

# Vasomotor rhinitis and rhinorrhea: a possible role for the anticholinergic effect of amitriptyline

*Rinite vasomotora e rinorreia: um possível papel para o efeito anticolinérgico da amitriptilina*

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## ABSTRACT

**Background:** Vasomotor rhinitis (VMR), also referred to as idiopathic rhinitis, is a type of nonallergic rhinitis. It can often be triggered by changes in temperature, especially with cold air and other airway irritants. Immunoglobulin E (IgE) levels and nasal cytograms are normal, and inhalant skin tests are negative. The etiology may be associated with dysregulation of the sympathetic and parasympathetic nervous systems in the nasal mucosa, with increased rhinorrhea and nasal obstruction. **Objective:** To evaluate the efficacy of amitriptyline in the control of VMR-related rhinorrhea. **Method:** We retrospectively evaluated 110 patients with VMR, of whom 12 (11%) had profuse rhinorrhea for more than 1 year, not completely controlled with nasal corticosteroids. In these 12 patients, rhinorrhea was treated with amitriptyline, a tricyclic antidepressant with intense anticholinergic activity, at a daily dose of 25 mg/50 mg. **Results:** Patients were evaluated using a symptom scale (modified from Wilson AM): 0 = absent; 1 = mild, well tolerated; 2 = discomfort interfering with concentration; and 3 = severe intensity interfering with sleep and concentration. Ten patients had grade 3 symptoms, and 2 had grade 2 symptoms. The score decreased to grade 0-1 after 4-6 weeks of amitriptyline use for reflex symptoms in the morning and at night. **Conclusion:** Further controlled studies with a larger sample size are needed to confirm the pharmacological effect of amitriptyline on VMR-related rhinorrhea.

**Keywords:** Vasomotor rhinitis, amitriptyline, rhinorrhea.

## RESUMO

**Introdução:** A rinite vasomotora (RVM), também denominada idiopática, é um tipo de rinite não alérgica. Pode ser muitas vezes ativada por mudanças de temperatura, especialmente com o ar frio e outras irritantes de vias aéreas. A dosagem de IgE e o citograma nasal são normais, e os testes de inalantes são negativos. A etiologia pode estar associada à desregulação de nervos simpáticos e parassimpáticos da mucosa nasal, onde aumenta a rinorreia e a obstrução nasal. **Objetivo:** Avaliar a eficácia da amitriptilina no controle da rinorreia vasomotora. **Método:** Através de estudo retrospectivo, avaliaram-se pacientes com RVM (n = 110), no qual um grupo de n = 12 (11%) apresentava rinorreia profusa há mais de um ano, não controlada, na sua totalidade, com corticosteroide nasal. Usou-se a amitriptilina, um antidepressivo tricíclico, com intensa atividade anticolinérgica com dose de 25 mg/50 mg diária para a rinorreia nesses pacientes. **Resultados:** Foram avaliados através de uma escala de sintomas (modificada de Wilson AM): 0 = ausente, 1 = leve, bem tolerado, 2 = desconforto interferindo com a concentração, 3 = forte intensidade interferindo no sono e na concentração. Dez pacientes catalogados apresentaram sintomas no grau 3, e dois, no grau 2. A pontuação foi reduzida para grau 0-1 após 4-6 semanas com o uso de amitriptilina por sintomas reflexivos matinais e noturnos. **Conclusão:** Futuros estudos controlados e com maior número de pacientes seriam necessários para confirmação do efeito farmacológico da amitriptilina na rinorreia da RVM.

**Descritores:** Rinite vasomotora, amitriptilina, rinorreia.

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## Introduction

Vasomotor rhinitis (VMR) is a type of nonallergic rhinitis that may be acute or chronic. It can often be triggered by changes in temperature and humidity, especially cold dry air, airway irritants, strong odors including tobacco smoke, and exercise.<sup>1</sup>

VMR is often a diagnosis of exclusion and commonly referred to as idiopathic rhinitis.<sup>1,2</sup> This denomination seems to be more appropriate than VMR because of the nonspecific triggers and the yet not fully elucidated mechanism. Family history of allergy and allergen-specific immunoglobulin E (IgE) testing are negative. Total serum IgE levels and nasal cytograms are normal, with few or no eosinophils.<sup>2</sup>

Although the etiology of VMR is not well understood, it is believed to be associated with dysregulation of the sympathetic, parasympathetic, and nociceptive nerves present in the nasal mucosa. The parasympathetic nervous system plays an important role in the response to external stimuli. The imbalance between mediators results in increased vascular permeability and mucus secretion from the submucosal glands.<sup>3</sup> Acetylcholine is the primary parasympathetic neurotransmitter that regulates mucus secretion and rhinorrhea.

The acronym VMR has been proposed by some authors and is currently used in clinical practice; therefore, VMR is used in this text rather than idiopathic rhinitis. Although the latter term is recommended by the IV Brazilian Consensus on rhinitis (2017), it is not universally accepted, since high levels of eosinophils and mast cells may be present, so the term VMR continues to be used.<sup>4</sup>

VMR accounts for approximately 71% of cases of nonallergic rhinitis. A worldwide prevalence of more than 200 million people is estimated, despite the weakness of epidemiological studies.<sup>5</sup>

VMR has an onset in adulthood, usually between 30 and 60 years of age. It is more common in women (58%-71%) and can last a lifetime.<sup>5-7</sup>

Profuse rhinorrhea may alter the patient's quality of life both physically and psychosocially if not properly treated. VMR symptoms may vary, consisting mainly of nasal obstruction and increased clear secretion, postnasal drip, and intermittent rhinorrhea. There are 2 subtypes, one with predominant nasal obstruction, and the other with predominant profuse rhinorrhea.<sup>2</sup> Sneezing and pruritus are less common, whereas cough may appear as an important component of VMR.<sup>2,4</sup>

Climate changes, including cold air, can trigger VMR. In Brazil, VMR has been mostly observed and is possibly more prevalent in the South region due to a low-temperature harsh winter season, followed by a spring season with a prolonged period of cold mornings and nights.

Treatment should be based on symptoms. The combination of a topical corticosteroid and an H1 antihistamine, such as azelastine nasal spray, may be used in patients with predominant rhinorrhea/nasal obstruction, whereas ipratropium bromide (IB), an anticholinergic agent, is recommended for those with predominant rhinorrhea.<sup>8</sup>

Amitriptyline is a medication approved for the treatment of depression in adults. It is a tricyclic antidepressant, with a high affinity for alpha-adrenergic receptor binding to histamine H1 and muscarinic (M1 subtype) receptors. It has a half-life of 10-28 hours and is metabolized into nortriptyline.<sup>9</sup> Its anticholinergic effects include blurred vision, dry mouth, tachycardia, angle-closure glaucoma, and urinary retention. The latter effect may be beneficial to treat patients with enuresis, as listed on the package insert. The pharmacological activity of amitriptyline might support its off-label use in the treatment of poorly controlled rhinorrhea.

The primary objective of this study was to retrospectively identify and analyze the use of amitriptyline in patients unresponsive to nasal corticosteroids for VMR-associated rhinorrhea.

## Anticholinergic drugs for nonallergic rhinitis

Anticholinergic drugs inhibit the binding of acetylcholine to muscarinic receptors and can be used topically or systemically.<sup>4</sup> The parasympathetic nervous system contributes to the pathophysiology of multiple forms of rhinitis, and its stimulation leads to activation of the gland that produces watery nasal secretion, which translates into anterior and posterior rhinorrhea.<sup>1</sup>

It has been shown that the transient receptor potential vanilloid 1 (TRPV1)-substance P (SP) nociceptive signaling pathway (cation channel subfamily) is upregulated in patients with idiopathic rhinitis and reduced after treatment with intranasal capsaicin.<sup>10</sup>

Based on its anticholinergic activity, IB nasal spray has been approved for the treatment of rhinorrhea in

allergic and nonallergic rhinitis.<sup>11,12</sup> In Brazil, it has been off the market for several years.

Azelastine hydrochloride nasal spray 0.1% is a second-generation antihistamine with pharmacological effects on inflammatory mediators. It improves both allergic rhinitis and VMR symptoms.<sup>4</sup> When combined with fluticasone nasal spray, it provides greater symptom relief.<sup>13</sup>

First-generation oral antihistamines are poorly selective for H1 receptors and can cause anticholinergic effects by inhibiting muscarinic receptors, which could be useful in VMR. However, because they cross the blood-brain barrier, sedation may occur, affecting daily activities and interfering with quality of life.<sup>14</sup>

Amitriptyline may be a promising candidate for potential control of VMR-associated watery rhinorrhea.

## Patients and methods

We retrospectively reviewed the clinical records of 110 patients with a diagnosis of VMR made from 2003 to 2021 at an Allergy and Immunology Clinic in Caxias do Sul, southern Brazil. The diagnosis was based on characteristic clinical features and anterior rhinoscopy (examination of the mucosa, septum, and nasal turbinates), combined with skin prick tests for aeroallergens when the results were negative. The allergens included in the test panel were *Dermatophagoide*s *pteronysinus*, *Dermatophagoide*s *farinae*, *Blomia tropicalis*, dog and cat epithelium, *Penicillium*, *Cladosporium*, *Lolium pollen*, and grass mix, using saline and histamine as negative and positive controls, respectively (10 mg/mL).

We included 12 patients (7 men) with VMR, assessed for the first time, from various clinics, with symptoms for more than 1 year. Mean patient age was 54 years, ranging from 26 to 80 years. The most common symptom was intermittent profuse rhinorrhea, not completely controlled with daily use of nasal corticosteroids for months.

Patients were evaluated with a modified 4-point symptom scale for rhinorrhea, with scores as follows: 0 = no rhinorrhea; 1 = mild, well tolerated not interfering with sleep or daily activities; 2 = discomfort interfering with concentration; and 3 = severe intensity interfering with sleep and daily activities.<sup>14</sup> Ten patients had grade 3 symptoms, and 2 had grade 2 symptoms. Nasal obstruction was rated as absent or mild (grade 0-1) by 11 patients (92%).

Amitriptyline (25-50 mg/day) was administered at night. We excluded risk factors such as patients with a history of seizures, impaired liver function, urinary retention, narrow-angle glaucoma or increased intraocular pressure, and cardiovascular disorders.

Amitriptyline was administered for 4-6 weeks and then at face-to-face medical visits for 8 consecutive weeks. Patients received information about the drug, including the most common side effects, such as dry mouth, reduced saliva production, and potential sedation. After being fully informed of the effects of the drug, they consented to the use of amitriptyline to try to control their “persistent bothersome rhinorrhea,” since this is an off-label indication.

## Results

All 12 patients had symptoms of profuse watery rhinorrhea, rated as grade 3 by 10 patients and as grade 2 by 2 patients.

After 4-6 weeks of amitriptyline 25-50 mg/day, both watery rhinorrhea and postnasal drip reduced significantly. The symptom score decreased to grade 0-1 according to morning and evening reflective symptoms.<sup>6</sup>

Two patients were excluded from the study due to adverse effects: one had constipation, and the other developed tachycardia and arrhythmia.

Mild daytime sleepiness was reported by patients receiving a dose of 50 mg/day, which was tapered over subsequent weeks with early evening administration.

The results are shown in Table 1.

## Discussion

Intranasal corticosteroids are effective in treating several forms of nonallergic rhinitis, including eosinophilic nonallergic rhinitis.<sup>4</sup> The fact that all patients had previously used nasal corticosteroids ruled out the diagnosis of eosinophilic nonallergic rhinitis, which could be a selection bias. Treatment with fluticasone furoate has not been effective in alleviating the symptoms of patients with allergic rhinitis due to temperature changes/cold, and it has been suggested that a distinct group of patients with VMR may be refractory to corticosteroids.<sup>15</sup> This is consistent with the subgroup included in the present study, in which 11% of a total of 110 patients with VMR had profuse

**Table 1**

Rhinorrhea in vasomotor rhinitis. Assessment with amitriptyline administration (mg/day)

Patient	Age	Sex	Pre-treatment symptoms Rhinorrhea	Amitriptyline dose (mg/day) Rhinorrhea	Post-treatment symptoms Adverse	Patients excluded due to adverse effects
1	45	F	3	25	1	–
2	33	M	3	25	0	–
3	58	M	3	25	0	*
4	61	F	3	50	1	–
5	55	F	2	25	0	–
6	56	M	3	25	0	–
7	26	F	2	25	0	–
8	42	M	3	25	0	–
9	67	M	3	50	0	–
10	63	F	3	25	0	–
11	80	M	3	50	0	–
12	67	M	3	25	0	**

**Symptom score:**

0 = None.

1 = Mild, well tolerated not interfering with sleep or daily activities.

2 = Discomfort interfering with concentration.

3 = Severe intensity interfering with sleep and daily activities.

Legend: – not detected, \* constipation, \*\* tachycardia/arrhythmia.

Modified from Wilson AM et al.<sup>15</sup>

rhinorrhea that was not completely controlled with nasal corticosteroids for months.

During the study period, no anticholinergic drug such as IB nasal spray was available in Brazil. The same occurred intermittently with azelastine nasal spray, which can be used in VMR. First-generation antihistamines with anticholinergic properties were available, but they were not indicated due to their side effects, such as daytime sedation.

We were able to evaluate the use of a potent anticholinergic drug such as amitriptyline for rhinorrhea, in line with its indication for nocturnal enuresis as listed on the package insert.<sup>9</sup>

A characteristic shared by our patients was that they had no or minimal nasal obstruction according to the symptom scale (grade 0-1).

**Conclusion**

Limitations of this study include those inherent in a retrospective data analysis and the small sample size, obtained from a subgroup of patients unresponsive to nasal corticosteroids for the management of rhinorrhea. Also, psychosocial assessment was not performed and anxiety or depression scales were not used. Amitriptyline may influence the reflective symptom scores due to its pharmacological effect on these conditions. Amitriptyline should be considered an option as it is a low-cost, accessible medication provided through the Brazilian public health system without patient charges.

Further controlled studies with a larger sample size are required to better evaluate the use of amitriptyline in VMR, especially in patients with predominant rhinorrhea.

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