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Title

Amitriptyline at Low-dose and Titrated for Irritable Bowel Syndrome in Primary Care: ATLANTIS: Randomised Controlled Trial

Priority 1 (Research Category)

Gastroenterology

Presenters

Hazel Everitt, PhD, MSc, MBChB, FRCGP, Robbie Foy, PhD, MBChB, Matthew Ridd, PhD, FRCGP, MBChB, Sarah Alderson, Ruth Thornton, Sonia Newman, Emma Teasdale, Heather Cook, deborah cooper, Catherine Fernandez, Amy Herbert, Matthew Chaddock, BA, Alexandra Wright-Hughes, Amanda Farrin, BSc, MSc, Suzanne Hartley, Alexander Ford, Felicity Bishop, Pei Loo Ow

Abstract

Context: Most patients with irritable bowel syndrome (IBS) are managed in primary care. If first-line therapies are ineffective, UK NICE Guidelines suggests considering low dose tricyclic antidepressants (TCAs), but effectiveness in primary care is unknown and TCA are infrequently prescribed for IBS in this setting. Objective: To determine the clinical effectiveness of low dose amitriptyline (10-30mg) for adults with IBS in primary care. Study Design and Analysis: Randomised, double-blind, placebo-controlled trial. Participants, clinicians, investigators, and analysts masked to allocation. Intention to treat analyses for effectiveness, according to treatment receipt for safety analyses. Trial Registration ISRCTN48075063. Setting: 55 UK primary care centres. Population Studied: Adults ≥18 years with Rome IV IBS of any subtype, with ongoing symptoms despite first-line therapies, a normal full blood count and C-reactive protein, negative coeliac serology, and no evidence of suicidal ideation. Intervention: Participants randomised (1:1) to 6 months low-dose oral amitriptyline (10-30mg once daily) or identical placebo, participant self-titration according to symptoms and tolerability. Outcome Measures: Primary and key secondary endpoint: IBS-SSS score and Subjective Global Assessment (SGA) of relief of IBS symptoms at 6 months. Results: 463 patients (mean age 48.5 yrs (SD 16.1 yrs), 315 (68.0%) female) randomised, December 2019 to April 2022, to amitriptyline (232) or placebo (231). Primary outcome analysis showed a significant difference in IBS-SSS score at 6 months (-27.0; 95% CI -46.9 to -7.10, p=0.008) in favour of amitriptyline. For SGA of relief of IBS symptoms, amitriptyline was superior to placebo at 6 months (125/204 (61.3%) vs. 88/195 (45.1%), OR 1.78; 95% CI 1.19 to 2.66, p=0.005). Amitriptyline was superior to placebo across other secondary endpoints but had no impact on anxiety or depression. 46 (19.8%) patients discontinued amitriptyline (30 (12.9%) due to adverse events) and 59 placebo (25.5%) (20 (8.7%) adverse events). 5 serious adverse reactions (2 amitriptyline, 5 placebo) and 5 serious adverse

events were unrelated to trial medication. Conclusions: This is the largest trial of a TCA in IBS ever conducted. Titrated low-dose amitriptyline was superior to placebo for IBS across multiple endpoints and safe. Primary care physicians should offer low-dose amitriptyline to patients with IBS whose symptoms do not improve with first-line therapies.