

**Doxepin is an effective therapy option in difficult-to-treat chronic urticaria:
a retrospective, cross-sectional study over a 20-year period from Turkey and review of
the literature**

Short title: Doxepin in difficult-to-treat chronic urticaria

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Key words: chronic urticaria, antihistamine, poor response, difficult-to-treat, doxepin, therapy

Manuscript type: Original article

Number of words (text only): 2301

Number of tables: 2

Number of figures: 2

Funding sources: None

Conflict of interest disclosure: None declared

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/dth.12993

Introduction

Chronic urticaria (CU) is defined as a common dermatological disorder characterized by recurrent wheals, angioedema or both for more than 6 weeks which may appear spontaneously due to known or unknown causes as in chronic spontaneous urticaria (CSU) or as a response to several specific reproducible eliciting factors as in chronic inducible urticaria (Zuberbier et al., 2018). It is associated with a significant emotional and financial burden and has a profound impact on patients' quality of life. To date, various international societies have developed guidelines for the management of CU based on scientific evidence and expert opinions (Shahzad Mustafa & Sánchez-Borges, 2018). The main principle of CU treatment is total symptom relief by using minimal pharmacotherapy with the least adverse effects (Zuberbier et al., 2018). Second-generation H1 antihistamines are the first-line treatment options for CU, by which the majority of patients could be kept under control either at conventional or higher (up to fourfold) doses (Zuberbier et al., 2018).

The management of CU patients with a poor response to antihistamines is challenging. Doxepin is an old-fashioned tricyclic antidepressant (TCA) with high H1 and H2 histamine and muscarinic receptor blocking activities. Although its efficacy in CU has been well-documented in several studies until 1990, there are limited data on its use in CU over the last three decades in the literature (Adhya & Karim 2015). This study aimed to assess the efficacy and safety of doxepin in the treatment of patients with CU who were poorly responsive to antihistamines, in a relatively large group of patients from Turkey.

Materials and Methods

This was a retrospective, cross-sectional, single-centre study based on the data of patients with difficult-to-treat CU who received doxepin therapy in our clinic between 1998

and 2017. Children younger than 13 years, pregnant and lactating women were excluded. Patients who had used doxepin for less than two weeks were not included in the study.

Patients' files were evaluated with regard to duration of the disease, age, gender, concomitant angioedema, previous treatments, histopathological diagnosis (if available), treatment outcomes according to weekly urticarial activity score (UAS7), and adverse effects of the doxepin therapy. Triggering factors such as food, drug, focal or systemic infections, and autoimmune or other systemic diseases were ruled out in all patients prior to the initiation of doxepin therapy. Patients who were diagnosed with urticarial vasculitis according to the histopathological findings were excluded as urticarial vasculitis is not considered among the subtypes of urticaria (Zuberbier et al., 2018).

Difficult-to-treat CU patients consisted of those who had a poor response to various combinations of the first and second-generation H1 antihistamines, high doses (up to 4 times/day) of second-generation H1 antihistamines, with/without H2 antihistamines over a minimum of a 2-month period. 12 patients (33.3%) required short-term systemic corticosteroids for the control of acute exacerbations. One patient was found to be resistant to both cyclosporine A and omalizumab.

Treatment outcomes were assessed by using the UAS7 which is an established symptom score that was developed to assess the disease activity and provide a valid score system for comparing the results of different trials from different centers (Zuberbier et al., 2018). It is based on the daily number of wheals (0–3 points) and the daily intensity of pruritus (0–3 points) (Młynek et al., 2008). The sum of the scores of seven consecutive days gives the UAS7 value (maximum 42 points) (Zuberbier et al., 2018).

UAS7 was performed at the beginning and every 1-4 weeks of doxepin therapy. A reduction of $\geq 90\%$ in UAS7 was defined as “complete response”, a reduction of 30-89% as

“partial response”, and a reduction of <30% as “no significant response”, as in a recent article (Metz, Ohanyan, Church, & Maurer, 2014).

The study was approved by the Ethical Committee of Istanbul University, Istanbul Faculty of Medicine (approval number: 2018/941) and conducted in accordance with the Declaration of Helsinki.

Results

A total of 36 patients (13 males and 23 females) were identified to receive doxepin therapy. The male: female ratio was 1:1.8. The age range was 17-75 years (median: 40.5 years). The duration of urticaria was 2-288 months (median: 21 months). Twenty six patients (72.2%) had accompanying angioedema, and 7 patients (19.4%) concomitant chronic inducible urticaria in the form of symptomatic dermographism. Patient characteristics are summarized in Table 1.

The median sum of the UAS7 was 24.5 (range: 12-40) before initiating doxepin therapy. Doxepin was used for 2-156 weeks (median: 8 weeks). It was started orally at a dose of 10-25 mg/day that was gradually increased to 10-25 mg tid/day. “Complete response” could be achieved in 16 patients (44.4%), and “partial response” in 11 patients (30.6%) with doxepin at doses ranging from 20 mg to 75 mg/day within a median time span of 2 weeks (range: 1-16 weeks). Nine patients (25%) showed “no significant response” to doxepin 20-50 mg/day used for 2-8 weeks (Fig. 1). Among 27 patients who responded to doxepin therapy, only 10 needed to use antihistamines concomitantly (Fig. 2), which could be reduced to lower doses in eight of them.

Psychiatric comorbidities such as anxiety or depression accompanied CU in 14 patients (38.9%). “Complete response” of CU was achieved in eight of them with no need for higher doses usually administered in psychiatric disorders, and “partial response” in five patients.

Doxepin was generally tolerated well. Mild sedation was the most frequent adverse effect reported in almost all of the patients, followed by dry mouth (n=2), and blurred vision (n=1) occasionally. None of the patients reported any systemic adverse effects on cardiovascular, gastrointestinal or other systems and none of them required cessation of doxepin therapy due to adverse effects.

The prognoses of the 27 respondents were as follows: No recurrence of urticaria was observed in three patients with “complete response” to doxepin therapy in a follow-up period of 2-6 months. Doxepin therapy was stopped due to loss of efficacy in three patients after a median therapy period of 3 months, and in 12 patients due to its cost during the time interval prior to 2014, while it was not covered by general health insurance. Six patients were lost to follow-up. Three patients were still on doxepin therapy by the time the study was conducted.

Discussion

Tricyclic antidepressants (TCAs) were originally introduced as antihistamines (Harto, Sendagorta, & Ledo, 1985) due to their well-known potent H1 and H2 receptor blocking activities (Goldsobel et al., 1986). Doxepin is a tertiary amine type of TCA (Greene, Reed, & Schroeter, 1985), which was found to be 783 times more potent than diphenhydramine, a first generation H1-antihistamine, in *in-vitro* studies (Richelson, 1979). In 1980s it has been shown to be effective for the modulation of histamine induced whealing response even in minute doses such as 5 mg (Sullivan, 1982). In addition to its antihistamine properties, doxepin inhibits the presynaptic reuptake of noradrenaline and serotonin in the central nervous system (CNS) and exhibits antimuscarinic activity (Goldsobel et al., 1986; Gupta & Gupta, 2001). The latter was held responsible for the inhibition of guanyl cyclase, an enzyme that promotes histamine release from mast cells (Figueiredo et al., 1990).

Ever since its first approval by the Food and Drug Administration (FDA) in 1969, doxepin has been used to treat patients with depression and/or anxiety disorders, mainly due

to its inhibitory effects on serotonin and norepinephrine reuptake in high-doses. However, the rationale of doxepin therapy in CU is based on its potent antihistamine properties (Goldsobel et al., 1986; Gupta & Gupta, 2001). Therefore, the recommended daily dosage of doxepin for the treatment of CU is 10-25 mg three times daily (Goldsobel et al., 1986; Gupta & Gupta, 2001), which is much lower than the dosage employed in psychiatric disorders, ranging from 150 mg/day to 250 mg/day (Figueiredo et al., 1990). The efficacy of low-dose doxepin therapy has also been evaluated in chronic pruritus (Kouwenhoven, van de Kerkhof, & Kamsteeg, 2017). In a randomized controlled trial which included 24 patients with end-stage renal disease who underwent hemodialysis, 20 mg/day doxepin has been found to improve recalcitrant uremic pruritus in most (87.5%) of the patients (Pour-Reza-Gholi, Nasrollahi, Firouzan, Nasli Esfahani, & Farrokhi, 2007). Complete resolution of pruritus was reported in 14 patients (58.3%) with doxepin compared to two patients (8.3%) with placebo (Pour-Reza-Gholi et al., 2007). Moreover, low-dose doxepin (3-6 mg/day) has recently been approved by FDA for the treatment of insomnia characterized by difficulty with sleep maintenance in adult and elderly patients (Yeung, Chung, Yung, & Ng, 2015).

Doxepin has been suggested as a third line therapy following antihistamines and leukotriene receptor antagonists, in the treatment algorithm of 2014 American Academy of Allergy, Asthma, and Immunology (AAAAI) and American College of Allergy, Asthma, and Immunology (ACAAI) chronic urticaria management guideline, prior to alternative agents including omalizumab and cyclosporine A (Bernstein et al., 2014). However, due to the scarce number of controlled trials and low level of evidence, it's not included in the main algorithm of the European Academy of Allergology and Clinical Immunology (EAACI), the EU-founded network of excellence, the Global Allergy and Asthma European Network (GA²LEN), the European Dermatology Forum (EDF) and the World Allergy Organization (WAO) urticaria management guideline which is also endorsed by AAAAI and ACAAI along

with Asian societies in 2017. It is rather placed in an “alternative treatment options” section (Zuberbier et al., 2018). Different from AAAAI and ACAAI guideline, the main treatment algorithm of EAACI/GA²LEN/EDF/WAO urticaria management guideline indicates omalizumab and cyclosporine A as the third and fourth line treatment options, respectively, if antihistamines in standard and high doses fail, despite the high cost of omalizumab, and relatively high adverse effect profile as well as the off-label use of cyclosporine A (Zuberbier et al., 2018).

Several studies reported noteworthy response rates in urticaria patients with low dose doxepin therapy within a relatively short period of time (Table 2) (Harto et al., 1985; Goldsobel et al., 1986; Greene et al., 1985; Figueiredo et al., 1990; Bernstein, 1982; Neittaanmäki, Myöhänen, & Fräki, 1984; Neittaanmäki & Fräki, 1988; Neittaanmäki, Jääskeläinen, Harvima, & Fräki, 1989; Ghose & Haldar, 1990; Mukhopadhyay et al., 1995).

In a randomized double-blind crossover trial carried out in patients with idiopathic cold urticaria using doxepin and conventional antihistamines, doxepin was found to be subjectively the most effective treatment option with fewer adverse effects compared to other agents (Neittaanmäki et al., 1984). In a double-blind crossover study on 50 patients with CU comparing the efficacy of doxepin (10mg tid) and diphenhydramine (25 mg tid), complete clearance of urticarial lesions could be achieved in 43% of patients treated with doxepin (Greene et al., 1985). The rate of a partial or total control of lesions was 74% in the doxepin group (Greene et al., 1985). Similarly, doxepin was effective in a majority (75%) of our patients within a short time of onset. Remarkably, 44.4% of these patients showed a “complete response”.

As another important advantage, the antihistamine dose could be lowered in eight patients after the induction of doxepin therapy in the present study. Similarly, in a double-blind placebo-controlled crossover trial for CU treatment, patients receiving doxepin (25mg

tid) were found to require less daily doses of concomitant antihistamines compared to placebo group (Goldsobel et al., 1986).

The blockade of multiple receptors generates multiple side effects in doxepin therapy including blurred vision, dry mouth, constipation, urinary retention due to anticholinergic properties; sedation due to H1 receptor blockade; and postural hypotension and the resultant reflex tachycardia from its anti- α -adrenergic effect (Goldsobel et al., 1986). Therefore, doxepin should be used with special caution in elderly patients and in those with cardiovascular disease including heart failure, conduction disorders and cardiac arrhythmias. In these patients, cardiovascular and ECG monitoring should be undertaken prior to starting treatment, at steady state, after dose increase or starting any potentially interacting medicine (FDA, 2007). However, these severe adverse reactions are mainly observed in patients with psychiatric disorders for which doxepin is prescribed in much higher doses than those for CU. This would explain the lack of significant adverse effects in our study as well as in previous studies in the literature (Table 2) (Harto et al., 1985; Goldsobel et al., 1986; Greene et al., 1985; Figueiredo et al., 1990; Bernstein, 1982; Neittaanmäki et al., 1984; Ghose & Haldar, 1990; Mukhopadhyay et al., 1995). Although sedation and anticholinergic effects were previously reported in several studies on CU, they were generally tolerated well by the patients (Harto et al., 1985; Goldsobel et al., 1986), comparable to our results. Moreover, in two studies, sedation and drowsiness were even more common in patients receiving diphenhydramine (Greene et al., 1985) or pheniramine maleate (Ghose & Haldar, 1990), respectively, when compared to patients receiving doxepin therapy.

Doxepin was also thought to influence urticaria via its central effect in the presence of psychiatric comorbidities (Greene et al., 1985). The response of CU in 8 of 14 patients with psychiatric comorbidities in our case series might also support this hypothesis, even though high dose doxepin was not administered in any of these patients. On the contrary, this

hypothesis was disagreed by some authors due to the well-recognized slow onset action of TCAs on the CNS (Ledo, Harto, & Sendagorta, 1985).

The major limitation of our study was its retrospective design that did not allow to assess the potential adverse effects of doxepin properly. Some of the side effects might be unlikely to be reported by the patients.

In conclusion, doxepin seems to be a reasonable, efficient, and affordable (the monthly cost of doxepin therapy is less than half of the monthly cost of omalizumab therapy in our country) alternative in the treatment of CU in patients poorly responsive to antihistamine therapy. We hope that, similar to US guidelines, this treatment option will also be considered in other international and national urticaria management guidelines prior to the induction of the more expensive or side-effective alternatives.

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Tables

Table 1. Characteristics of patients with chronic urticaria who received doxepin therapy

	Patient's characteristics
Gender	Female (n=23)
	Male (n=13)
Age (years)	Range: 17-75
	Median: 40.5
Accompanying angioedema	Present (n=26, 72.2%)
Concomitant chronic inducible urticaria	Dermographism (n=7, 19.4%)
Histopathology	Classical urticaria (n=7)
Disease duration prior to doxepin therapy (months)	Range: 2-288
	Median: 21
UAS7 before doxepin therapy	Range: 12-40
	Median: 24.5
Previous therapies	Antihistamine (various combinations of H1 ± H2 antihistamines) (n=36)
	Systemic corticosteroid (n=12)
	Colchicine (n=1)
	Cyclosporine A (n=1)
	Omalizumab (n=1)
Accompanying psychiatric disorder	Depression ± anxiety (n=14, 38.9%)

Table 2. Review of the literature (case reports and clinical trials) regarding doxepin therapy in urticaria

Author (year)	Study type	Study design	Evaluation parameters	Number (n), gender and age range of patients	Type of urticaria (n)	Previous treatment	Dose and duration of doxepin therapy	Outcomes	Side effect (n)
Bernstein (1982)	Open trial	Initial dose: 25 mg tid If no response within 1 week, dose increase to 50 mg tid.	CR and PR	11 NM NM	Chronic urticaria (9) Acute urticaria (2)	Ah (11)	75-150 mg/day 2-18 months	CR with high doses in 11 patients (100%)	Mild sedation
Neittaanmäki (1984)	Trial 1 and 2: Double blind, placebo-controlled, crossover trial	Trial 1: Doxepin 10 mg tid, cinnarizine 10 mg tid and placebo were given separately for 2 weeks followed by 1 week off medication.	Trial 1 and 2: Patients' subjective opinion on the effectiveness of the drug	Trial 1: 10 4F/6M 14-42 years	Idiopathic cold urticaria	NM	Trial 1: 30 mg/day 2 weeks	Trial 1: Eight patients considered doxepin as the most effective treatment.	Trial 1: Tiredness (6)
		Trial 2: Doxepin 10 mg tid, cyproheptadine 4 mg tid, hydroxyzine 10 mg tid and placebo were given separately for 2 weeks followed by 1 week off medication.		Trial 2: 12 6F/6M 15-43 years			Trial 2: 30mg/day 1 week	Trial 2: Six patients found doxepin as the most effective treatment. No statistically significant difference among the drugs in the ice cube test.	Trial 2: Tiredness (5) Dry mouth (2) Headache (1)
	Trial 3: Open trial	Trial 3: Doxepin 10 mg tid, cyproheptadine 4 mg tid, hydroxyzine 10 mg tid and placebo were given separately for 1 week followed by 1 week off medication and an ice cube test was performed once a week.	Trial 3: Grading of the wheal response	Trial 3: 10 4F/6M 14-42 years			Trial 3: 75mg/day 2 days	Trial 3: Doxepin suppressed the wheal and itching responses and shortened the wheal response duration.	Trial 3: NM
		Trial 3: Doxepin 75 mg/day Ice cube test to show							

		suppression of the wheal response							
Harto (1985)	Double-blind, placebo-controlled, crossover trial	Doxepin 5 mg bid, mequitazine 5 mg bid and placebo were administered separately for a 2-week period with an interview at the end of each 2-week period.	Mean weekly urticarial scores Patients' subjective opinion regarding the effectiveness of the drug	27 (24 completed the trial) 18F/9M 16-60 years	Chronic urticaria	NM	10mg/day 2 weeks	7 patients found doxepin as the most effective drug, while 9 preferred mequitazine. No significant difference was seen among the drugs in the patients' response analysis.	Drowsiness (6) Dry mouth (3)
Greene (1985)	Double-blind, crossover trial	Doxepin 10 mg tid and diphenhydramine 25 mg tid were given separately for a 2-week period with a 3-day wash-out period with placebo in between.	CR and PR by using daily symptom scores to evaluate itching and hives Patients' subjective opinion on the effectiveness of the drug	50 34F/16M 18-82 years	Chronic urticaria*	Ah (46) Cs (24) Doxepin (6)**	30mg/day 2 weeks	CR was greater with doxepin (43%) compared to diphenhydramine (5%). CR or PR (response rate) was greater with doxepin (74%) compared to diphenhydramine (10%). Patients found doxepin at low doses statistically more effective than diphenhydramine.	Dry mouth (21) Sedation (11) Increased appetite (2)
Goldsobel (1986)	Double-blind, placebo-controlled,	Doxepin 25 mg tid and placebo were given separately for a 4-	Mean total symptom scores	16 14F/2M 22-72	Chronic urticaria	Ah (15) Cs (7)	75 mg/day 4 weeks	Significantly lower symptom scores in	Dry mouth (12) Drowsiness

	crossover trial	week period.		years				doxepin-treated patients.	(12) Constipation (6) Increased appetite and weight gain (4) Dry eyes (1) Blurred vision (1) Fixed drug eruption? (1)
		Patients were administered several antihistamines concomitantly when needed.	Need for concomitant antihistamine use					A 91% decrease in concomitant antihistamine use compared to placebo group.	
		Intradermal histamine and codeine injections were performed to evaluate skin wheal response.	Skin wheal responses					Significant suppression of histamine and codeine-induced wheal responses compared to placebo group.	
Neittaanmäki (1988)	Case report	Doxepin 25 mg bid Heat challenge test 2 hours after the second dose	Suppressive effect of doxepin on heat challenge test reactions in terms of erythema, wheal and itching	2 F: 37 and 40 years	Localized heat urticaria, delayed cold urticaria and dermatographism (1) Localized heat urticaria and idiopathic cold urticaria (1)	NM	50 mg/day 24 hours	Doxepin suppressed the wheal and itching responses at the site of heat challenge test. ***	NM
Neittaanmäki (1989)	Case report	Doxepin started as 25 mg tid during the phototest, and continued as 10 mg tid during the summer time	Minimum time to provoke a wheal reaction in phototest Suppressive effect of doxepin on solar urticaria and dermatographism	1F 28 years	Solar urticaria and dermatographism	Beta-carotene 20 mg canthaxanthine 30 mg	Started as 75mg/day, continued as 30 mg/day during the summer time	Minimum time to provoke a wheal reaction was prolonged. Doxepin successfully suppressed dermatographism and solar urticaria (the patient only experienced erythema on sun-	None

								exposed skin).	
Figueiredo (1990)	Clinical experience from an open trial	Doxepin 25 mg bid was administered for 4 weeks. If no significant response, the dose was increased to 75 mg/day for the following 2 weeks.	Patients' subjective opinion on the effectiveness of the drug CR rate	15 5F/10M 20-70 years	Chronic urticaria	Ah (15) Cs (5)	50-75 mg/day 4-6 weeks	12 patients found doxepin more effective than previous treatments. CR in 6 patients (40%) after 4-6 weeks of therapy.	Drowsiness (3)
Ghose (1990)	Double blind, randomized controlled trial	Two groups of 28 patients were selected randomly to receive doxepin 10 mg tid and pheniramine maleate 22.5 mg tid.	CR and PR rates	28 19F/9M 18-59 years	Chronic urticaria	NM	30mg/day 3 weeks	CR was achieved in 8 doxepin receiving patients (28.6%); it was found more effective than pheniramine maleate (CR in 3 patients, 10.7%). PR was achieved in 18 patients (64.3%) in doxepin group; it was found more effective than pheniramine maleate (PR in 11 patients, 39.3%).	Dry mouth (18) Drowsiness (10)
Mukhopadhyay (1995)	Randomized, comparative trial	Several regimens consisting of chlorpheniramine maleate 4 mg tid alone (Regimen I) or in combination with ranitidine 150 mg bid (Regimen II), cyproheptadine 4 mg bid (Regimen III), doxepin 25 mg tid	Response rates graded as good response (corresponding to CR), fair response (corresponding to PR), poor response. "Good" and "fair"	26 NM NM	NM	NM	75mg/day 4 weeks	The most satisfactory response was observed in regimen IV in 23 patients (88.5%). CR in 16 (61.5%), PR in 7 (26.9%) patients.	Drowsiness (9) Constipation (4) Dry mouth (2) Blurred vision (1)

		(Regimen IV), and levamisole 150 mg/day (3 consecutive days every week) (Regimen V) were given randomly to 127 urticaria patients.	responses were designated as “satisfactory” response.						
Present study (2019)	Retrospective	Data of patients, who had a poor response to antihistamines, and received doxepin therapy, were analysed.	CR and PR rates	36 23F/13M 17-75 years	Chronic urticaria (29) Chronic urticaria + dermographism (7)	Ah (36) Cs (12) Colchicine (1) Cy A (1) Omalizumab (1)	20-75 mg/day 2-156 weeks	CR in 16 patients (44.4%) PR in 11 patients (30.6%)	Mild sedation Dry mouth (2) Blurred vision (1)

tid: three times a day, CR: complete response, PR: partial response, NM: not mentioned, Ah: antihistamine, F: female, M: male, bid: twice a day, Cs: systemic corticosteroid for acute exacerbations, Cy A: cyclosporine A.

*Three patients showed leucocytoclastic vasculitis in the histopathology.

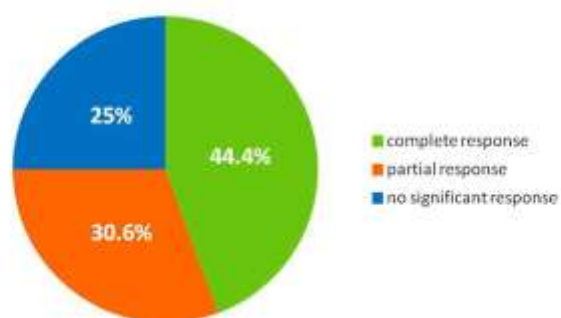
** These patients admitted to poor compliance with previous doxepin therapy.

*** One patient continued to use doxepin 10 mg tid after the study was finished and the symptoms of heat urticaria and dermographism resolved during the doxepin treatment, whereas there was no change in her delayed cold urticaria.

Legends for Figures

Figure 1. Response rate of patients (in %) to doxepin therapy

Figure 2. The need for additional use of antihistamines among doxepin responsive patients

Figure 1.**Figure 2.**