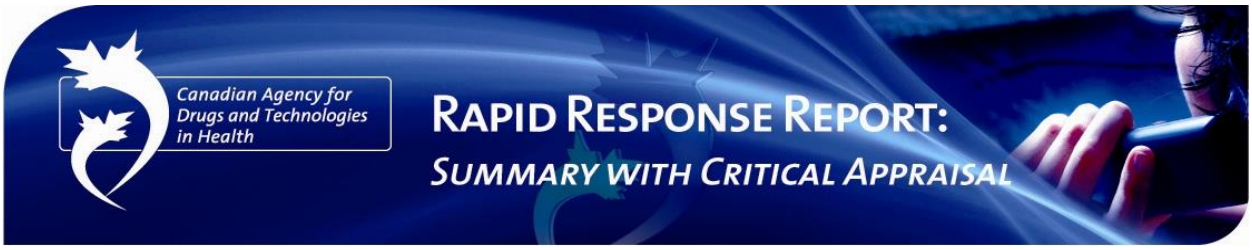

TITLE: Dicyclomine for Gastrointestinal Conditions: A Review of the Clinical Effectiveness, Safety, and Guidelines

DATE: 03 December 2015

CONTEXT AND POLICY ISSUES

Dicyclomine, also known as dicycloverine, is used to treat hypermotility in gastrointestinal (GI) conditions that involve smooth muscle spasm such as irritable bowel syndrome (IBS) which, according to US data, may affect 10-15% of the population[1,2] and ulcerative colitis.[3] Dicyclomine (Bentyl) is an antispasmodic and anticholinergic agent that relieves muscle spasms and cramping in the gastrointestinal tract by blocking the activity of acetylcholine on cholinergic receptors on the surface of muscle cells.[4] Bentyl (dicyclomine hydrocloride) is available in capsule or syrup form for oral use, or in aqueous solution for intramuscular injection, and is associated with side effects ranging from dry mouth, nausea, blurred vision and dizziness to severe constipation, stomach pain, confusion, palpitation, difficulty urinating and seizures.[5] Inappropriate anticholinergic use, including dicyclomine, was found in one in ten older adults in a recent US national cross-sectional study.[6] Dicyclomine abuse with signs of anticholinergic toxicities has also been reported.[7]

This Rapid Response report aims to review the clinical effectiveness and safety of dicyclomine for GI conditions. Evidence-based guidelines associated with the use of dicyclomine in the management of GI conditions will also be examined.

RESEARCH QUESTIONS

1. What is the clinical effectiveness and safety of dicyclomine for gastrointestinal tract conditions involving smooth muscle spasm?

2. What are the evidence-based guidelines for the use of dicyclomine for gastrointestinal conditions?

KEY FINDINGS

Recent evidence on the use of dicyclomine for GI tract conditions involving smooth muscle spasm is lacking. A limited amount of evidence published before 2005, identified in selected guidelines, has shown that dicyclomine is superior to placebo in improving IBS global assessment, and leads to more adverse events. Guidelines based on this evidence have recommended dicyclomine as a pharmacological treatment of IBS, as well as other antispasmodics such as mebeverine and alverine citrate. The recommendation was considered by the authors to be "definitive" based on low-quality evidence with uncertain trade-offs between benefits and harms.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2005 and October 27, 2015.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and examined the full-text publications for the final article selection. Selection criteria are outlined in Table 1.

Table 1: Selection Criteria

Population	Adults and adolescents with gastrointestinal conditions involving smoot muscle spasm (mucous colitis, spastic colon, irritable bowel syndrome, spastic constipation)
Intervention	Dicyclomine HCl (Bentyl)
Comparator	Any active comparator Placebo
Outcomes	Q1: Clinical effectiveness (also patient safety) Q2: Guidelines
Study Designs	Health technology assessments (HTA), systematic reviews (SR), and meta-analyses (MA), randomized controlled trials (RCTs), evidence-based guidelines.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria in Table 1, if they were published prior to January 2005, if they were duplicate publications of the same study, or if they were referenced in a selected systematic review. Guidelines that with unclear methodology or were not evidence-based were also excluded.

Critical Appraisal of Individual Studies

The quality of the included guideline was assessed using the AGREE checklist.[8] A numeric score was not calculated, instead the strengths and limitations of the study are summarized and presented narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 203 citations, with two additional citations identified from the grey literature search. After screening of abstracts from the literature search and from other sources, seven potentially relevant studies were selected for full-text review. After screening full texts, one evidence-based guideline on the management of irritable bowel syndrome, including the use of dicyclomine, is included in the review. The PRISMA flowchart in Appendix 1 details the process of the study selection.

Summary of Study Characteristics

The included evidence-based guideline was developed in 2007 by the Clinical Services Committee of the British Society of Gastroenterology on the management of irritable bowel syndrome (IBS). The guideline provided recommendations for the diagnosis of IBS as well as the treatment with dietary, psychological, or pharmacological interventions. In terms of pharmacological interventions, antispasmodics, tricyclic antidepressants, SSRIs (selective serotonin reuptake inhibitors), 5-HT_4 antagonists, 5-HT_3 antagonists, probiotics, antibiotics, and fibre supplements were considered in the guideline. Evidence was graded according to the quality of the evidence, with placebo-controlled RCTs being of highest quality. Evidence was categorized as “high”, “moderate”, “low” or “very low”. Recommendations were based on the trade-off between benefit and harm, and categorized as “net benefit”, “trade-off”, “uncertain trade-off”, or “no net benefits”. Final recommendations were characterized as “definitive” or “qualified”.

Summary of Critical Appraisal

The included guideline[9] had specific and unambiguous recommendations, with clearly described method of searching for and selecting the evidence, methods used to formulate the recommendations. The evidence search included multiple databases, though the criteria for selecting the evidence were unclear. Health benefits, and risks were stated, and procedures to update the guidelines were provided. Potential costs implications of applying the recommendations were included and patients’ view and preferences were sought. It is unclear whether the guideline was piloted among target users.

Details of the strengths and limitations of the included guideline are summarized in Appendix 2.

Summary of Findings

Main findings of included studies are summarized in detail in Appendix 3.

1. What is the clinical effectiveness and safety of dicyclomine for gastrointestinal tract conditions involving smooth muscle spasm?

There was no evidence identified on the clinical effectiveness and safety of dicyclomine for gastrointestinal tract conditions involving smooth muscle spasm.

2. What are the evidence-based guidelines for the use of dicyclomine for gastrointestinal conditions?

An evidence-based guideline was developed in 2007 by the Clinical Services Committee of the British Society of Gastroenterology on the management of IBS.[9] Antispasmodics, tricyclic antidepressants, SSRIs, 5-HT_4 antagonists, 5-HT_3 antagonists, probiotics antibiotics and fibre supplements were recommended for the treatment of IBS with different levels of quality evidence, benefits and harms, and strength of recommendation. The guideline suggested antispasmodic agents as first line pharmacological treatment of pain or bloating without distension associated with IBS. The guideline recommended dicyclomine as a pharmacological treatment of IBS, as well as other antispasmodics such as mebeverine and alverine citrate. The strength of the recommendation for the use of dicyclomine is ranked "definitive" ("*a judgment that most informed people would make*"; p 1771), the benefit/harm was ranked "uncertain trade-offs" ("*it is not clear whether the intervention does more good than harm*"; p 1771), and the quality of evidence was ranked "very low" ("*estimate of effect is very uncertain*"; p 1771).

Limitations

The limited number of studies included in the review caution the interpretation of the findings. The quality of the relevant guideline is summarized in the "summary of critical appraisal" section. The guideline fulfilled most criteria according to the AGREE checklist, but it is unclear whether the guideline was piloted among target users. The quality of the evidence on dicyclomine was ranked "very low", based on a single placebo-controlled RCT published in 1981. Recent evidence on the clinical effectiveness and safety of dicyclomine in the treatment of GI conditions is lacking.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Recent evidence on the use of dicyclomine for GI tract conditions involving smooth muscle spasm is lacking. Guidelines based on clinical evidence recommended dicyclomine as a pharmacological treatment of IBS, together with other antispasmodics such as mebeverine and alverine citrate. The strength of the recommendation for the use of dicyclomine is ranked "definitive", the quality of evidence was ranked "very low", and the benefit/harm was ranked "uncertain trade-offs".

A double-blind, randomized controlled trial (RCT) published by Page et al. in 1981 compared the clinical effectiveness and safety of dicyclomine to placebo in 97 patients (aged 18 to 65 years) with IBS.[10] Dicyclomine (40mg, four times a day) was found to be superior to placebo in the Physicians' Global Assessment (pain, tenderness, bowel habits and overall conditions) after two weeks of treatment (32/48 patients or 67% in the treatment group; 20/49 patients or 41% in the placebo group); the differences were statistically significant. 69% of patients on dicyclomine reported one or more adverse reactions as compared to 16% in the placebo group. The adverse reactions were related to the anticholinergic effect of dicyclomine and included primarily dry mouth, dizziness and blurred vision.

The RCT by Page et al. was the sole study on dicyclomine identified in a 2012 systematic review and meta-analysis of the effects of antispasmodic agents as compared to placebo in the treatment of IBS. The review included 18 RCTs (including 17 RCTs on different antispasmodic drugs and the single RCT on dicyclomine by Page et al.).[11] The pooled estimate of all studies showed patients in the antispasmodic treatment group experienced improvement on the IBS global assessment as compared to the placebo group (odds ratio [OR] 1.559; 95% confidence interval [CI] 1.33 to 1.83). The pooled estimate for adverse events showed an OR of 0.738 favoring placebo (95% CI 0.55 to 0.98), or a 26% higher risk of adverse reactions.

A double-blind RCT published by Grillage et al. in 1990 compared the clinical effectiveness of dicyclomine (10mg, three times a day) versus another anticholinergic agent mebeverine (135 mg, three times a day) in 71 young adults (aged 12 to 35 years) with a history of abdominal pain for at least three months.[12] There were no statistically significant differences in clinical global improvement scores between the 2 groups after 8 weeks of treatment. The mebeverine group experienced fewer attacks of pain (P = 0.05). 39% of the dicyclomine group versus 13% of the mebeverine group experienced a variety of adverse reactions such as nausea, diarrhea and agitation.

In summary, despite antispasmodics as a class having been shown to be more effective than placebo in the treatment of GI conditions such as IBS, recent evidence comparing the efficacy and safety of dicyclomine versus placebo or other antispasmodic drugs for GI conditions are lacking. Novel GI drugs such as lubiprostone, linaclotide and asimadoline are being tested in phase I to IV clinical trials, and seem to be more effective than placebo, and generally well tolerated in patients with IBS (there is no reported pooled estimate).[13] Further studies comparing the novel drugs to other pharmacological treatments such as antispasmodic agents in general, and dicyclomine in particular, may shed more light on the place of dicyclomine in the treatment of GI conditions.

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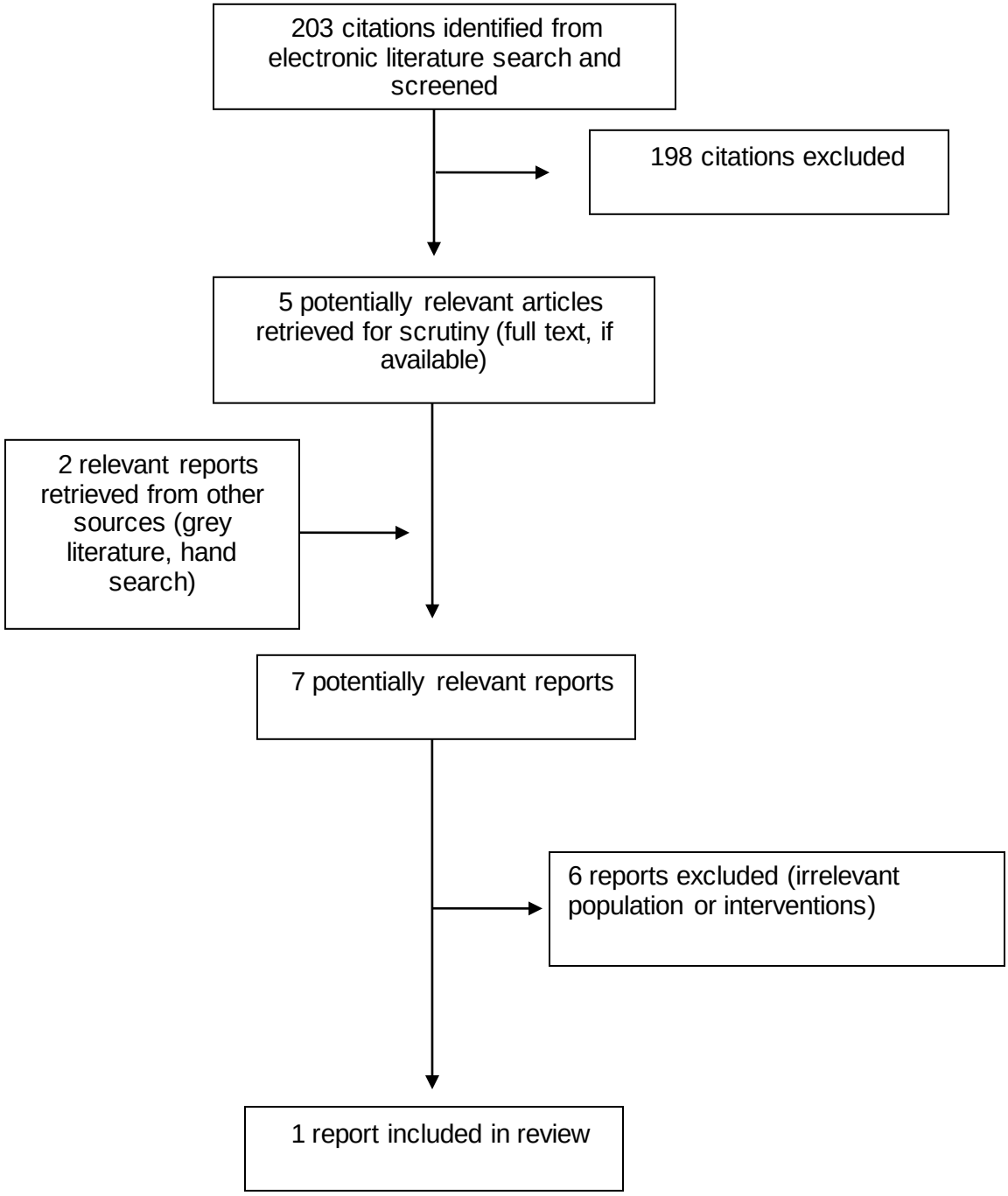
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Summary of Critical Appraisal of Included Study

Table A1: Summary of Critical Appraisal of Included Study		
Critical appraisal of included guidelines (AGREE[8])		
Spiller,[9] 2007	• scope and purpose of the guidelines are clear • the recommendations are specific and unambiguous • the method for searching for and selecting the evidence are clear • methods used for formulating the recommendations are clearly described • health benefits, side effects and risks were stated in the recommendations • procedure for updating the guidelines provided • target users of the guideline are clearly defined • patients' views and preferences were sought • potential cost implications of applying the recommendation were included	• unclear whether the guideline was piloted among target users

APPENDIX 3: Main Study Findings and Authors' Conclusions

Table A2: Main Study Findings and Authors' Conclusions

First Author, Publication Year	Main Study Findings	Authors' Conclusions
Research question 1 (clinical effectiveness and safety of dicyclomine for gastrointestinal tract conditions involving smooth muscle spasm)		
There was no evidence found on the clinical effectiveness and safety of dicyclomine for GI conditions		
Research question 2 (evidence-based guidelines on the use of dicyclomine for GI conditions)		
Spiller,[9] 2007	Dicyclomine for irritable bowel syndrome Strength of recommendation: definitive Benefit/harm: uncertain trade-offs Quality of evidence: very low	Not applicable