ATLANTIS

Investigating amitriptyline as second-line treatment for IBS

Summary of Results for General Practices

Background

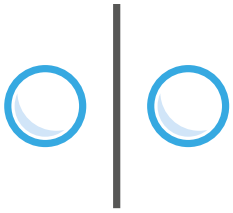
Most patients with irritable bowel syndrome (IBS) are managed in primary care.

When first-line therapies for IBS are ineffective (dietary and lifestyle changes, soluble fibre, laxatives, antispasmodics, or anti-diarrhoeals), the National Institute for Health and Care Excellence guideline suggests considering low-dose tricyclic antidepressants (e.g., amitriptyline) as second-line treatment, but their effectiveness in primary care is unknown and they are infrequently prescribed for IBS in primary care.

Aim

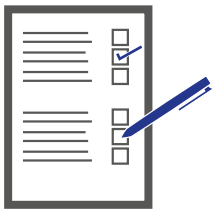
We assessed the clinical effectiveness of **low-dose amitriptyline (10–30mg) for adults with IBS in primary care**.

Method



We undertook a **randomised, double-blind, placebo-controlled trial of low-dose amitriptyline versus placebo** in 55 general practices in England.

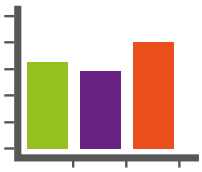
Eligible participants were aged 18 years or over with IBS of any subtype, ongoing symptoms despite dietary changes and first-line therapies, and no contraindications to amitriptyline. They had a normal full blood count and C-reactive protein, negative coeliac serology, and no evidence of suicidal ideation.



Participants were randomised (1:1) to low-dose oral amitriptyline or placebo for 6 months, with participant-led dose titration over 3 weeks (10mg to 30mg once daily), according to symptoms and tolerability. Participants, their general practitioners (GPs), investigators, and the analysis team were masked to treatment allocation. The primary outcome was the IBS Symptom Severity Score (IBS-SSS) at 6 months. A key secondary outcome was subjective global assessment of relief of IBS symptoms at 6 months.

A nested qualitative study explored participant and GP experiences of treatment and trial involvement.

Results



From December 2019 to April 2022, we randomised 463 patients (mean age 48.5 years, 315 (68.0%) female) to amitriptyline (232) or placebo (231). Primary outcome analysis showed **a significant difference in favour of amitriptyline** in IBS-SSS score at 6 months (-27.0; 95% CI -46.9 to -7.10, p=0.008). For subjective global assessment 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 scores.

46 (19.8%) participants discontinued amitriptyline, 30 (12.9%) because of adverse events, and 59 (25.2%) discontinued placebo, 20 (8.7%) because of adverse events. Five serious adverse reactions (two amitriptyline, three placebo) and five serious adverse events were **unrelated to trial medication**. Most adverse events with amitriptyline were mild and in keeping with its known anticholinergic effects. Those occurring with more frequency with amitriptyline compared with placebo included dry mouth, drowsiness, blurred vision, and urinary problems.

Qualitative interviews revealed low-dose amitriptyline for IBS is likely to be **acceptable to, and welcomed by**, both GPs and patients as an additional treatment option.

However, its association with depression may **hinder its uptake**, so it was felt important that there was a clear explanation that it was not being used for its antidepressant effects. Resources to support GP-patient communication to **distinguish low-dose amitriptyline for IBS from amitriptyline for other conditions** (especially depression) would be beneficial.

Conclusions

This is the **largest trial of a tricyclic antidepressant in IBS** ever conducted. Titrated low-dose amitriptyline was superior to placebo for IBS across multiple endpoints and was safe.

Primary care clinicians can **offer low-dose amitriptyline to patients with IBS whose symptoms do not improve with first-line therapies**, with appropriate support to guide patient-led dose titration, such as using the self-titration document developed for this trial. **Low-dose amitriptyline** could be added to first-line therapies already being taken by patients, as it was in this trial.

For more information, visit: https://ctru.leeds.ac.uk/atlantis/

This trial is registered with the ISRCTN (ISRCTN48075063).

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