



Surveillance report 2017 – Irritable bowel syndrome (2008) NICE guideline CG61

Surveillance report

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Surveillance decision

We will not update the guideline on [irritable bowel syndrome \(IBS\)](#) at this time.

During surveillance editorial or factual corrections were identified. Details are included in [appendix A](#): summary of evidence from surveillance.

Reason for the decision

Assessing the evidence

We found 156 studies through surveillance of this guideline.

This included evidence suggesting possible effects of ondansetron and dietary supplements such as vitamin D and a herbal medicine combination of fennel oil plus curcumin. We asked topic experts whether this evidence would affect current recommendations. Generally, the topic experts thought that an update of these areas was not needed.

We also identified evidence that supports current recommendations on:

- diagnosis of irritable bowel syndrome, including evidence that supports NICE diagnostic guidance on [SeHCAT \(tauroselcholic \[75 selenium\] acid\) testing for bile acid malabsorption](#) and on [faecal calprotectin testing](#)
- low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) diet, other exclusion diets, dietary supplements and probiotics
- physical activity interventions
- drug treatments including antispasmodics, laxatives, antidepressants
- psychological therapies such as cognitive behavioural therapy (CBT)
- alternative therapies, for example, hypnotherapy, biofeedback, relaxation, acupuncture and herbal medicine.

We found evidence on serotonin 5-HT₃ and 5-HT₄ receptor antagonists, which was not covered in the guideline. However, the evidence was insufficient to add new recommendations in this area at this time.

For any new evidence relating to published or ongoing NICE technology appraisals, the guideline surveillance review deferred to the technology appraisal decision. This included a study of eluxadoline, which is currently being evaluated, and technology appraisal guidance is expected in 2017.

Equalities

No equalities issues were identified during the surveillance process.

Overall decision

After considering all the evidence and views of topic experts and stakeholders, we decided that no update is necessary for this guideline.

See [how we made the decision](#) for further information.

Commentary on selected evidence

With advice from topic experts we selected 2 studies for further commentary.

Clinical management of IBS – on-demand alverine plus simeticone

We selected the pragmatic cluster randomised controlled trial (RCT) by [Ducrotte et al. \(2013\)](#) for a full commentary because it shows effectiveness of a combination of 2 widely available treatments for IBS – alverine plus simeticone.

What the guideline recommends

The [irritable bowel syndrome](#) guideline recommends that healthcare professionals should consider prescribing antispasmodic agents for people with IBS. These should be taken as required, alongside dietary and lifestyle advice. Alverine is an antispasmodic. The guideline has no recommendations on simeticone. However, this anti-foaming agent is available on general sale in the UK, marketed for the relief of symptoms of gastrointestinal gas. No combination products containing both treatments are available in the UK.

Methods

Ducrotte et al. (2013) conducted a pragmatic randomised controlled trial (RCT; n=436) in adults with moderate to severe IBS symptoms (IBS symptom severity score of 175 to 400) lasting between 1 year and 10 years. GPs (n=87) in France were randomly assigned to prescribe either on-demand alverine 60 mg plus simeticone 300 mg or to the physician's choice of usual treatment. The randomisation of physicians rather than patients was designed to avoid possible investigator bias that could arise if a GP treated both groups of patients.

In the on-demand alverine plus simeticone group, participants were instructed to take the treatment 3 times daily, before meals, until the end of the pain episode. In the usual care group, physicians were not allowed to prescribe alverine plus simeticone, but prescribed what they considered to be the most appropriate treatment, which could include antispasmodics. Irritant laxatives were not allowed for treatment of constipation in either group.

The primary endpoint was the change in total IBS quality-of-life score (measured by IBSQoL) after 6 months. Secondary endpoints included individual IBSQoL domains and change in symptom severity. Exclusion criteria were digestive disorders with organic or other causes, untreated endocrine disorders, or neurological disease. People were also excluded if they were treated with alverine plus simethicone in the 6 months before the study.

Results

The mean age of participants was 54 years and 73% were women. Participants had a mean duration of IBS of 6 years and a median of 5 abdominal pain episodes per year. In the usual treatment group, 58% were prescribed 1 treatment, 31% were prescribed 2 treatments and 9% were prescribed at least 3 treatments. Most people were prescribed an antispasmodic (94%), with 20% of people prescribed a laxative, 3% prescribed analgesics and 2% prescribed bulking agents.

The mean change in IBSQoL score (adjusted for baseline value) over 6 months was 13.8 in the alverine plus simeticone group compared with 8.4 in the usual care group. The between-group difference was therefore 5.4 (95% confidence interval [CI] 2.3 to 8.6, $p=0.0008$). Most of the individual domains of IBSQoL also showed significant between-group differences, including mental health, sleep, energy, food, and social life, (all $p\leq 0.01$). The effects on physical status, physical activity and sexual activity were not reported clearly, although they appear to not have shown significant differences between groups.

Severity of symptoms reduced over the course of the study in both groups, but the reduction was significantly greater in the alverine plus simeticone group than in the usual care group. The between-group difference was -59.3 (95% CI -77.8 to -40.8 , $p=0.0001$).

Adverse events were reported by 41% of people in both groups. The paper reported that no serious adverse events were drug-related, but did not report the number of serious adverse events.

Strengths and limitations

Strengths

This study was designed as a pragmatic trial to show effectiveness in a real-world setting, which increases the likelihood of the results applying to general practice in the UK. This study attempted to account for missing data, although the method, last observation carried forward, may not reliably account for patients' results at those times.

The study measured outcomes that were considered to be important in the guideline, and shows effectiveness of a combination of 2 widely available treatments.

Limitations

The authors intended to include 500 patients as indicated by their power calculation plus an allowance for drop-outs. However, actual recruitment was substantially lower with only 430

people analysed. This could have led to the study being underpowered to detect a difference between the groups, although the effect size was large enough for this not to be a problem.

Participants in each cluster may have similarities in baseline characteristics or response to treatments. However, the analysis did not appear to account for the cluster design. The use of last observation carried forward as a method for accounting for missing data may not accurately reflect participants' outcomes.

The study was funded by the manufacturer of the alverine plus simethicone combination product. However, it is not clear whether the effects were attributable to one of the components or the combination. Because 94% of people in the usual care group were prescribed antispasmodics it is possible that the simethicone was responsible for the effects. Yet, the possibility of the combination having synergistic effects cannot be ruled out.

Finally, the report included little detail on adverse events.

Impact on guideline

The prescription of on-demand alverine is consistent with current recommendations to consider prescribing antispasmodic agents to be taken as needed. Use of simethicone is not currently recommended by the guideline, but an update is not thought to be necessary at this time because simethicone is widely available in the UK without prescription.

Clinical management of IBS – ondansetron

We selected the RCT by [Garsed et al. \(2013\)](#) for a full commentary because it was conducted and funded in the UK and suggests that ondansetron may have effects on diarrhoea-predominant IBS. Ondansetron is a 5-HT₃ receptor antagonist used to prevent nausea and vomiting after chemotherapy, radiotherapy, or surgery. It does not have marketing authorisation for use in IBS in the UK.

What the guideline recommends

The guideline has no recommendations on ondansetron.

Methods

Garsed et al. (2013) conducted a crossover RCT (n=120) in adults (aged 18 to 75 years) with diarrhoea-predominant IBS. Participants were randomly assigned to either ondansetron then

placebo for 5 weeks each or to placebo then ondansetron for 5 weeks each. The dosage of ondansetron was 1 or 2 tablets (4 mg per tablet) taken 3 times daily. Participants underwent a 3-week dose titration period at the beginning of each stage of the study, and a 2 to 3 week washout period was used before the crossover.

Titration started at 1 capsule daily, and was increased if participants had diarrhoea and reduced if the participant became constipated. Loperamide 2 mg was allowed as rescue medication if participants had uncontrolled diarrhoea.

Participants had tests to exclude other causes of diarrhoea, and stopped any previously prescribed antidiarrhoeal drugs. Additionally, women who were pregnant or breastfeeding and people who had undergone abdominal surgeries (except for appendectomy or cholecystectomy) were excluded. The exclusion criterion 'being in the opinion of the investigator unsuitable' was not explained. A small sample of healthy volunteers (n=21) was also studied to obtain data for normal colon transit times.

The primary outcome was stool consistency, measured by the Bristol Stool Form score. Secondary outcomes included symptoms of IBS, including pain, frequency or urgency of defaecation and bloating. Outcome data values were average scores from the last 2 weeks of each treatment period.

Results

Stool form was significantly improved when people with IBS were taking ondansetron than when taking placebo (stool form difference -0.9 , 95% CI -1.1 to -0.6 , $p<0.001$). Additionally, the IBS symptom score was reduced significantly more (by 83 points) with ondansetron compared with placebo (by 37 points, 46 point between-group difference, $p=0.001$).

However, people with worse diarrhoea at baseline did not respond as much as those whose diarrhoea was less severe. In the lower quartile of diarrhoea severity (average stool form 4.9), ondansetron was associated with a difference in stool form of -1.0 (95% CI -1.3 to -0.7 , $p<0.001$). In the upper quartile of diarrhoea severity (average stool form 5.9), ondansetron was associated with a difference in stool form of -0.7 (95% CI -1.0 to -0.4 , $p<0.001$).

Gut transit time was 46 hours in healthy volunteers but only 16 hours when people with IBS were taking placebo. Ondansetron increased gut transit time by 10 hours (95% CI 6 to 14, $p<0.001$).

Constipation occurred in 9% of people taking ondansetron and 2% of people taking placebo. Reducing the dose of ondansetron resolved all cases of constipation. Other side effects seen in 1 or 2 people in each group included headache, rectal bleeding, backache and abdominal pain.

Strengths and limitations

Strengths

After the washout phase, before starting the second treatment phase, both groups showed a slight improvement in stool form from baseline of -0.2 points. Differences in symptoms were also seen from baseline but between-group differences were not significant. The authors noted this showed that symptoms at the start of the second treatment period were not affected by the treatment received in the first period.

Limitations

The study recruited the number of participants that their sample size calculation indicated was needed to detect a significant difference between groups. However, the intention-to-treat analysis excluded people who dropped out of the study, leaving 98 people for analysis. This may have been because no methods to account for missing data were used. This could have resulted in the trial being underpowered to detect a difference between groups, although results were statistically significant.

The study reported little data on adherence to treatment or dosage of ondansetron taken. The median number of tablets per day was reported, with fewer tablets taken in the ondansetron group than in the placebo group, (median 2, interquartile range 1 to 5). People could take up to 6 capsules daily, and it was not clear whether the low dosage actually taken was caused by poor adherence or whether this accurately represented the doses that participants were taking at the end of the titration period.

Another drug of this class, alosetron, was withdrawn because of severe constipation (in 25% of people taking alosetron), and rarely, ischaemic colitis, although it was reintroduced for limited use in some markets, such as the US. The short duration of the treatment phase of 5 weeks may not adequately show the long-term safety of ondansetron. Although oral ondansetron has not raised safety concerns, its licensed uses of preventing nausea and vomiting after surgery, chemotherapy or radiotherapy are short-term uses.

Impact on guideline

This study suggests that ondansetron may be useful for diarrhoea-predominant IBS. However, topic experts thought that the available data were not sufficient to update the guideline at this time. Another study of ondansetron in diarrhoea-predominant IBS was [recommended for funding](#) from the Efficacy and Mechanism Evaluation Programme of the Medical Research Council and National Institute for Health Research in June 2016. This new study may strengthen the case for using ondansetron in diarrhoea-predominant IBS.

How we made the decision

We check our guidelines regularly to ensure they remain up to date. We based the decision on surveillance 8 years after the publication of NICE's guideline on [irritable bowel syndrome \(CG61\)](#) in 2008.

For details of the process and update decisions that are available, see [ensuring that published guidelines are current and accurate](#) in developing NICE guidelines: the manual.

Previous surveillance [update decisions](#) for the guideline are on our website.

Evidence

We found 104 studies in a search for randomised controlled trials and systematic reviews published between 1 September 2013 and 18 July 2016. We also considered additional studies identified by members of the guideline committee who originally worked on this guideline.

We also considered evidence identified in previous surveillance 3 years and 6 years after publication of the guideline. This included 52 studies identified by search.

From all sources, we considered 156 studies to be relevant to the guideline.

We also checked for relevant ongoing research, which will be evaluated again at the next surveillance review of the guideline.

See [appendix A](#): summary of evidence from surveillance for details of all evidence considered, and references.

Views of topic experts

We considered the views of topic experts, including those who helped to develop the guideline and other correspondence we have received since the publication of the guideline.

Views of stakeholders

Stakeholders commented on the decision not to update the guideline. Overall, 2 stakeholders commented. See [appendix B](#) for stakeholders' comments and our responses.

One stakeholder agreed with the decision to not update the guideline but suggested minor amendments to existing recommendations on fibre consumption. However, evidence is insufficient to support such changes at this time. One commentator disagreed with the decision to not update the guideline and suggested adding guidance on intolerance to protein in cows' milk. However, evidence in people with IBS is insufficient to support an update decision at this time.

See [ensuring that published guidelines are current and accurate](#) in developing NICE guidelines: the manual for more details on our consultation processes.

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