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Low-dose Tricyclic Antidepressants for Irritable Bowel Syndrome: Definitive Evidence of Benefit from ATLANTIS

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This summary reviews Ford AC, Wright-Hughes A, Alderson S, et al. Amitriptyline at Low-Dose and Titrated for Irritable Bowel Syndrome as Second-Line Treatment in Primary Care (ATLANTIS): A Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial. Lancet 2023; 402: 1773-85.

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STRUCTURED ABSTRACT

Question: Is amitriptyline 10 mg-30 mg nightly superior to placebo for improvement in irritable bowel syndrome (IBS) symptoms at 6 months in the primary care setting?

Design: Multicenter, double-blind, placebo-controlled randomized controlled trial (RCT) with 1:1 randomization.

Setting: Fifty-five general practices/primary care centers in England.

Patients: Inclusion criteria included: (a) ≥ 18 years old; (b) IBS based on ROME IV criteria; (c) IBS-Symptom Severity Score (IBS-SSS) >75 (0-500); (d) failure to respond to first-line treatments defined as dietary modification, soluble fiber, antispasmodics, or laxatives/ antidiarrheals; and, (e) normal hemoglobin, normal c-reactive protein, negative anti-tissue transgluaminase (TTG) antibodies to exclude celi-

ac disease, and no evidence of suicidal ideation since amitriptyline can be fatal in overdoses.

Interventions/Exposure: Amitriptyline 10 mg nightly (qhs) vs placebo. Patients were educated to titrate their dose upward to a maximum of 3 tablets (30 mg amitriptyline or 3 placebo tablets) over 3 weeks based on improvement in IBS symptoms. Throughout the study, patients could further titrate their dose up or down based on severity of IBS symptoms or side effects.

Outcome: The primary outcome was change in IBS-SSS from baseline at 6 months. The IBS-SSS requires patients to quantify severity of abdominal pain, abdominal distention, satisfaction with bowel habits, impact of IBS symptoms on quality of life based on a visual analog scale of 0-100 plus number of days with abdominal pain in past 10 days (X 10). The IBS-SSS range is 0-500, with mild IBS 75-175, moderate IBS 176-300, and severe IBS >300. A change of 35 points in IBS-SSS was considered to be a minimal clinically important difference.[1]

The key secondary outcome was subjective global assessment of relief of IBS symptoms at 6 months, which was defined as having somewhat relieved or better (ordinal scale of global IBS symptoms being worse, unchanged, somewhat relieved, considerably relieved, completely relieved compared to baseline).

Data Analysis: Intention-to-treat analysis. Primary outcome assessed using a linear regression model.

Funding: National Institute for Health and Care Research (NIHR) Health Technology Assessment Program.

Results: Between October 2019 and April 2022, 463 IBS patients were enrolled. The mean age was 48-49 years old; 67%-69% female; mean IBS-SSS at baseline 273. Over 80% of patients had IBS with diarrhea (IBS-D) or IBS-mixed (IBS-M), 84% had normal scores on HADS-Depression instrument, and 85% had moderate-severe IBS based on baseline IBS-SSS score with median IBS duration of 10 years.

At 6 months, mean IBS-SSS decreased from 273 to 170 in amitriptyline group versus decrease from 272 to 200 in the placebo group for mean difference in IBS-SSS score of -27.0; 95% confidence interval (CI) -46.9 to

-4.6, $P = 0.008$. Similar reduction was also seen after 3 months of treatment. For the key secondary outcome, amitriptyline-treated patients were more likely to achieve at least somewhat relief of global IBS symptoms (odds ratio [OR] 1.78, 95% CI 1.19-2.66) or for considerable/complete relief of global IBS symptoms (OR 1.88, 95% CI 1.20-2.95). (**Figure 1**) There was no evidence of effect on HADS-Depression scores at 3 or 6 months.

Discontinuation of study medication due to adverse events was 13% vs 9% for amitriptyline vs placebo, respectively. The most common adverse events were due to known anticholinergic effects in the amitriptyline group, including dry mouth (54%), drowsiness (53%), blurred vision (17%), and difficulty with urination (22%).

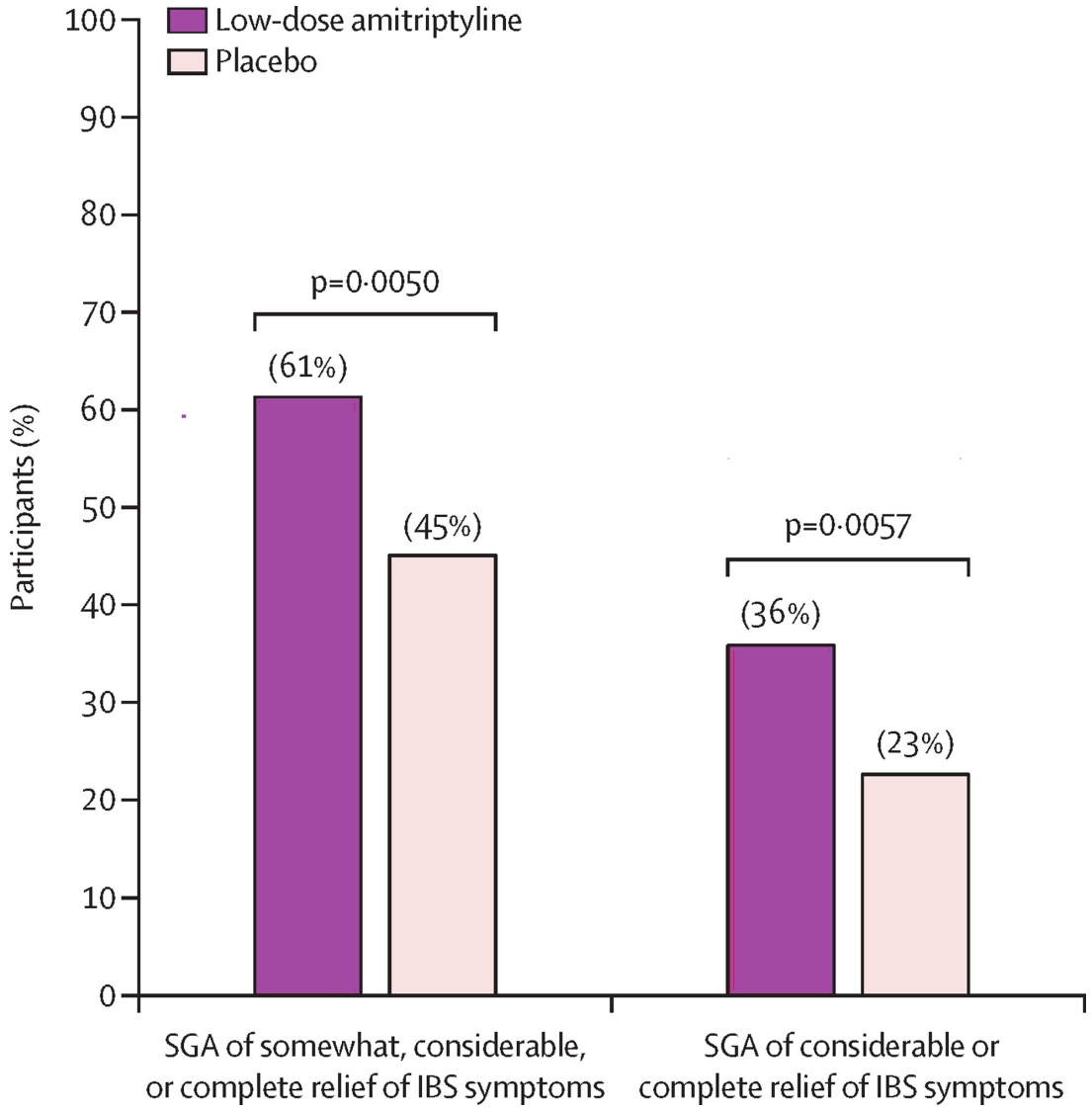

Figure 1. Key secondary outcome of subjective global assessment (SGA) of relief of irritable bowel symptoms (IBS symptoms at 6 months).

COMMENTARY

Why Is This Important?

Optimal treatment of IBS requires improvement in abdominal discomfort symptoms as well as bowel symptoms. The American College of Gastroenterology (ACG) guidelines on management of IBS[2] as well as the American Gastroenterological Association (AGA) guidelines on management of IBS-D[3] provide conditional recommendations suggesting that tri-cyclic antidepressants (TCAs) may be used for global IBS symptoms. Low-dose TCAs are used for neuropathic pain, including fibromyalgia, chronic pelvic pain, and migraines, because they modify central nervous system-mediated pain signaling.

There is limited RCT data supporting the use of TCAs in IBS. Although 12 RCTs have evaluated these agents, only about 650 patients have been enrolled and 6 different TCAs have been examined. These studies also have various design limitations, which is why the ACG and AGA guidelines only provide conditional recommendations that suggest TCA use in IBS. Therefore, the ATLANTIS study is a major achievement that quantifies the benefit of amitriptyline in a large, methodologically rigorous RCT which assessed patients over 6 months. Ford and colleagues should be commended for this effort.

Key Study Findings

Amitriptyline was superior to placebo for decreasing IBS-SSS and for achieving somewhat, considerable, or complete relief of global IBS symptoms at 6 months.

Caution

Since TCAs may cause constipation, I do not use them in IBS-C or IBS-M patients and reserve them for IBS-D patients where the constipation side effect is beneficial. The inclusion of IBS-C patients in this trial may have decreased the observed benefit of amitriptyline in the overall IBS population, although only 17% of study patients had IBS-C.

Since the study was performed in the primary care setting in a diverse IBS population, the more rigorous responder endpoints required by the US Food and Drug Administration and the European Medicines Agency for drug trials in IBS -D and IBS-C were not used. Ultimately, the benefit observed with amitriptyline was modest and did not meet the minimal clinically important difference in IBS-SSS reduction of 35 points compared to placebo.

My Practice

In my practice, TCAs are a cornerstone of IBS-D treatment: nortriptyline 25 mg every evening at bedtime and I may increase to 50 mg every evening at bedtime. Nortriptyline, which is a secondary amine, is my preferred agent

because it generally has less antihistaminic and anticholinergic side effects compared to a tertiary amine, like amitriptyline. I educate patients that TCAs modify their perception of central nervous system-mediated pain and that's helpful since defects in brain-gut communication and visceral hypersensitivity lead to abdominal pain in IBS. I also educate patients that low-dose TCAs are not appropriate nor intended to treat depression or anxiety symptoms, while also proactively communicating that they may feel drowsy, feel a little fatigued or get a dry mouth with these agents. It may take at least 12 weeks to see abdominal pain improvement. Furthermore, set appropriate expectations: "success" means decrease in frequency of abdominal discomfort and decrease in severity of symptoms when they do occur. Near-total resolution of symptoms is not the expected goal, although it does happen for some patients.

I do not prescribe selective serotonin reuptake inhibitors (SSRIs), like fluoxetine or paroxetine, which have not demonstrated clear benefit in some small RCTs with study design limitations. The ACG and AGA guidelines[2-3] both suggest against using SSRIs for IBS. However, if a patient can't tolerate TCAs or if the patient has IBS-C, then I frequently prescribe serotonin and norepinephrine reuptake inhibitors (SNRIs), which are effective neuromodulators of chronic pain. My preferred agent is duloxetine, which is FDA-approved for diabetic neuropathic pain and fibromyalgia. I start at 30 mg daily and will increase to 60 mg daily after 2 months depending on symptom response. However, it's important to note that there are no well-designed, large RCTs of duloxetine in IBS-C patients.

For Future Research

Future research should assess frequency and efficacy of TCAs in real-world settings, especially among IBS-D patients. Implementation research could assess why gastroenterologists may be hesitant to use TCAs for IBS and what interventions would overcome any barriers.

Conflict of Interest

Dr. Schoenfeld reports serving on advisory boards or speakers bureaus for Ironwood Pharmaceuticals, Salix Pharmaceuticals, AbbVie Pharmaceuticals, and Ardelyx Pharmaceuticals.

The authors of this article are active on social media. Tag them to discuss their work and this EBGI summary:

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