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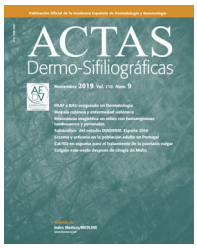

CONTROVERSIES IN DERMATOLOGY

[Translated article] Hyperhidrosis, Anticholinergics, and Dementia

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Abstract In recent decades, the use of certain oral anticholinergics for the treatment of hyperhidrosis has become widespread, often off-label but supported by multiple studies, including clinical trials, demonstrating their effectiveness and an apparently good safety profile. Similarly, various studies published in recent years have associated the use of anticholinergics to the development of dementia, particularly in elderly patients. Additionally, other studies have suggested that hyperhidrosis itself may be an early symptom of developing dementia. However, to date, no research has specifically linked the use of oral anticholinergics for hyperhidrosis treatment with the development of dementia. We present the currently available data on this controversial topic.

PALABRAS CLAVE
Hiperhidrosis;
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Oxibutinina

Hiperhidrosis, anticolinérgicos y demencia

Resumen En las últimas décadas se ha extendido el uso de algunos anticolinérgicos orales en el tratamiento de la hiperhidrosis, con uso fuera de ficha técnica, aunque respaldado por múltiples estudios, incluyendo ensayos clínicos, que mostraron su efectividad y su aparente buen perfil de seguridad. De igual forma, se han publicado en los últimos años diferentes trabajos que relacionan el uso de anticolinérgicos con el desarrollo de demencia, especialmente en pacientes de edad avanzada, y otros que han relacionado la propia aparición de hiperhidrosis como síntoma incipiente *per se* de desarrollo de demencia. Hasta el momento no se ha publicado ningún

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trabajo que relacione el uso de anticolinérgicos orales en el tratamiento de la hiperhidrosis y el desarrollo de demencia. En este trabajo procuramos exponer los datos con los que contamos en la actualidad respecto a este controvertido tema.

Introduction

Acetylcholine is the key neurotransmitter in cholinergic pathways, playing both stimulating and inhibitory roles in the central nervous system (CNS), autonomic nervous system (ANS), and somatic system. In the CNS, it's crucial for memory, learning, arousal, and motor control.[1–3] Therefore, there are theoretical reasons to believe that drugs with an anticholinergic effect (ACE) could promote the development of dementia, and that one way to reduce the number of people who will develop dementia would be to avoid (or at least decrease) their prescription.[1,2,4,5]

Furthermore, cumulative exposure to anticholinergics (especially in older individuals taking ACE drugs for various disorders) seems to be underestimated. The concept of ''anticholinergic burden (ACB),'' also known as ''antimuscarinic burden'',[1,4,6] is highly significant. ACB can be defined as the cumulative effect of taking one or more drugs capable of producing anticholinergic adverse effects.

Two factors influence the overall burden: the anticholinergic potency of each drug and the dose used. In recent years, various scales and indices have been developed to measure this ACB, though homogeneous criteria for doing so are lacking,[1,2,4,6,7] which explains the variability in its measurement across different studies. Most meta-analyses and clinical trials use the ACB scale.[1,2] Tools such as the anticholinergic burden calculator[6] also exist, enabling the simultaneous calculation of 9 anticholinergic scales. The risks associated with this ACB would increase with the patient's age and frailty, although there's considerable inter-individual variability in response to different ACE drugs, as well as in the anticholinergic dose and how related symptoms and signs manifest.

Anticholinergics and dementia

Different factors play a role in the adverse effects that ACE drugs might cause in the CNS, including their affinity for M1 muscarinic receptors in the brain, which primarily mediate memory and cognition,[3,4] and their potential ability to cross the blood-brain barrier (BBB). Generally, drugs only cross the BBB if they are lipophilic,[3] and several ACE drugs used for treating overactive bladder, such as oxybutynin (also the most common ACE drug for hyperhidrosis), are lipophilic.[3,4] Moreover, ACE drugs would counteract acetylcholinesterase inhibitors used in dementia, thereby reducing their efficacy.[6]

The most common ''central'' anticholinergic adverse effects include cognitive disorders, confusion, disorientation, agitation, hallucinations, delirium, falls, attention deficit, concentration problems, and memory disorders.[4,6,8]

Of note, ACE drugs are frequently used in clinical practice to manage multiple disorders that particularly affect older individuals.[1] These drugs are prescribed for common problems such as urinary incontinence or overactive bladder, allergic rhinitis, pruritus, insomnia, depression, epilepsy, Parkinson's disease, psychotic symptoms,[2,4,6] and so on.

For some of these drugs, the anticholinergic effects are precisely their mechanism of action for achieving their therapeutic effect (e.g., oxybutynin). For others, however, anticholinergic effects are incidental side effects relative to their primary mechanism of action, as seen with antidepressants such as amitriptyline, some opioids, or antihistamines like hydroxyzine, often used to treat pruritus.[1,6]

Some adverse effects of ACE drugs appear in the short term, such as dry mouth or constipation, while others have an insidious and irreversible onset. Long-term adverse effects that various studies and systematic reviews have associated with ACB include an increased risk of physical function deterioration, increased risk of falls and mortality, and a possible contribution to the development of cognitive impairment and dementia.[1,6,8,9]

However, there is significant individual variability in the impact of ACB on health. This is not surprising concerning cognitive decline, where an individual's response is likely influenced by multiple factors, such as how easily the specific drug crosses the BBB, certain comorbidities, or even the patient's socioeconomic status.[1,6]

A recent systematic review[2] tried to determine whether ACB, as defined by various recognized scales, is a prognostic factor for future cognitive decline or for the development of dementia in older adults without previous cognitive impairment. Twenty-five studies were reviewed, with 968,428 participants and a mean age range of 52–83 years. The meta-analysis found a consistent direct relationship between ACE drug use and the risk of future dementia. However, the authors also concluded that it was not possible to establish if these drugs play a causal role. If they did, they estimated it could double the risk of an exposed person developing dementia (vs an unexposed person), with a greater ACB correlating to a greater risk. Nevertheless, the authors themselves acknowledge that these claims are limited by the low quality of the scientific evidence identified. For instance, in 23 of the 25 studies, the duration and exposure to ACE drugs and adherence to treatment were not determined, making it difficult to assess the impact of ACB. In real-world situations, it's estimated that only 30% of drugs are taken as prescribed.[10] Similarly, psychiatric history was not collected in almost half of the studies, which could be a confounding factor (e.g., depression can be an early symptom of dementia and increase the estimated ACB due to antidepressants used to treat it).[1,2,6] All

data were obtained through observational studies, making it impossible to exclude selection biases between groups. Furthermore, the reporting of adverse effects in these studies and the method of measuring possible cognitive impairment varied, complicating the meta-analysis of the data. Additionally, most studies were short-term, with follow-up ranging from a few weeks to 5 years, and typically include younger patients with fewer comorbidities and a lower risk of developing drug-induced adverse effects. This makes demonstrating a definitive causal relationship between the drug and adverse effects challenging, especially in the context of a ''geriatric syndrome'' with falls or delirium, which has an insidious onset after years of drug exposure.[1,2]

Another systematic review and meta-analysis[5] reviewed 14 longitudinal and case-control studies with more than 1.5 million patients. The authors concluded that there was an increased risk for dementia development with ACE drug use, both at high and low ACB levels, and found a dose-dependent relationship between ACE drugs and dementia risk.

Meanwhile, a different research[11] focused on potential biases in these studies. It emphasized that in observational studies examining the relationship between drug exposure and an adverse outcome, the outcome might not be due to exposure per se, but rather to the indication for which the drug was prescribed. Protopathic bias ('before the disease' in Greek) refers to situations where, although exposure precedes the outcome, this exposure occurred precisely because of that impending outcome. For example, older patients with depressive symptoms (which might be a sign of incipient, subclinical dementia) who take antidepressants for those symptoms. A longitudinal study of such patients might show that older patients who took antidepressants are at higher risk of developing dementia than those who did not.

It is also notable that an association has been found between the development of dementia in patient groups with very low total ACE drug doses, used for short periods, and independently of the ACE drug's potency: finding a mechanism of action to explain this effect is difficult.[11]

Some studies linked these cognitive symptoms only to certain groups of ACE drugs, such as antiepileptics, loop diuretics, or antidepressants,[7] but not to others, such as antipsychotics and urological drugs; while in others,[12] the increased risk of dementia was found only for antidepressants, antipsychotics, and bladder antimuscarinics. One systematic review and meta-analysis found an increased risk of dementia only for antiparkinsonian, urological, and antidepressant drugs.[5]

On the other hand,[11] these increases in the relative risks of developing dementia were greater for the development of vascular dementia than for the development of Alzheimer's, which would contradict studies that hypothesized that ACE drugs would cause brain inflammation and amyloid deposition, in addition to changes that would favor the development of Alzheimer's.[11] In fact, a study that reviewed autopsies found no relationship between the use of ACE drugs in the 10 years *pre mortem* and the development of atherosclerosis or cerebral microinfarcts.[13]

The inconsistencies found in the literature, with no clear relationship among dose, potency, or duration of ACE drug use and their response, the variation in the relationship depending on the ACE drug group, and the difficulty of ruling out confounding by indication, the lack of symptom improvement after ACB reduction... have led many authors to point out that another factor independent of the anticholinergic effect could be the cause of this association between ACE drugs and dementia.[7,11]

Another recent systematic review[14] with 299 participants corresponding to a cognitively mixed population (some healthy, others with dementia) found no evidence (after a maximum of 3 months) that ACB reduction measures in older adults improved cognitive parameters. Nor is there evidence that ACB reduction improves other parameters such as mortality, quality of life, physical function, need for hospitalization, falls, cardiovascular diseases, or neurobehavioral traits.

In short, reviews of the available evidence do not allow demonstrating the hypothesis of an anticholinergic mechanism as the cause of dementia development, although the data do indicate that exposure to (some groups of) ACE drugs could represent a marker for dementia development, without a causal mechanism being able to be explained,[5,11] and conclude by indicating that, if they are indeed a causal factor, it would represent an important modifiable risk factor, although so far the reduction of this ACB has not demonstrated symptom improvement.[11,14]

In any case, although evidence on the causal relationship is not conclusive, caution is recommended when prescribing ACE drugs to older patients, as they are considered potentially inappropriate drugs in this population, according to the Beers criteria.[4] Various risk situations (dementia, chronic constipation, etc.), as well as the concomitant use of >2 ACE drugs,[15] would be ''STOPP criteria'' (recommending avoiding their use).

Anticholinergics in the treatment of hyperhidrosis

The adverse effects of ACE drugs on the peripheral nervous system are related to decreased muscle contraction and glandular secretion: dry mouth, eyes, and skin, decreased salivary secretion, altered thermoregulation, constipation, decreased peristalsis, problems with visual accommodation, pupillary dilation, urinary retention, tachycardia or erectile dysfunction, and they also cause a decrease in sweating (which is why they are used in hyperhidrosis).[4,6]

Although there is no oral ACE drug approved for the treatment of hyperhidrosis, the most widely used for this purpose (off-label) is oxybutynin,[16] whose indication approved by the FDA (in 1975) is the treatment of urinary incontinence or neurogenic bladder.[3] It is the most widely used ACE drug in the world for the treatment of overactive bladder, probably due to its low cost.[3] This and other ACE drugs reduce urinary frequency and urgency by blocking M3 receptors in the detrusor muscle, although muscarinic receptors are widely present in other organs and systems.[3] Oxybutynin can potentially inhibit all 5 existing muscarinic receptors, thus increasing the possibility of adverse effects at different levels.[3]

Its usefulness in the treatment of hyperhidrosis was described in 1988,[16] although since then there have been > 50 publications on the matter (including placebo-controlled

clinical trials and systematic reviews) that do not report serious adverse effects.[17]

A recent systematic review on the use of ACE drugs in overactive bladder[4] noted cognitive impairment among patients with or without baseline cognitive impairment who used oxybutynin (in 5 of 8 reviewed studies), although 7 of the 8 studies included patients with baseline cognitive impairment. In addition, the use of oxybutynin was associated with functional, mental, and behavioral deterioration in patients with Alzheimer's.[4] In contrast, no cognitive impairment was observed among patients taking other ACE drugs, such as trospium and darifenacin,[4] apparently due to their different pharmacokinetics (darifenacin has higher affinity for M3 receptors than for M1, and trospium is hydrophilic, which hinders its passage to the CNS).

Other studies[18,19] compared the use of ACE drugs with beta-3 agonists (mirabegron) in the treatment of overactive bladder, attempting to eliminate the possible protopathic risk (considering that urinary incontinence per se could constitute a symptom of incipient dementia) and found a slight increase in the risk of developing dementia (HR, 1.23; $p < 0.01$) in those on ACE drugs vs those on mirabegron[19]; although, in another,[18] an even greater risk of developing dementia was observed if ACE drugs and beta-3 agonists were combined, even postulating a possible association between beta-3 agonists and dementia.

Other oral ACE drugs have also shown their usefulness in the treatment of hyperhidrosis, notably glycopyrrolate (glycopyrronium). With an approved indication for the treatment of peptic ulcers, its chemical composition makes it very poorly lipophilic, which hinders its passage to the CNS, although its use is less widespread due to its much higher price and lower availability (currently in Spain it can be obtained as foreign drug or as a magistral formula).[16] In recent years, several topical ACE drugs have been approved for the treatment of hyperhidrosis, whose systemic absorption is much lower than that of the oral form.[20] In Spain, currently the only one approved (for severe axillary hyperhidrosis in adults) is glycopyrronium bromide cream.[21]

Hyperhidrosis and dementia

The etiopathogenesis of hyperhidrosis lies in a complex alteration of the autonomic nervous system, resulting in hyperactivity of the eccrine sweat glands. Recent studies revealed a reciprocal effect between autonomic nervous system alterations and dementia.[22] A population study conducted in China, with 5958 participants older than 65 years, without institutionalized patients or those with other mental disorders, found a dementia prevalence of 10.17% among participants, with Lewy body dementia prevalence of 1.41% and hyperhidrosis prevalence of 14.97%. It was estimated that participants with hyperhidrosis were 1.27 times more likely to have dementia and 3.62 times more likely to specifically have Lewy body dementia than those without hyperhidrosis. Similarly, they found a statistically significant positive relationship between the duration of hyperhidrosis and the result of the dementia symptom detection test, the Mini-Mental State Examination (MMSE): ($r = 0.21$; $p < 0.001$; Durbin–Watson test = 1.81). Although this is a cross-sectional study, the authors point out that hyperhidrosis could be a distinctive clinical finding that helps predict a future diagnosis of dementia, although it is not clear whether hyperhidrosis would have an independent effect on the development of dementia or would increase this risk through other associated comorbidities, such as anxiety, depression, or sleep disorders, which also increase the risk of dementia.[23]

Discussion and conclusions

Multiple studies have investigated the relationship between dementia development and ACB: while this causal relationship is not proven or ruled out, we cannot ignore it.[1,5,6]

Clinical trials are underway to assess the risk of exposure to ACB, which will compare the long-term effects of its withdrawal versus its maintenance, aiming to minimize possible associated biases. It will probably be years before we have enough evidence on whether ACB directly contributes to the development of cognitive deficit and dementia in older individuals.[1]

For now, it is proposed that we should reduce ACB as much as possible, making therapeutic decisions in consensus with the patient, after providing complete information based on the best available scientific evidence and evaluating the benefit-risk, in addition to reviewing the anticholinergic drugs used by older individuals. On the other hand, we should actively search for (and modify, if possible) other risk factors that may favor cognitive deficit, trying to implement non-pharmacological interventions as much as possible.[1,6]

In the case of hyperhidrosis, we should only consider the use of oral ACE drugs in cases of severe impact on quality of life, include an informed consent for off-label use, and consider their possible adverse effects. It is advisable to avoid them in individuals with risk factors, such as the elderly, especially if there is pre-existing cognitive impairment or the use of other ACE drugs. If used, we should aim for the lowest effective daily dose, preferably intermittently, and if there is no clear improvement, discontinue the treatment. In individuals with risk factors, it is advisable to consider ACE drugs with lower potential risk, such as glycopyrrolate. Finally, we must consider that hyperhidrosis itself could constitute a marker of the risk of developing dementia.

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Conflicts of interest

None declared.

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