site of activation is rerouted *via* the central nervous system (CNS) to a distant location resulting in neurogenic inflammation at a second location. Such a phenomenon is proposed in fibromyalgia pain syndromes. Similar rerouting of neurogenic impulses has also been implicated in CIU as an unexpectedly high proportion of patients with urticaria are diagnosed with fibromyalgia.¹³ Such neurogenic switching may explain why patients with CIU exacerbate with emotional stress and mood fluctuation.

TREATMENT OPTIONS

The management and therapy of chronic urticaria must reflect the individual need and situation of each patient and depend on the results of patients' medical histories, clinical examinations, and diagnostic procedures. Nonsedating H₁-blockers are regarded as first-line therapy in patients with chronic urticaria.¹⁴ If standard dosing is not effective, increasing the dosage up to fourfold is recommended.¹⁵ Evidence supporting this approach is sparse, and well performed double-blind, placebo-controlled studies comparing normal and off-label doses are missing.¹⁶ Unfortunately, antihistamines are not always effective. Only 31% of pa-

tients have a good response to antihistamines.¹⁷ For patients who do not respond it is recommended that second-line therapies should be added to the antihistamine treatment.¹² Some controlled studies have shown that H₂-receptor antagonists may provide statistically significant benefit if they are added to H₁-receptor antagonists, although others have found only little benefit over anti-H₁-therapy alone. Immunosuppressive drugs are very effective in most chronic urticaria patients, but their potential toxicity limits a wide clinical use.^{18,19}

The incomplete understanding of the pathogenesis of chronic urticaria has hampered the search for new low-toxicity active drugs.²⁰ Psychotropics in combination with antihistamines and antiallergics are significantly effective in suppressing urticaria, especially in patients with a higher level of anxiety or depression or who are psychosomatic-symptom prone.²¹ These lower-toxicity drugs that have been shown in the literature to be effective will be discussed (Table 1).

Doxepin

The tricyclic antidepressant oral doxepin dosed at 10–25 mg three times daily has been shown to be effective in the treatment of CIU. The efficacy of doxepin in CIU is not thought to be directly related to its antidepressant effects. The H₁- and H₂-antihistaminic and anticholinergic properties of the tricyclic antidepressants are important reasons for their efficacy. Dermal blood vessels possess both H₁- and H₂-histamine receptors, and combined H₁- and H₂-antihistamine therapy is more effective than H₁-antihistamines alone in chronic urticaria. Doxepin has potent antihistaminic activity with nearly 800 times more potent than diphenhydramine and six times more potent than cimetidine.^{22,23} Although the most common side effect of doxepin is sedation, one-half of the patients studied by Goldsobel *et al.* found sedation resolution in 3–4 days.

Table 1 Alternative psychotropic treatment options in chronic urticaria

Drug	Dosage	Comments/Adverse Cutaneous Effects	Patients Studied
Doxepin	10–25 mg t.i.d.	Can cause sedation; avoid in elderly patients because it can cause cardiac arrhythmias; can cause angioedema, rash, urticaria, and photosensitivity	CIU
Topical doxepin	5% cream	Mild somnolence despite topical application; can cause eczema exacerbation, application site reaction, and allergic contact dermatitis	Postburn pruritis, LSC, nummular eczema, or contact dermatitis
SSRIs (paroxetine, fluvoxamine and sertraline)	20–40 mg daily; 50–150 mg daily; 50–100 mg daily	Exact mechanism unknown; linked to many cutaneous adverse reactions, sometimes accompanied by urticaria	Chronic pruritis (fluvoxamine and paroxetine) and PBC (sertraline)
Nalmefene	10–20 mg daily	Sixty-seven percent of patients experienced dizziness, fatigue, and nausea	CIU and atopic dermatitis
Naltrexone	50 mg daily	High cost and can cause rash	Pruritic eczema
Topical naltrexone	1% cream	Not commercially available	Atopic dermatitis and pruritic skin disease
Mirtazapine	15 mg daily	Can cause photosensitivity	Chronic urticaria
Gabapentin	300 mg daily; 1200 mg t.i.d.	Gabapentin with stronger antipruritic effect than pregabalin	Pruritis
Bupropion	150–300 mg daily	Possibly neurogenic switching; can cause rash	Atopic dermatitis and psoriasis vulgaris
Alprazolam	2 mg t.i.d.	Can cause drowsiness and possible dependency; can cause rash	CIU

CIU = chronic idiopathic urticaria; LSC = lichen simplex chronicus; PBC = primary biliary cirrhosis; SSRIs = selective serotonin reuptake inhibitors.

Most patients were able to perform normal daily activities without impairment. Doxepin should be administered cautiously in the elderly and those with cardiovascular disease because of risk of cardiac arrhythmias.

Topical Doxepin

The topical use of doxepin is used for itch treatment with a similar mechanism of action as the oral form. Postburn pruritus patients treated with an oral antihistamine were randomized into a standard care group or doxepin cream group. The itching focus disappeared in 75% of patients in the treatment arm compared with 20% in the control group.¹⁸ In another study, patients with lichen simplex chronicus, nummular eczema, or contact dermatitis were randomly assigned doxepin cream or vehicle cream. Nearly 60% of patients using

doxepin experienced pruritus relief within 24 hours, which increased to 84% after a total of 7 days.²⁴ Despite topical application, 10% of patients experienced a mild somnolence comparable with an oral antihistamine.²⁵

Paroxetine and Fluvoxamine

In an open-labeled, two-arm prospective study, fluvoxamine and paroxetine were tested in patients with chronic pruritus. Paroxetine boasts the highest serotonin reuptake inhibitory effect. Fluvoxamine has been reported to have a favorable benefit/side effect profile. Results showed that both substances mediated considerable and stable antipruritic effects in chronic generalized pruritus on average after 4.9 weeks. Patients with psychological comorbidity showed slight but insignificantly higher response rates. It is speculated that the antipruritic

effects of selective serotonin reuptake inhibitors are also caused by a down-regulation of 5HT₃ receptors. Another hypothesis focuses on the effect of SSRIs on opioid receptors. Relevant animal studies indicate that the antinociceptive effect of paroxetine was significantly inhibited by naloxone, an opioid receptor antagonist, suggesting the involvement of opioidergic mechanisms.²⁶ Although the exact mechanisms leading to suppression of pruritus are not fully understood, a CNS suppression of pruritus may be likely given the response of several forms of pruritus to SSRI therapy.

Sertraline

Sertraline, another SSRI, was retrospectively found to improve pruritus in patients with primary biliary cirrhosis. Patients with chronic pruritus secondary to liver disease were dose titrated with sertraline until either pruritus resolved, side effects were intolerable, or no further benefit with additional dose increases were observed. Subsequently, sertraline was discontinued for washout followed by randomization to sertraline treatment or placebo. The optimal dose of sertraline was identified at 75–100 mg. Sertraline treatment was clearly associated with improvement in pruritus. In both the open-label and the randomized portions of the study, improvement in itch scores ($p = 0.009$), itch distribution, duration, direction, and physical scratching was noted.²⁷ Given the severe clinical pruritus associated with biliary disease and its improvement with sertraline, its application in CIU may be warranted.

Adverse Reactions of SSRIs

Although adverse effects of SSRIs are most often associated with alimentary tract symptoms such as nausea, vomiting, loss of appetite, and diarrhea, the use of SSRIs is also linked to many cutaneous adverse reactions. A macular or exanthematic rash often occurs during the 1st weeks of SSRI treatment, sometimes accompanied by urticaria.²⁸ In several patients that developed urticaria with fluoxetine, the urticaria subsided when the medication was stopped. In addition, using a desensitization protocol when reintroducing the medication 6–23 months later, the medication was well tolerated.²⁹ Thus, randomized control trials investigating the use of SSRIs in patients with chronic urticaria may be helpful in assessing its usefulness in disease management.

Nalmefene

Nalmefene is a potent opiate antagonist. It has been hypothesized that because central opioid receptors modulate itch, an opiate antagonist might block pruritus. In two randomized, double-blind placebo-controlled studies with severe pruritus caused by chronic urticaria and atopic dermatitis, different doses of nalmefene were tested for efficacy and safety. In eval-

uation of the therapeutic response to the treatments, 60% of patients taking 10 mg of nalmefene and 35% of patients taking 20 mg of nalmefene reported an excellent response defined as the virtual elimination of pruritus. Only 14% of the control group reported similar results. However, 67% of patients experienced adverse effects including dizziness, fatigue, and nausea.³⁰

Naltrexone

Thirty-eight patients with pruritic eczema were randomly allocated to naltrexone or placebo. Within the naltrexone group, six patients achieved total remission of pruritus, which did not occur in any of the patients in the placebo group. Other studies have also shown significant antipruritic responses of naltrexone in patients with psoriasis and cutaneous lymphoma but no significant effect in patients with uremia.³¹ Clinical and experimental observations have shown that pruritus can be evoked or intensified by endogenous or exogenous opioids. Therefore, reversing this effect by μ -opioid antagonists results in inhibition of pruritus, explaining the efficacy of medications such as naltrexone, nalmefene, and naloxone. However, initial side effects as well as high cost lead to second-line use in chronic pruritus.³²

Topical Naltrexone

Human epidermal keratinocytes, fibroblasts, and melanocytes express μ -opioid receptors (MOR). In normal skin, the nerve endings are rather thick and wind through the epidermis. In patients with chronic atopic dermatitis, the nerve endings are thinner and run straight through the epidermis with minimal MOR expression on keratinocytes. This decreased expression is hypothesized to increase the binding of endogenous ligands to MOR on epidermal nerve endings resulting in an intensified itch signal to the CNS. In patients with chronic pruritic disorders topical naltrexone has been shown to up-regulate epidermal MOR expression. Subsequent binding of the free opiate ligands to epidermal keratinocytes may reduce pruritus. Additionally, naltrexone may have a direct effect on the opioid receptor signaling in peripheral nerve endings.³³

The topically applied opioid receptor antagonist was studied in different forms of pruritus because of the side effects with systemic MOR antagonists. Naltrexone 1% cream was topically applied to patients with pruritic skin disease not responding to traditional treatment with antihistamines or topical steroids. After 15–30 minutes, >70% of these patients experienced a significant reduction of itching that lasted between 2 and 6 hours. Subsequently, patients with atopic dermatitis were placed in a double-blind, placebo-controlled, crossover study with topical naltrexone when compared with placebo. The naltrexone cream had a 29.4% better effect and reduced itch symptoms to 50%

in a median of 46 minutes compared with 74 minutes for the placebo formulation.

Mirtazapine

Mirtazapine is a noradrenergic and specific serotonergic antidepressant that acts by antagonizing adrenergic α -2-heteroreceptors in addition to blocking 5HT₂ and 5HT₃ receptors. It also has H₁-antihistamine properties. A patient with severe chronic urticaria unresponsive to high doses of classic and low sedation H₁-antihistamines, H₂-antihistamines, and brief courses of oral steroids was reported. Fluoxetine and lorazepam were started for her anxiety and depression reactive to the disease. Fluoxetine was discontinued and mirtazapine at 15 mg daily was initiated for additional antipruritic effects. After 7 days of treatment the urticaria unexpectedly resolved. Over a 10-day period, all of her other medications were withdrawn without recurrence of urticaria. After 1 month, mirtazapine was also discontinued and the patient's urticaria relapsed after 6 days. Mirtazapine was restarted at 15 mg daily in addition to ebastine and hydroxyzine. Subsequently, the antihistamines were stopped and the mirtazapine was continued with excellent control.³⁴ Mirtazapine has a good tolerability and safety profile.³⁵

Gabapentin/Pregabalin

Gabapentin is an anticonvulsive drug with additional analgesic properties. Its primary effect is inhibition of voltage-dependent calcium ion channels located in the spinal cord hindering transmission of nociceptive sensations to the brain. This blockades postsynaptic calcium channels and can possibly effect nerve membrane stabilization or inhibit the synthesis of neurotransmitters. Gabapentin is also known to secondarily inhibit the release of calcitonin gene-related peptide (a mediator of itching) through a primary increase of gaba-aminobutyric acid in the spinal cord. Furthermore, it has been hypothesized that the mechanism of action of gabapentin also involves opioid receptors that may affect the central perception of itching. In two patients with pruritus of unknown origin, gabapentin was started and titrated to symptom control. Both patients had an excellent response with complete control of the itching within the 1st month. The dose of gabapentin is initially 300 mg/day and can be increased up to 1200 mg three times a day. It has a low clinical toxicity ratio, minimizing the chances of adverse effects even with very high overdoses.³⁶ Pregabalin is a new substance that displays similar effects to gabapentin with a better side effect profile. Pregabalin modulates the presynaptic release of excitatory neurotransmitters and reduces the substance P-related activation of glutamate receptors on noradrenergic synapses, total transmitter release, and neuronal activity. In clinical experience, ga-

bapentin showed stronger antipruritic effects than pregabalin.³⁷

Bupropion

Bupropion is an antidepressant that primarily works through inhibition of noradrenaline and dopamine re-capture. One patient with a 30-year history of atopic dermatitis was published reporting improved dermatologic symptoms after starting bupropion for smoking cessation therapy. After 9 weeks of therapy, he discontinued the medication. After 3 weeks, his dermatitis injuries returned and only disappeared once the medication was restarted.³⁸ Patients with atopic dermatitis and psoriasis vulgaris were studied in a single-track, open-label treatment protocol sequentially for 6 weeks with increasing doses of bupropion followed by a 3-week washout period. Six of the 10 patients with atopic dermatitis and 8 of the 10 patients with psoriasis vulgaris had ~50% reduction in affected body surface area after 6 weeks of treatment with bupropion. After bupropion discontinuation, coverage increased toward the prestudy baseline. There is no known effect of bupropion on the skin, making it difficult to postulate a mechanism of action for the observed improvement. It is possible that neurogenic switching is responsible for this effect, especially because neuroendocrine, immunologic, and catecholaminergic abnormalities have all been implicated in the pathogenesis of both atopic dermatitis and psoriasis.³⁹ It is thus plausible that bupropion would have similar effects in chronic urticaria.

Alprazolam

A small study in Spain showed improvement of CIU using alprazolam. Twelve patients with severe refractory idiopathic urticaria for >10 years were randomized to 2 mg of alprazolam three times daily or 10 mg of rupatadine three times daily, a new antihistamine platelet-activating factor inhibitor. The drugs were given in identical empty capsules and administered. Of the eight patients, the urticaria disappeared in six patients treated with alprazolam and persisted in the two patients treated with rupatadine. Urticaria reappeared after 36 hours after withdrawal of alprazolam and improved 8 hours after readministration.⁴⁰

SUMMARY

CIU remains a challenging clinical disease with typically poor treatment outcomes. Standard regimens of antihistamine therapy are associated with significant adverse effects, particularly sedation and weight gain. Compliance with such treatment regimens is difficult, resulting in social and work limitations. The psychological component of CIU remains poorly defined but is clinically relevant. Small studies and case reports summarized here reveal a modality of treatment with

clinical benefits. Although the psychopathophysiology remains difficult to elicit, therapeutic options for CIU psychiatric comorbidity currently exist. The recommendation of psychotropic treatment discussed in this article warrant careful consideration by the clinician with a risk-to-benefit analysis on an individual patient basis. The involvement of a psychiatric subspecialist in the care of CIU also should be considered. Furthermore, current treatment options noted here require further validation with larger, randomized, placebo-controlled studies.

REFERENCES

1. Fromer L. Treatment options for the relief of chronic idiopathic urticaria symptoms. *South Med J* 101:186–192, 2008.
2. Peroni A, Colato C, Schena D, et al. Urticarial lesions: If not urticaria, what else? The differential diagnosis of urticaria. *J Am Acad Dermatol* 62:541–555, 2010.
3. Baiardini I, Giardini A, Pasquali M, et al. Quality of life and patients' satisfaction in chronic urticaria and respiratory allergy. *Allergy* 58:621–623, 2003.
4. Khan DA. Chronic urticaria: Diagnosis and management. *Allergy Asthma Proc* 29:439–446, 2008.
5. Koo JY, and Pham CT. Psychodermatology. Practical guidelines on pharmacotherapy. *Arch Dermatol* 128:381–388, 1992.
6. Uguz F, Engin B, and Yilmaz E. Quality of life in patients with chronic idiopathic urticaria: The impact of Axis I and Axis II psychiatric disorders. *Gen Hosp Psychiatry* 30:453–457, 2008.
7. Delong LK, Culler SD, Saini SS, et al. Annual direct and indirect health care costs of chronic idiopathic urticaria: A cost analysis of 50 nonimmunosuppressed patients. *Arch Dermatol* 144:35–39, 2008.
8. O'Donnell BF, Lawlor F, Simpson J, et al. The impact of chronic urticaria on the quality of life. *Br J Dermatol* 136:197–201, 1997.
9. Yosipovitch G, Greaves MW, and Schmelz M. Itch. *Lancet*. 361:690–694, 2003.
10. Teshima H, Nagata S, Kinara H, et al. Psychobiological studies on the onset of allergic disease. A Japanese approach. *Advances* 3:143–149, 1986.
11. Locala J. Current concepts in psychodermatology. *Curr Psychiatry Rep* 11:211–218, 2009.
12. Torresani C, Bellafiore S, and De Panfilis G. Chronic urticaria is usually associated with fibromyalgia syndrome. *Acta Derm Venereol* 89:389–392, 2009.
13. Meggs WJ. Neurogenic switching: A hypothesis for a mechanism for shifting the site of inflammation in allergy and chemical sensitivity. *Environ Health Perspect* 103:54–56, 1995.
14. Zuberbier T, Asero R, Bindslev-Jensen C, et al. EAACI/GA2LEN/EDF/WAO guideline: Management of urticaria. *Allergy* 64:1427–1443, 2009.
15. Staevska M, Popov TA, Kralimarkova T, et al. The effectiveness of levocetirizine and desloratadine in up to 4 times conventional doses in difficult to treat urticaria. *J Allergy Clin Immunol* 125:676–682, 2010.
16. Asero R, and Tedeschi A. Emerging drugs for chronic urticaria. *Expert Opin Emerg Drugs* 11:265–274, 2006.
17. Champion RH, Robert SOB, Carpenter RG, et al. Urticaria and angioedema. *Br J Dermatol* 81:588, 1969.
18. Morgan M, and Khan DA. Therapeutic alternatives for chronic urticaria: An evidence based review, Part 1. *Ann Allergy Asthma Immunol* 100:403–311, 2008.
19. Morgan M, and Khan DA. Therapeutic alternatives for chronic urticaria: An evidence based review, Part 2. *Ann Allergy Asthma Immunol* 100:517–526, 2008.
20. Asero R, and Tedeschi A. Emerging drugs for chronic urticaria. *Expert Opin Emerg Drugs* 11:265–274, 2006.
21. Hashiro M, and Yamatodani Y. A combination therapy of psychotropic drugs and antihistamines or antiallergics in patients with chronic urticaria. *J Dermatol Sci* 11:209–313, 1996.
22. Gupta MA, and Gupta AK. The use of antidepressant drugs in dermatology. *Eur Acad Dermatol Venereol* 15:512–518, 2001.
23. Goldsobel AB, Rohr AS, Siegel SC, et al. Efficacy of doxepin in the treatment of chronic idiopathic urticaria. *J. Allergy Clin Immunol* 86:7–873, 1986.
24. Drake LA, and Millikan LE. The antipruritic effect of 5% doxepin cream in patients with eczematous dermatitis. Doxepin Study Group. *Arch Dermatol* 131:1403–1408, 1995.
25. Demling R, and DeSanti L. Topical doxepin significantly decreases itching and erythema in the chronically pruritic burn scar. *Wounds Res* www.woundsresearch.com/article/1747, 2003.
26. Duman EN, Kesim M, Kadioglu M, et al. Possible involvement of opiodergic and serotonergic mechanisms in antinociceptive effect of paroxetine in acute pain. *J Pharmacol Sci* 94:161–165, 2004.
27. Mayo MJ, Handem I, Saldana S, et al. Sertraline as a first-line treatment for cholestatic pruritus. *Hepatology* 45:666–674, 2007.
28. Krasowska D, Szymanek M, Schwartz RA, et al. Cutaneous effects of the most commonly used antidepressant medication, the selective serotonin reuptake inhibitors. *J Am Acad Dermatol* 56:848–853, 2007.
29. Leznof A, Binkley KE, Joffe RT, et al. Adverse cutaneous reactions associated with fluoxetine strategy for reintroduction of this drug in selected patients. *J Clin Psychopharmacol* 12: 355–357, 1992.
30. Monroe E. Efficacy and safety of nalmefene in patients with severe pruritus caused by chronic urticaria and atopic dermatitis. *J Am Acad Dermatol* 21:135–136, 1989.
31. Malekzad F, Arbabi M, Mohtasham N, et al. Efficacy of oral naltrexone on pruritus in atopic eczema: A double-blind, placebo-controlled study. *J Eur Acad Dermatol Venereol* 23:948–950, 2009.
32. Ständer S, Weisshaar E, and Luger TA. Neurophysiological and neurochemical basis of modern pruritus treatment. *Exp Dermatol* 17:161–169, 2008.
33. Bigliardi PL, Stammer H, Jost G, et al. Treatment of pruritus with topically applied opiate receptor antagonist. *J Am Acad Dermatol* 56:979–988, 2007.
34. Bigata X, Sais G, and Soler F. Severe chronic urticaria: Response to mirtazapine. *J Am Acad Dermatol* 53:916–917, 2005.
35. Antilla SA, and Leinonen EV. A review of the pharmacological and clinical profile of mirtazapine. *CNS Drug Rev* 7:249–264, 2001.
36. Yesudian PD, and Wilson NJ. Efficacy of gabapentin in the management of pruritus of unknown origin. *Arch Dermatol* 141:1507–1509, 2005.
37. Ständer S, Weisshaar E, and Luger TA. Neurophysiological and neurochemical basis of modern pruritus treatment. *Exp Dermatol* 17:161–169, 2008.
38. González E, Sanguino RM, and Franco MA. Bupropion in atopic dermatitis. *Pharmacopsychiatry* 39:229, 2006.
39. Modell JG, Boyce S, Taylor E, and Katholi C. Treatment of atopic dermatitis and psoriasis vulgaris with bupropion-SR: A pilot study. *Psychosom Med* 64:835–840, 2002.
40. Dueñas-Laita A, Ruiz-Muñoz P, Armentia A, et al. Successful treatment of chronic drug-resistant urticaria with alprazolam. *J Allergy Clin Immunol* 123:504–505, 2009. □

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