In The Name of God

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

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Introduction

- Irritable bowel syndrome
- Quality of life
- NICE (national institute for health and care excellence) guidelines for first line therapies
- NICE guidelines for second line treatment
- Tricyclic antidepressants and IBS
- Amitriptyline : a good choice

Methods

- Randomised, double-blind, placebo-controlled
- ATLANTIS was conducted in 55 general practices in three regions, termed hubs, in England
- Eligible participants
- Inclusion criteria
  - Normal haemoglobin, white cell and platelet count, and C-reactive protein within 6 months
  - Negative anti-tissue transglutaminase antibodies
  - No evidence of suicidal ideation (given that amitriptyline can be fatal in overdose)
  - If female and not post-menopausal or surgically sterile, willingness to use highly effective contraception
  - Ability to complete questionnaires, trial assessments, and provide written informed consent

Methods

- Eligible participants
- Exclusion criteria
  - Age 61 years or older with no general practitioner review in the 12 months prior to screening
  - Suspected lower gastrointestinal cancer; celiac disease or inflammatory bowel disease
  - Previous colorectal cancer
  - Pregnancy, breastfeeding, or planning to become pregnant
  - Current use of, or allergy or contraindications to, a tricyclic antidepressant

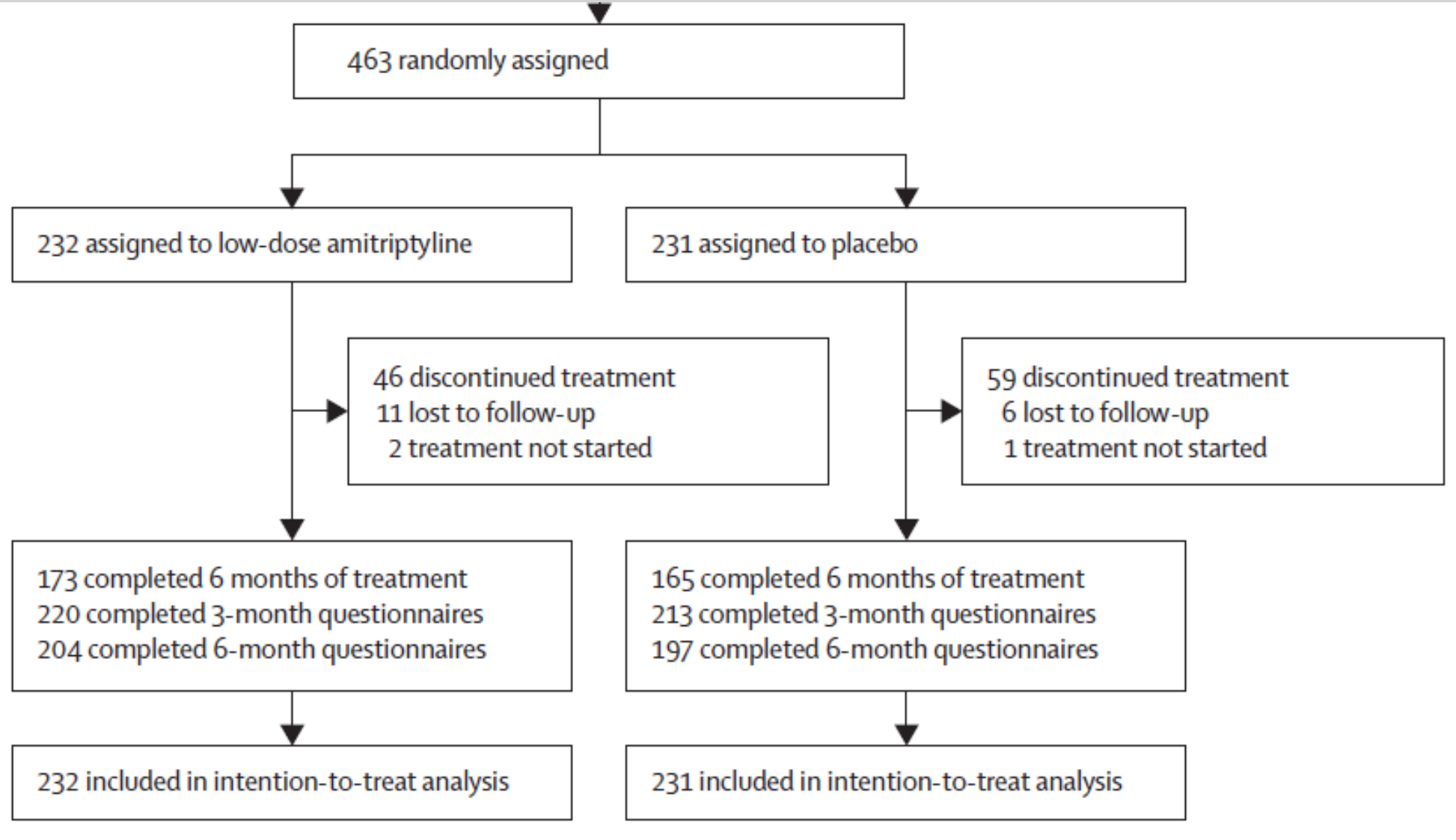
Procedure

- Participants received titrated low-dose oral amitriptyline or placebo tablets for 6 months
- All participants were provided with the first-line dietary advice sheet for IBS
- Usual care for IBS was provided by the participant's general practitioner, except that amitriptyline, other tricyclic antidepressants, or drugs contraindicated with tricyclic antidepressants
- Dose titration over 3 weeks (maximum of 30 mg at night)
- Telephone support , questionnaires and weekly question

Outcome

- Questionnaire data measured by the IBS-SSS and SGA
- Weekly response to the question “Have you had adequate relief of your IBS symptoms?
- IBS-associated somatic symptoms using the Patient Health Questionnaire-12 (PHQ-12)
- Anxiety and depression scores, via the HADS
- Ability to work and participate in other activities, using the Work and Social Adjustment Scale (WSAS)
- Self-reported adherence to treatment, and tolerability of treatment, using the validated Antidepressant Side-Effect Checklist (ASEC)

Results


463 randomly assigned
232 assigned to low-dose amitriptyline
231 assigned to placebo
46 discontinued treatment
11 lost to follow-up
2 treatment not started
59 discontinued treatment
6 lost to follow-up
1 treatment not started
173 completed 6 months of treatment
220 completed 3-month questionnaires
204 completed 6-month questionnaires
165 completed 6 months of treatment
213 completed 3-month questionnaires
197 completed 6-month questionnaires
232 included in intention-to-treat analysis
231 included in intention-to-treat analysis

	Low-dose amitriptyline (n=232)	Placebo (n=231)
Mean age, SD	49·2 (16·2)	47·8 (15·9)
Sex		
Female	156 (67%)	159 (69%)
Male	76 (33%)	72 (31%)
Ethnicity		
White	226 (97%)	225 (97%)
Other*	6 (3%)	6 (3%)
IBS subtype		
IBS-C	40 (17%)	37 (16%)
IBS-D	92 (40%)	89 (39%)
IBS-M	93 (40%)	98 (42%)
IBS-U	7 (3%)	7 (3%)
Hub		
West Yorkshire	43 (19%)	44 (19%)
West of England	92 (40%)	92 (40%)
Wessex	97 (42%)	95 (41%)
IMD quintile†		
1	13/229 (6%)	13/230 (6%)
2	34/229 (15%)	27/230 (12%)
3	38/229 (17%)	33/230 (14%)
4	75/229 (33%)	74/230 (32%)
5	69/229 (30%)	83/230 (36%)
Median years from IBS diagnosis, IQR	10 (4–21)	9 (4–18)
Mean IBS-SSS‡, SD	273·4 (90·5)	272·1 (90·3)
IBS-SSS severity§		
Mild (75–174)	37 (16%)	26 (11%)
Moderate (175–299)	98 (42%)	103 (45%)
Severe (300–500)	94 (41%)	97 (42%)

(Table 1 continued in next column)

	Low-dose amitriptyline (n=232)	Placebo (n=231)
(Continued from previous column)		
Mental health		
Mean PHQ-12 score‡, SD	6·3 (3·5)	6·3 (3·6)
Mean HADS-anxiety score‡, SD	7·3 (4·3)	7·7 (4·3)
HADS-anxiety score ≥8	106 (46%)	112 (48%)
Previously treated for anxiety	80 (34%)	79 (34%)
Mean HADS-depression score‡, SD	4·4 (3·6)	4·1 (3·2)
HADS-depression score ≥8	37 (16%)	36 (16%)
Previously treated for depression	79 (34%)	99 (43%)
Mean WSAS score‡, SD	11·2 (8·2)	11·5 (7·6)
Previous first-line treatments¶	232 (100%)	231 (100%)
Previous dietary changes	232 (100%)	231 (100%)
Antispasmodics	176 (76%)	183 (79%)
Antidiarrhoeals	70 (30%)	75 (32%)
Fibre supplements	52 (22%)	52 (23%)
Laxatives	51 (22%)	34 (15%)
Peppermint oil	18 (8%)	27 (12%)

	3 months				6 months			
	Low-dose amitriptyline (n=232)	Placebo (n=231)	Effect*, 95% CI	p value	Low-dose amitriptyline (n=232)	Placebo (n=231)	Effect*, 95% CI	p value
Primary outcome								
IBS-SSS†								
Mean total IBS-SSS‡, SD	173·0 (106·6), n=219	194·6 (107·5), n=213	−23·3 (−42·0 to −4·6)	0·014	170·4 (107·7), n=204	200·1 (114·5), n=197	−27·0 (−46·9 to −7·1)	0·0079
Change in IBS-SSS from baseline, SD	−99·8 (107·7)	−76·1 (107·1)	..	..	−99·2 (112·9)	−68·9 (109·3)	..	..
Secondary outcomes								
SGA of relief of IBS symptoms§	139/220 (63%)	105/213 (49%)	1·70 (1·15 to 2·53)	0·0080	125/204 (61%)	88/195 (45%)	1·78 (1·19 to 2·66)	0·0050
Adequate relief of IBS symptoms for 50% of weeks during the 6 months¶	NA	NA	NA	..	90/222 (41%)	67/221 (30%)	1·56 (1·20 to 2·03)	0·0008
Mean PHQ-12 score†, SD	NA	NA	NA	..	5·7 (3·4), n=202	5·9 (3·2), n=192	−0·04 (−0·58 to 0·49)	0·88
Mean HADS-anxiety score†, SD	6·5 (4·4), n=220	6·6 (4·0), n=212	0·05 (−0·53 to 0·63)	0·86	6·7 (4·4), n=203	6·9 (4·0), n=193	0·08 (−0·49 to 0·65)	0·78
Mean HADS-depression score†, SD	3·5 (3·3), n=220	3·6 (3·2), n=212	−0·22 (−0·71 to 0·26)	0·37	3·9 (3·6), n=202	4·0 (3·5), n=193	−0·20 (−0·75 to 0·34)	0·46
Mean WSAS score†, SD	9·3 (7·6), n=210	9·5 (6·3), n=198	−0·27 (−1·36 to 0·83)	0·63	8·1 (7·6), n=195	9·4 (7·8), n=184	−1·04 (−2·30 to 0·23)	0·11
Acceptability of treatment	NA	NA	NA	..	122/211 (58%)	100/213 (47%)	1·60 (1·08 to 2·35)	0·018
Adherence to treatment‖	193/232 (83%)	183/220 (83%)	..	..	172/232 (74%)	155/228 (68%)	..	..

ASEC (Antidepressant side effect checklist)

	3 months		6 months	
	Low-dose amitriptyline (n=231)*	Placebo (n=229)*	Low-dose amitriptyline (n=232)†	Placebo (n=228)†
Number of participants on treatment	194	196	174	164
Number of participants on treatment and completing the ASEC	193	192	166	152
Total ASEC score‡				
Mean, SD	9·9 (6·0); n=193	8·4 (5·7); n=192	9·3 (6·1) ; n=166	8·7 (6·2); n=152
Mean difference (95% CI); p value§	1·39 (0·29 to 2·50); p=0·013	..	0·26 (–0·98 to 1·51); p=0·68	..
Side effect				
No side effects reported	5/193 (3%)	7/192 (4%)	2/166 (1%)	3/152 (2%)
≥1 mild to severe side effect	188/193 (97%)	185/192 (96%)	164/166 (99%)	149/152 (98%)
≥1 moderate to severe side effect	156/193 (81%)	154/192 (80%)	127/166 (77%)	113/152 (74%)
≥1 severe side effect	58/193 (30%)	46/192 (24%)	45/166 (27%)	37/152 (24%)

Discussion

- To our knowledge, this is the largest trial of a tricyclic antidepressant in IBS ever undertaken and the first based entirely in a primary care setting
- It addresses a key research priority identified by NICE guidance for management of IBS in primary care
- The 6 month duration of treatment in ATLANTIS is longer than most drug trials in IBS
- Effectiveness analyses were conducted on all participants, irrespective of adherence, with imputation of missing data. Therefore, it is unlikely we have overestimated the effectiveness of low-dose amitriptyline for IBS in primary care

Discussion

- Using current recommended symptom-based criteria, the Rome IV criteria, together with limited diagnostic testing to exclude known organic mimics of IBS in all participants, in line with UK guidance
- Recruiting participants with IBS, irrespective of predominant stool pattern, with symptoms of varying severity, from a broad range of general practices in three different regions of the UK, meaning that these results are likely to be generalisable to many patients in this setting
- Follow-up rates for participant-reported outcomes at 6 months were 87%, preserving power despite the slightly smaller than projected sample size
- ATLANTIS leaned strongly towards the pragmatic end for six of the nine PRECIS-2 criteria, including eligibility, setting, organisation, flexibility of delivery of the intervention, primary outcome, and primary analysis.

Discussion

- Participants were primarily White, despite considerable efforts to reach out to people of different ethnicities with IBS during the trial
- Unlike many treatment trials in IBS more than 30% of recruited participants were male
- Over 80% of participants had IBS-D or IBS-M, meaning effectiveness of low-dose amitriptyline in those with IBS-C or IBS-U might be more difficult to judge.
- Our participant information leaflet mentioned constipation was a potential side-effect of amitriptyline, and perhaps deterred patients with IBS-C from participating
- Given the higher rates of anticholinergic side-effects in the amitriptyline group, there is the possibility that some participants guessed correctly they were receiving the active drug, and that this has influenced findings

Discussion

- Previous meta-analyses of tricyclic antidepressants in IBS demonstrate these drugs, as a class, are superior to placebo, the included trials have been relatively small, with a maximum treatment duration of 3 months, and none have been conducted entirely in primary care
- The largest RCT to date used 150 mg desipramine once daily daily, recruiting a mixed population of 216 female patients with functional bowel disorders, 172 of whom had IBS. With a 60% response rate with desipramine versus 47% with placebo
- In another trial conducted in 54 patients with IBS-D in secondary care, response rates with 10 mg amitriptyline once daily were 70%, compared with 41% for placebo, but this was not statistically significant

Discussion

- In our trial, treatment effects were generally larger in those with IBS-C or IBS-D, lower baseline HADS-anxiety scores, higher baseline IBS-SSS scores, and among men. The magnitude of the difference in treatment effect increased between months 3 and 6, This underlines the importance of allowing adequate time for low-dose amitriptyline to have a beneficial effect in IBS, and is compatible with reports of a decrease in placebo response rates as trial duration increases.
- No effect of low-dose amitriptyline on somatoform symptom-reporting, anxiety, or depression scores during the 6 months of treatment.
- This supports a benefit of low-dose amitriptyline in IBS arising from its peripheral actions on gastrointestinal motility and pain sensation, rather than improvements in extra-intestinal symptoms, anxiety, or depression, which are often associated with IBS.
- Nor was there any impact on ability to work or social functioning, according to the WSAS at 6 months, although reduction in scores was generally greater in the low-dose amitriptyline group. It could be that the treatment duration was too short to see any meaningful improvement

Conclusion

- In conclusion, this trial of low-dose amitriptyline, 10 mg to 30 mg once daily, as second-line therapy in 463 participants with IBS in primary care has addressed an important unanswered question. Amitriptyline was more effective than placebo across a range of IBS symptom measures, and was safe and well tolerated, when titrated according to symptom response and side-effects. When the rationale for use of a tricyclic antidepressant for IBS is explained clearly, as in the information materials provided to participants in this trial, with appropriate support, many people with IBS find it acceptable and beneficial. General practitioners should offer low-dose amitriptyline to patients with IBS in whom first-line therapies are ineffective

Thanks for your attention