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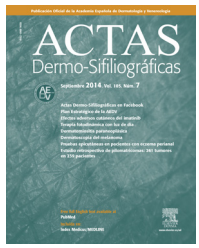

NOVELTIES IN DERMATOLOGY

Systemic Treatment of Hyperhidrosis☆

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KEYWORDS
Hyperhidrosis;
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Abstract Until quite recently, clinical guidelines and reviews on the treatment of hyperhidrosis advised against the use of systemic therapies based on their unacceptable adverse effects and a lack of evidence of usefulness. Numerous studies published over the past few years, however, have shown that, when used appropriately, these treatments are effective and in general have a favorable tolerability profile, making them an additional option for the treatment of hyperhidrosis, particularly for disease that is widespread, multifocal, or resistant to other treatments. In this review, the first of its kind, we examine the systemic therapies available for hyperhidrosis, including antihypertensives, psychoactive agents, and in particular oral anticholinergics, although none of these drugs are currently approved for this indication.

PALABRAS CLAVE
Hiperhidrosis;
Oxibutinina;
Glicopirrolato

Tratamiento sistémico de la hiperhidrosis

Resumen Hasta hace pocos años las guías clínicas y revisiones sobre tratamientos de la hiperhidrosis consideraban que no existía evidencia de la utilidad de los tratamientos sistémicos, y que se asociaban a un perfil intolerable de efectos adversos, siendo desaconsejados. Sin embargo, en los últimos años diferentes estudios han ido mostrando la eficacia de los mismos, asociándose a un perfil de efectos adversos por lo general aceptable cuando se usan de forma apropiada, convirtiéndose en una alternativa terapéutica más en el tratamiento de la hiperhidrosis, de especial relevancia en casos de hiperhidrosis generalizada, multifocal o resistente a otros tratamientos. Mediante esta revisión, la primera centrada en este tema, se repasarán los diferentes tratamientos sistémicos actualmente disponibles para la hiperhidrosis, incluyendo antihipertensivos, psicofármacos y, fundamentalmente, los anticolinérgicos orales, aunque ninguno tiene indicación aprobada en el tratamiento de la hiperhidrosis.

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Introduction

Hyperhidrosis, which refers to the excessive production of sweat, i.e., the production of more sweat than the body needs, affects an estimated 3% of the general population.[1]

A brief overview of the mechanisms involved in the production of sweat is provided to aid understanding of the various treatments available for hyperhidrosis. Sweat glands are activated by the sympathetic nervous system. The signals are transmitted from the ''thermoregulation center'' in the hypothalamus to the sweat glands through preganglionic and postganglioinic sympathetic nerves. Acetylcholine is a key neurotransmitter in these synapses, as it stimulates the nicotinic receptors located between the preganglionic and postganglionic fibers at the synapses and the muscarinic receptors (primarily muscarinic M3) in the sweat glands.[1]

Multiple treatments exist for hiperhidrosis, including topical antiperspirants (mainly aluminum salt solutions), topical anticholinergics (mainly glycopyrrolate), botulinum toxin, iontophoresis, sympathectomy, and ablative surgical techniques targeting the sweat gland tissue.[1–7] There is, however, no consensus on what treatment strategies should be applied in the different types of hyperhidrosis. Whatever the case, individual treatment should be guided by the area of the body affected, the intensity of sweating and its impact on the patient's quality of life, response to previous treatments (effectiveness and tolerance), personal history (e.g., other diseases, age, regular medication), and of course, the cost and availability of treatments. It is generally advisable to start with the least aggressive and the least expensive options.

Despite the range of treatments available, however, optimal control of sweating is frequently not achieved due to poor response or tolerance, fear of adverse effects or complications, or simply the lack of availability or cost of certain treatments.

In this article, we focus on systemic rather than topical treatment of hyperhidrosis. Systemic treatments target the muscarinic receptors of sweat glands throughout the body, and there is therefore no risk of compensatory hyperhidrosis. These treatments tend to be cheap and associated with good patient adherence. Table 1 provides a summary of the systemic treatments available for hyperhidrosis, together with the corresponding levels of evidence based on the criteria in Table 2.[8]

Systemic therapies targeting the cause. Systemic treatments that target the cause of excessive sweating are used to treat cases of secondary hyperhidrosis. An example would be hormone replacement therapy in the case of postmenopausal hyperhidrosis,[2] but it should be noted that this option is not free of adverse effects.

We will focus on treatments that act on the mechanisms of sweat production, as most patients have primary rather than secondary hyperhidrosis. Signed informed consent must be obtained for each of the treatments described below, as they are not approved for use in hyperhidrosis.

Antihipertensives. The most widely used antihypertensives in hyperhidrosis are clonidine, diltiazem, and propranolol.

Clonidine is an α-adrenergic agonist that reduces sympathetic tone and increases the drive of the parasympathetic nervous system. It has been used in hyperhidrosis since 1984, even though its usefulness in this condition is supported by isolated experiences.[9–13] In a recent study of 13 patients treated with clonidine, there were 6 responders and 7 treatment failures, including 3 nonresponders and 4 patients who developed hypotension,[14] which is an adverse effect that needs to be considered with this drug. According to some authors, clonidine might be most useful in the treatment of craniofacial hyperhidrosis in postmenopausal women or women with flushing,[13,14] although there have been isolated reports of clonidine patches being successfully used to treat gustatory facial sweating.[11]

Diltiazem is a calcium channel blocker approved for the treatment of mostly mild to moderate hypertension and certain arrhythmias; it is also used in the treatment and prevention of ischemic heart disease. There have been anectodal reports of good results in patients with hyperhidrosis treated with doses of between 30 and 60 mg of diltiazem administered 4 times a day.[15] The effect of this drug in hyperhidrosis has been attributed to the important role of calcium in the stimulation of sweat secretion.

Propranolol has been widely used in dermatology for some years now following demonstration of its value in the treatment of infantile hemangiomas.[16] It is a β-blocker indicated for the treatment of hypertension, ischemic heart disease, and tachycardia. Its usefulness in hyperhidrosis is probably linked to its anxiolytic effect.[1]

Psychoactive drugs. Psychoactive drugs include antidepressants, antipsychotics, and anticonvulsants. Their use in hyperhidrosis is somewhat paradoxical considering that one of their possible adverse effects is excessive sweating. Their effectiveness in this condition might be due to the fact that they cause a certain indifference among patients to emotional triggers that frequently lead to sweating,[1] but their anticholinergic and noradrenergic functions also probably have a role.[17–19]

The selective serotonin reuptake inhibitor paroxetine is used at a dose of 10 to 20 mg/d.[20,21]

Of note in the group of benzodiazepines used to treat hypertrichosis is the antiepileptic drug clonazepam.[22]

Quetiapine[17] and topiramate[18,19] have also been reported to be effective in patients with hyperhidrosis.

Oral anticholinergics. Oral anticholinergics are the most widely used group of drugs in the systemic treatment of hyperhidrosis and as such will be discussed in more detail. They inhibit sympathetic activation by competing for acetylcholine receptors on sweat glands.

Their most common adverse effects occur in the gastrointestinal tract (mainly dry mouth and throat, although they can also cause constipation and even paralytic ileus), the eyes (mydriasis and cycloplegia, possibly leading to narrow-angle glaucoma), and the genitourinary tract (urinary frequency and even acute urinary retention). Central nervous system adverse effects (sleepiness, nervousness, headache, nausea, asthenia etc.) are relatively uncommon, as are cardiovascular effects such as tachycardia and palpitations.

Before prescribing an anticholinergic, thus, it is essential to obtain an accurate medical history, including personal history and current medications, and to inform patients of possible adverse effects. These drugs are absolutely or relatively contraindicated in individuals with urinary retention or with risk factors for this condition (e.g., patients with