

Phase 3 trial finds amitriptyline helps relieve IBS symptoms

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A cheap and widely available prescription drug can improve symptoms of irritable bowel syndrome in patients seen in GP surgeries, new research presented today at [UEG Week 2023](#) has found.

Amitriptyline, which is commonly used at low doses for a range of health concerns, has been found to improve irritable bowel syndrome (IBS) symptoms too, according to the results of the ATLANTIS trial.

Led by researchers at the Universities of Leeds, Southampton, and

Bristol, the study was conducted in primary care. GPs prescribed the drug and patients managed their own dose based on the severity of their symptoms, using an adjustment document designed for the trial. Most people with IBS are seen and managed in primary care by their GP, which means that the results of this trial are likely to be applicable to many people with the condition.

[The results](#), published today in *The Lancet*, showed that patients taking [amitriptyline](#) were almost twice as likely to report an overall improvement in symptoms as those taking a placebo.

Now the trial team is recommending that GPs support their patients with IBS to use amitriptyline to manage their symptoms—and has made the dose adjustment document available for clinicians and patients.

Co-chief Investigator Alexander Ford, Professor of Gastroenterology in the University of Leeds's School of Medicine, said, "Amitriptyline is an effective treatment for IBS and is safe and well tolerated. This new rigorously conducted research indicates that general practitioners should support patients in primary care to try low-dose amitriptyline if their IBS symptoms haven't improved with recommended first-line treatments."

IBS, which affects around 1 in 20 people worldwide, causes [abdominal pain](#) and changes to bowel movements. The long-term condition, which has no known cure, fluctuates in severity over time. It can have a substantial impact on quality of life and ability to work and socialize. Most treatments only have a modest effect and people often have ongoing troublesome symptoms.

Amitriptyline belongs to a group of medications called tricyclics. Originally used at high doses to treat depression, today these are rarely used for this condition because newer treatments have been developed.

Previous small trials of low-dose tricyclic antidepressants for IBS suggested a possible benefit in patients seen in hospital clinics, who often have more difficult to treat symptoms, but this new study is the first randomized controlled trial of low-dose amitriptyline versus a placebo tablet for IBS in primary care. It is also the largest trial of amitriptyline for IBS undertaken worldwide.

GPs already prescribe low-dose amitriptyline to treat chronic nerve and back pain, and to help prevent migraine attacks. NICE guidelines currently state that GPs could consider using a low dose tricyclic like amitriptyline for IBS, but until now, the evidence for a benefit has been uncertain.

Based on the results of the trial, which showed a clear benefit of amitriptyline, GPs can offer low-dose amitriptyline to people with IBS as part of shared decision making if symptoms don't improve with first-line treatments.

Co-chief Investigator Hazel Everitt, Professor of Primary Care Research at the Primary Care Research Centre, University of Southampton, said, "Prior to ATLANTIS, GPs haven't often prescribed amitriptyline for IBS as the research evidence was uncertain, but our new research provides good evidence of benefit.

"GPs already prescribe low-dose amitriptyline for other conditions, such as chronic pain and poor sleep, and when we interviewed GPs as part of this research, they were willing to prescribe it for IBS if the research evidence supported this. Participants were also keen to have another option to try to help their IBS symptoms and most were happy to self-adjust their dose depending on symptoms and side effects."

Some 463 people with IBS from three regions across the UK—West Yorkshire, Wessex, and West of England—took part in the ATLANTIS

trial. The participants were recruited from 55 general practices.

They were put at random into two groups—those receiving amitriptyline and those receiving a placebo. Participants controlled how many tablets of the trial medication they took, receiving support via the patient dose adjustment document that was developed with patient representatives especially for this trial. This enabled participants to increase or decrease the number of tablets based on their IBS symptoms and any side effects experienced.

Participants taking amitriptyline reported a bigger improvement in their symptom scores after six months compared with those taking a placebo. Those taking amitriptyline were almost twice as likely as those taking a placebo to report an overall improvement in IBS symptoms, with amitriptyline performing better across a wide range of IBS symptom measures.

Researchers monitored participants' anxiety or depression scores and found that they were not altered—suggesting that the beneficial effects of the medication were via the gut, not because of any effect as an antidepressant.

No safety concerns were identified and side effects in people on amitriptyline were mostly mild, such as a dry mouth in the morning.

Matthew Ridd, GP and Professor of Primary Health Care at the Centre for Academic Primary Care, University of Bristol, said, "Pragmatic trials like this are always challenging to do in [primary care](#) and the team worked hard to overcome the additional challenges of the COVID-19 pandemic. It's fantastic that we've found that amitriptyline is an effective and safe option for patients with IBS to try."

Amanda Farrin, Professor of Clinical Trials and Evaluation of Complex

Interventions, who leads the Complex Intervention Division of the Leeds Clinical Trials Research Unit, said, "The participants in the ATLANTIS trial had moderate to severe symptoms and an average duration of IBS of 10 years. The fact that amitriptyline had such a big effect over a placebo is significant because it can help improve the quality of life of patients with this condition."

Professor Andrew Farmer, Director NIHR's Health Technology Assessment (HTA) Programme, said, "The results of this study are hugely encouraging. It shows that a drug already widely available to treat a number of other conditions appears to be safe and effective for people with IBS. The findings the research team have shared around the adjustment of dosages can be tremendously helpful to GPs in guiding them when treating patients."

"IBS affects a significant number of people in the UK and can have a debilitating effect on their day-to-day lives. This is another excellent example of how high-quality research can lead to positive changes in health and social care practice and treatments for the benefit of patients and health care professionals."

More information: Amitriptyline at Low-Dose and Titrated for Irritable Bowel Syndrome as Second-Line Treatment in primary care (ATLANTIS): a randomised, double-blind, placebocontrolled, phase 3 trial, *The Lancet* (2023). DOI: 10.1016/S0140-6736(23)01523-4 , [www.thelancet.com/journals/lan ... \(23\)01523-4/fulltext](https://www.thelancet.com/journals/lan.../fulltext)

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