

High-dose doxepin for the treatment of chronic, intractable scalp pruritus



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INTRODUCTION

Pruritus is one of the most common symptoms seen in dermatology and can be as detrimental to quality of life as chronic pain.¹ Finding adequate treatment for management of chronic pruritus is challenging, especially for patients with pruritus refractory to conventional treatments. We report a patient with chronic, refractory scalp pruritus that did not respond to over 40 different treatments but that has now been well controlled for 3 years on 280 mg of doxepin daily.

CASE REPORT

A 67-year-old man presented to our clinic with a 5-year history of intractable scalp pruritus. He first noticed the abrupt onset of itch and pain on his scalp in 2011. The itch sensation started in the occipital region and spread to the rest of his scalp. Itch with a severity between 8 and 10 on a scale of 1 to 10 was often noted and was significantly impacting his quality of life. Burning sensations, followed by pruritus, tended to occur in the morning, worsened during the day, and resolved during the night. Physical examination was notable only for diffuse mild erythema over the scalp.

After visiting multiple dermatologists, the patient tried numerous topical, systemic, procedural, and complementary and alternative therapies, including oral and topical doxepin, for his scalp pruritus, all of which failed (Table D). He tried oral doxepin 20 mg daily with no side effects or benefits. Despite adherence to these treatments for at least 1 to 2 months each, his pruritus did not improve. Topical clobetasol provided minimal temporary

relief but never fully addressed his pruritus and burning scalp sensations. Biopsies of the scalp were consistently negative for folliculitis or a primary inflammatory process. His medical history was significant for hypothyroidism and bacterial folliculitis, both of which had been long resolved. His psychiatric history was unremarkable, with mental status examination negative for depression and anxiety.

The patient was using topical lidocaine 3 times per week when he first presented to our clinic, but he still noted an itch severity of 10. Because he reported no side effects from low doses of doxepin previously and treatment failure from underdosing of doxepin is a common occurrence, doxepin was deliberately reintroduced with the intention to increase the dose until the patient either responded or could not tolerate the side effects. He was started on 10 mg of doxepin daily, which was gradually titrated to 170 mg daily over 8 months (Fig 1). At this dose, he experienced no drowsiness or other side effects, but he experienced no benefits, and his serum doxepin level was undetectable. Electrocardiograms performed periodically were normal, with no prolongation of the corrected QT interval. Electrocardiograms were usually performed before a dose increase. After the dose reached 170 mg daily, the dose was increased with extra care at the rate of only 10 mg every 2 to 4 weeks. At 16 months, the dose had reached 280 mg daily. At this point, his serum doxepin level was finally within the target therapeutic range for the antidepressant effects of doxepin, which is typically between 50 and 250 ng/mL, and he reported complete resolution of itch with no side effects.² For the past 3 years, the patient has continued this regimen of doxepin 280 mg daily, and

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Table I. Comprehensive medication history for chronic scalp pruritus

Topical medications

Antifungals: ketoconazole shampoo, selenium sulfide shampoo
 Antibiotics: clindamycin
 Calcineurin inhibitor: tacrolimus
 Corticosteroids: clobetasol, fluocinolone acetonide scalp oil
 Neuropathic: lidocaine-capsaicin, doxepin, gabapentin

Systemic medications

Antibiotics: doxycycline, dapsone, sulfamethoxazole-trimethoprim
 Antifungals: itraconazole, fluconazole, ketoconazole, terbinafine
 Antihistamines: hydroxyzine, fexofenadine, cetirizine, loratadine
 Corticosteroid: prednisone
 Histamine H2 receptor antagonist: famotidine
 Immunosuppressants: hydroxychloroquine, mycophenolate mofetil
 Neuropathic: amitriptyline, mirtazapine, gabapentin, paroxetine, doxepin
 Neurokinin receptor 1 antagonists: aprepitant, serlopitant
 Opioid receptor antagonist: naltrexone
 Retinoid: isotretinoin
 Skeletal muscle relaxer: baclofen

Procedural

Botulinum toxin injection and zinc supplementation
 Triamcinolone acetonide 40 mg/mL injection
 C3,C4 transforaminal epidural steroid injection

Complementary and alternative medicine

Acupuncture
 Hypnosis

Our patient tried more than 40 treatments, including various topical, systemic, procedural, and complementary and alternative treatments for chronic scalp pruritus.

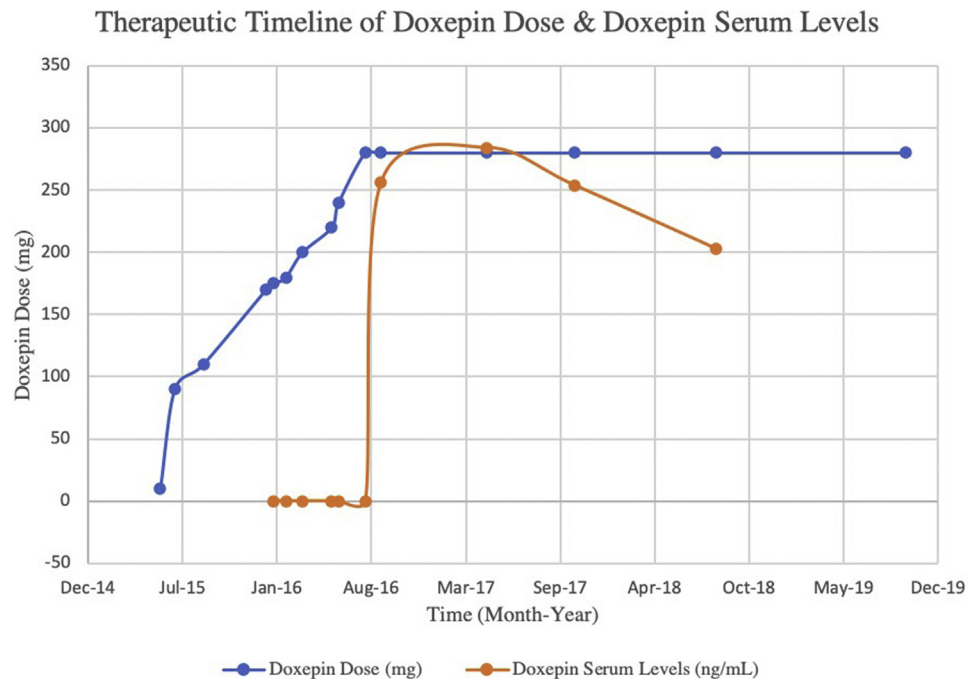


Fig 1. Therapeutic timeline of doxepin dose and doxepin serum levels from May 2015 to September 2019. The indicated doxepin serum levels are the combined total of doxepin ($\mu\text{g/L}$) and *N*-desmethyl doxepin ($\mu\text{g/L}$).

his itch has remained well controlled and is no longer interfering with his daily life.

DISCUSSION

Doxepin is a tricyclic antidepressant that is perhaps the most powerful antipruritic agent available to dermatologists, with antihistamine (H1) potency 783 and 56 times greater than that of diphenhydramine and hydroxyzine, respectively.³ Its use at low doses of 25 mg or less is a well-known therapy for chronic pruritus among dermatologists, yet many dermatologists are unaware that the metabolism of doxepin varies significantly between individuals. The metabolism of doxepin is mediated by cytochrome P450 enzymes. In some patients, genetic polymorphisms in these enzymes can cause ultrafast metabolism of doxepin, resulting in insufficient serum levels and treatment failure.⁴ Consequently, patients with intractable pruritus who are not treated with an adequate dose of doxepin may be mislabeled as “treatment failures,” when in fact they are cases of insufficient dosing. Because of this wide variation in metabolism, the US Food and Drug Administration approves doxepin doses of up to 300 mg per day. Unlike other antihistamines, tests for trough doxepin level (≥ 12 hours after the last dose) are widely available, which makes it easy to titrate individual doxepin dosing for patients to ensure that they reach therapeutic serum concentrations. Since the therapeutic range for doxepin’s antipruritic effects has not been

established, the therapeutic range for doxepin’s antidepressant effects may serve as a guide for the safe use of doxepin when the dermatologist needs to go beyond the typical dose of 10 to 25 mg per day. When prescribing high-dose doxepin, the authors recommend taking periodic electrocardiograms to monitor for potential cardiac side effects. The main side effect of doxepin is sedation, so dermatologists should also monitor for abnormal drowsiness. This case highlights the critical importance of monitoring doxepin trough plasma levels in a patient unresponsive to typical dermatologic doses and reminds dermatologists that doxepin can be safely titrated up to 300 mg per day to treat intractable, chronic pruritus.

Conflicts of interest

None disclosed.

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