Amitriptyline as an adjunct in the management of gastroesophageal reflux disease

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Dear editors of "Acta Médica Colombiana,"

Cordial greetings.

After carefully reading the article titled "Impact of treatment optimization in patients with gastroesophageal reflux disease who do not respond to esomeprazole" (1), I would like to respectfully make the following comments.

In this study, it is noteworthy that the majority of patients fell into the 60-74 year-old age group (43.2%); in other words, were older adults. Medication prescription in this age group entails idiosyncrasies related to the physiological changes of advanced age, polypharmacy, and polypathology, in addition to cognitive, emotional and social circumstances.

The Beers Criteria (2) is a widely-used tool in geriatric practice in which an expert consensus determines which medications are potentially inappropriate for use in older adults, among which amitriptyline holds a prominent place.

Amitriptyline, in addition to blocking serotonin and noradrenaline reuptake, has a high affinity for H1 histamine and M1 muscarinic receptors and, as with other tricyclic antidepressants, is used less and less, especially since the advent of serotonin reuptake inhibitors (3).

Its unfavorable adverse drug reaction profile is more relevant in older adults, especially its anticholinergic (dry mouth, blurred vision, constipation), alpha adrenergic (cardiac effects, prolonged QT interval, arrhythmias and orthostatic hypotension), and sedative (increasing the risk of falls, fractures and delirium) effects, along with a lowered seizure threshold, sexual dysfunction, diaphoresis and tremors. These effects are dose-dependent, but in the elderly, they occur beginning at low doses. In fact, treatment interruption due to side effects occurred more frequently with low-dose tricyclics (4).

In addition, the efficacy of tricyclic antidepressants, especially amitriptyline, as visceral neuromodulators has been highly questioned (5). In fact, the 2017 version of the "Global Guidelines of the World Gastroenterology Organisation" on the management of gastroesophageal reflux disease (6) and the "Practical Evidence-based Guidelines for Gastroesophageal Reflux Disease" published by the Japanese Society of Gastroenterology in 2015 (7) do not suggest it as part of the therapeutic arsenal.

In conclusion, the side effects of tricyclic antidepressants usually make them less tolerable compared with selective serotonin reuptake inhibitors (SSRIs) and other, newer antidepressants (8). Therefore, if an antidepressant is needed for visceral modulation, the choice would be inclined towards the latter groups.

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Answer

Heartburn is not the same as gastroesophageal reflux disease (GERD)

Dear Editor,

We appreciate Dr. Alexánder Morales-Eraso's interest in reading our article, "Impact of treatment optimization in patients with gastroesophagel reflux disease who do not respond to esomeprazole," recently published in the journal (1).

The purpose of our paper was to determine if treatment optimization in patients with GERD could control the symptoms. Optimization consisted of verifying and correcting the dose of the proton pump inhibitor (PPI), recommending "general measures" with proven efficacy in the treatment of GERD (losing weight if the body mass index is ≥ 25, stopping smoking, controlling stress) (2, 3), and prescribing a second dose of PPI before dinner. If the patients continued to have heartburn (retrosternal burning), a low dose of a "visceral neuromodulator" was added. For this study, we selected amitriptyline at doses of 12.5 to 25 mg at bedtime, because it has been previously used for functional gastrointestinal disorders (4, 5). The decision to use the neuromodulator was based on the previous demonstration that in 75-90% of patients with GERD who continue to have heartburn despite receiving two doses of PPIs, this is due to the coexistence of a functional disorder (now known as gut-brain axis interaction disorders), such as functional heartburn or reflux hypersensitivity (6-9). In these entities, there is hyperalgesia or "allodynia" in the esophagus, which explains the heartburn (4, 8, 9). These entities cause heartburn, as do other diseases besides GERD (4, 6, 8), and therefore heartburn is not the same as GERD (4, 6, 8, 10). In our paper, the neuromodulator was added when heartburn was refractory; that is, persisted despite two correctly prescribed doses of PPI for 8-12 weeks. As can be understood, low-dose antidepressants or "visceral neuromodulators" (which is the term used when lower doses are used than those for depression) (4, 6, 12), have not been used to treat GERD but rather "refractory heartburn." The cornerstone of GERD treatment is acid secretion inhibition using PPIs, with which all the international guidelines and experts agree (3, 4, 9, 12, 13), along with the guidelines mentioned by Dr. Morales. No guideline recommends visceral neuromodulators or antidepressants for the treatment of GERD, and neither do we. The objective of the study was to determine the efficacy of a sequential approach to patients with refractory GERD symptoms, including a neuromodulator at the end (1). The approach to patients with refractory heartburn and GERD is much broader and includes adding prokinetic agents, taking esophageal biopsies to rule out eosinophilic esophagitis, esophageal impedance-pH monitoring (4, 8, 9, 11, 12) and, more recently, colesevelam, a gastric bile acid sequestrant (13).

With regard to the use of antidepressants in older adult patients (≥ 65 years), we agree with Dr. Morales, but in our study we did not use these medications at antidepressant doses. The efficacy of "visceral neuromodulators" in refractory heartburn or reflux hypersensitivity has not been proven for all antidepressants. Many options have been proposed, such as tricyclic antidepressants (imipramine, amitriptyline), selective serotonin reuptake inhibitors (citalopram, fluoxetine, sertraline), serotonin reuptake inhibitors and norepinephrine (venlafaxine, duloxetine) (8, 10, 12). None of these medications has been approved for treatment of functional esophageal disorders (4, 5, 8). However, given the previous experience with them in other diseases, they can be used "off label," with prior informed consent. We chose amitriptyline due to its greater analgesic effect, low cost and safety profile at low doses (5, 11, 13). We agree that it has pro-arrhythmic potential due to its effect on rapid sodium channels, which warrants a pretreatment EKG to identify risk factors (prolonged QT, left bundle branch block, bifascicular block). These patients were excluded from our study (1). Serotonin reuptake inhibitors are an option, and there are some preliminary studies on reflux hypersensitivity (15). However, in a recent meta-analysis in patients with functional dyspepsia, selective serotonin reuptake inhibitors (SSRIs) showed no benefit over the placebo (RR = 1.00, 95% CI 0.86-1.17, I2 = 0%, p= 0.82) (15). In our study, amitriptyline doses of ≤ 25 mg were used in patients with refractory GERD symptoms, which are lower than the dose suggested for other functional disorders (25-100 mg/day) (4, 5, 10). Our focus is a setting previously unexplored in gastroenterology, but suggested by experts (6, 8). It is an exploration of the management of these patients in our environment, considering the high cost of esophageal physiology testing.

We appreciate Dr. Morales's interest in reading our paper and agree with the importance of considering the adverse cardiovascular effects of amitriptyline in older adults, which is why low doses were used, as recommended (4, 5, 15).

Cordially,

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