# Treatment of erythromelalgia with a serotonin/noradrenaline reuptake inhibitor.

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2002 British Association of Dermatologists, British Journal of Dermatology, 146, 331-344

(Letter to the Editor)
SIR, Erythromelalgia is an unusual disorder characterized by the triad of red, hot and painful extremities. The symptoms are exacerbated by heat and improved by cold. Its aetiology is not fully understood. Numerous different medications including aspirin, gabapentin, amitriptyline, benzodiazepines and opiates have been used in attempts to treat the symptoms of erythromelalgia, with varying success.[1] We report our experience with the use of venlafaxine (Efexor®; Wyeth Ayerst Pharmaceuticals, St Davids, PA, USA), a serotonin and noradrenaline reuptake inhibitor, in the treatment of primary erythromelalgia. Venlafaxine has previously been reported to improve the symptoms in one case of Raynaud's phenomenon [2] and two cases of erythromelalgia.[3]

Ten patients with primary erythromelalgia were studied. Appropriate investigations were performed to exclude associated causes. Patients were subsequently treated with oral venlafaxine 37.5 mg twice daily. The patients were examined weekly for evaluation of symptoms, as well as for severity and extent of skin warmth and erythema.

All patients were able to tolerate the treatment without major side-effects. Following 1 week of therapy, a marked improvement in pain and burning was reported by all patients. There was also an appreciable decrease in the warmth and erythema in all patients. The most common side effect was nausea, reported in two patients. The patients continued the treatment for up to 6-18 months with continued benefit, and no adverse reactions.

Primary erythromelalgia is a rare condition, usually diagnosed clinically, based on history, signs and symptoms. Investigation to exclude associated medical conditions, particularly myeloproliferative disorders, is required. Microscopic evaluation of skin biopsies is not always diagnostic. The pathogenesis of primary erythromelalgia is not entirely known. [1,4-6] A localized defect in the vascular and neural function of the involved skin has been proposed.[6] Arteriovenous shunting in the affected skin, with subsequent hypoxia and metabolic deficit, may play a significant role. Inhibition of serotonin uptake by platelets has been shown to decrease platelet function and reduce platelet plug formation under shear stress.[7,8] We hypothesize that venlafaxine exerts its therapeutic benefit in erythromelalgia in part through this mechanism. The vasoactive properties of serotonin are not clearly understood, and the potential effects of serotonin

reuptake inhibitors on the microvasculature are not known.[3] Histological examination of erythromelalgia skin has shown a decrease in the sympathetic innervation and deficient sympathetic regulation in the affected skin.[4,9] The implications of this decreased sympathetic innervation in the pathogenesis of erythromelalgia are not evident. Venlafaxine has been shown to inhibit noradrenaline uptake,[10] which may be an additional mechanism of action in erythromelalgia. Therefore, via its influence on noradrenaline as well as serotonin, venlafaxine may have dual efficacy in treating the underlying neurovascular phenomenon involved in erythromelalgia, rendering a therapeutic advantage over other selective serotonin reuptake inhibitors.

Venlafaxine has been used for the treatment of depression, anxiety and obsessive-compulsive disorders.[10] It has a low affinity for muscarinic, histaminergic and ál-adrenergic receptors, and has a low side-effect profile. The most common side-effects include nausea, somnolence and dry mouth, which decrease in severity with long-term therapy. [3,10] The recommended starting dose of venlafaxine for depression is 37.5 mg twice daily, and may be increased up to 375 mg daily.[10]

The results of this pilot study indicate that venlafaxine may be a safe and effective therapeutic option for patients with primary erythromelalgia. A placebo effect cannot be ruled out. This study is also limited by the small patient numbers and the lack of an objective measure of clinical improvement such as blinded assessment of photographs. A double-blind placebo-controlled randomized study is under way; however, it has been limited by the low incidence of this disorder.

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**References**

1. Cohen JS. Erythromelalgia: new theories and new therapies. J Am Acad Dermatol 2000; 43: 841-7.
2. Jaffe IA. Serotonin reuptake inhibitors in Raynaud's phenomenon. Lancet 1995; 345: 1378.
3. Rudikoff D, Jaffe L9. Erythromelalgia response to serotonin reuptake inhibitors. J Am Acad Dermatol 1997; 37: 281-3.
4. Mork C, Asker CL, Salerud EG, Kvernebo K. Microvascular arteriovenous shunting is, a probable pathogenetic mechanism in erythromelalgia. I Invest Dermatol 2000; 114: 643-6.
5. Davis MD, Rooke TW, Sandroni P. Mechanisms other than shunting are likely contributing to the pathophysiology of erythromelalgia. J Invest Dermatol 2000; 115:

1166-7.
6. Littleford RC, Khan F, Belch JJ. Impaired skin vasomotor reflexes in patients with erythromelalgia. Clin Sci 1999; 96: 507-12.
7. Serebruany VL, Gurbel PA, O'Connor CM. Platelet inhibition by sertraline and n-desmethylsertraline: a possible missing link between depression, coronary events, and mortality benefits of SSRIs. Pharmacol Res 2001; 43: 453-62.
8. Hergovich N, Aigner M, Eichler HG. Paroxetine decreases platelet serotonin storage and platelet function in human beings. Clin Pharmacol Ther 2000; 68: 435-42.
9. Staub DB, Munger BL, Uno H, Dent C. Erythromelalgia as a form of neuropathy. Arch Dermatol 1992; 128: 1654-5.
10. Harvey AT, Rudolph RL, Preskom SH. Evidence of the dual mechanisms of action of venlafaxine. Arch Gen Psychiatry 2000; 57: 503-9.