Helicobacter pylori eradication for Parkinson’s disease (Review)

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Helicobacter pylori eradication for Parkinson’s disease

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ABSTRACT

Background
Levodopa is the mainstay of treatment for alleviating the motor symptoms associated with Parkinson’s disease. However, patients often experience fluctuations in their symptoms over time and 'wearing off' which may be partly related to variable absorption of the drug. There is some evidence that treatment of the common gastrointestinal infection Helicobacter pylori (H pylori) with antibiotics may improve levodopa absorption in the gut and hence improve symptoms.

Objectives
1) What is the prevalence of H pylori in Parkinson’s disease patients?
2) Does treatment of H pylori infection with antibiotics improve symptoms in Parkinson's disease patients? Is this effect dependent on improvements in the absorption of levodopa?

Search methods
We searched electronic databases (including CENTRAL, MEDLINE, EMBASE, PsycINFO and CINAHL) and trial registers, hand-searched conference proceedings and carried out citation searching on key articles. All searching was updated in August 2009. We contacted authors to provide additional information where necessary.

Selection criteria
Clinical trials in patients with a well-defined definition of Parkinson’s disease and who were H pylori-positive. Two people independently selected studies for inclusion using predetermined criteria. We used recruitment figures from clinical trials and other studies identified from the searching to determine the prevalence of H pylori in Parkinson’s disease.

Data collection and analysis
Two authors abstracted data from the source papers and assessed methodological quality independently. We presented results descriptively.
**Main results**

Two completed and one ongoing clinical trial met the inclusion criteria. One trial (34 patients randomised) examined the effects of *H pylori* eradication on levodopa absorption and motor symptoms and found significant improvements in both. The ongoing trial has similar objectives and aims to recruit 100 patients. The other completed trial (20 patients analysed) sought to find a causal link between infection with *H pylori* and Parkinsonism and was non-contributory. A worsening of symptoms was noted with eradication failure.

The prevalence of *H pylori* in Parkinson's disease was reported in four studies and ranged from 37% to 59% which is similar to that of the general population.

**Authors' conclusions**

There is currently a lack of evidence on the effects of screening and treating *H pylori* in patients with Parkinson’s disease. There is limited evidence to suggest that *H Pylori* eradication improves the absorption of levodopa and improves motor symptoms. Results from an ongoing trial will inform the evidence base and will be incorporated in an update of this review. There is a need for well-conducted randomised controlled trials with standard outcome measures for motor symptoms and incorporating the costs of screening and treatment.

**Plain Language Summary**

[Does eradication of the organism *Helicobacter pylori* from the gut of patients with Parkinson's disease improve the absorption of the main drug used to treat patients symptoms?]

*Helicobacter pylori* (*H pylori*) is a common infection of the gut and is often associated with duodenal and gastric ulcers. The exact mechanism is unknown but there is some evidence that infection with *H pylori* can interfere with the absorption of some drugs in the gut. One such drug is levodopa, the main drug used to treat the motor symptoms of Parkinson's disease. Whilst levodopa is very effective for treating Parkinson's symptoms, after time it can become less effective in some patients which may be due to variable absorption. If *H pylori* is eradicated with the use of antibiotics then absorption of levodopa may be improved and in turn the patient's motor symptoms may be improved.

It is unknown how many people with Parkinson's disease are also infected by *H pylori* and this needs to be established. We searched the literature for all studies of *H pylori* and Parkinson's disease and found four studies which reported that between 37% and 59% of Parkinson's disease patients are *H pylori*-positive. This is similar to the rate in the general population.

We used clinical trials to see if treatment of *H pylori*-positive Parkinson's disease patients with antibiotics improved the absorption of levodopa and improved their motor symptoms. Only two completed trials were found from our searching. We did not pool these as they had different objectives and used different outcome measures. One of the trials reported a significant increase in levodopa absorption and improvement in motor symptoms when antibiotics were used to eradicate *H pylori*. The other completed trial did not have any usable results. A further trial of *H pylori* eradication in Parkinson's disease is still underway and the results, which are due in 2010, will help inform further studies.

Very little information was found about *H pylori* eradication in Parkinson's disease. More clinical trials are needed using standard measures of motor symptoms. It will be important also to look at the cost of both screening for *H pylori* and treatment of *H pylori* in Parkinson's disease patients to see if this is worthwhile.

**Background**

*Helicobacter pylori* eradication for Parkinson's disease (Review)  Copyright © 2011 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
compacta. Clinical features include resting tremor, bradykinesia, muscular rigidity and postural instability. Treatment of Parkinson’s disease focuses on the replacement of lost dopamine. The administration of levodopa (a precursor of dopamine) is the mainstay of treatment for Parkinson’s. Most patients on levodopa experience fluctuations in their motor responses, including a decrease in the duration of ‘on time’ and dyskinesia after some years of therapy (Fabbrini 1987). These motor fluctuations may be due in part to the variable delivery of levodopa across the blood brain barrier.

**Description of the intervention**

*Helicobacter pylori* (*H. pylori*) is a common bacterial infection of the gut. It is usually acquired in childhood and persists into adulthood, and is highly associated with duodenal and gastric ulcers (Graham 1992). The site of levodopa primary absorption is the duodenum (Kurlan 1988) and there is some evidence that treatment of *H pylori* infection with antibiotics improves the absorption of levodopa (Lahner 2009).

**How the intervention might work**

*H pylori* eradication in Parkinson’s disease may improve the absorption of levodopa and hence reduce fluctuations in motor responses, increasing the duration of ‘on time’. Various mechanisms have been proposed for the interaction between *H Pylori* and levodopa. An in-vitro study has demonstrated a direct interaction of levodopa with outer membrane proteins of *H Pylori* responsible for the adhesion to gastric epithelial cells (Niehues 2009). Another study suggests the direct utilisation of levodopa by *H Pylori* to maintain its ecological niche within the gastrointestinal tract (Lyte 2010). However, not all patients are infected with *H pylori* and very little is known about the prevalence of *H pylori* in Parkinson’s disease. The potential to improve symptoms will be affected by the numbers with Parkinson’s infected with *H pylori*. *H pylori* in the general population is distributed worldwide and prevalence varies by region with estimates ranging from 36% to 52% in Western Europe, 34% to 48% in North America and 61% to 76% in the Far East (Raghunath 2003). The prevalence of *H pylori* the general population also increases with age. In one study of 485 healthy asymptomatic volunteers in North America aged 15 to 80 years prevalence rose at a rate of 1% per year (Graham 1991).

**Why it is important to do this review**

Very little is known about the potential of *H pylori* eradication in Parkinson’s disease. The recent systematic review by Lahner and colleagues (Lahner 2009) examined the effects of *H pylori* eradication on drug absorption, where levodopa was one of three drugs identified from their literature searching. We aimed to update and expand this systematic review by also exploring the prevalence of *H pylori* in Parkinson’s disease, and the potential effects of *H pylori* eradication on motor symptoms as well as levodopa absorption.

**OBJECTIVES**

The following questions were addressed:

1. What is the prevalence of *H pylori* in Parkinson’s disease patients? We sought epidemiological studies and recruitment figures for clinical trials to address this question.

2. Does treatment of *H pylori* infection with antibiotics improve symptoms in Parkinson’s disease patients? Is this effect dependent on improvements in the absorption of levodopa? We sought secondary prevention trials to address this question.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

*Prevalence of *H pylori* in Parkinson’s disease*  
Epidemiological studies and recruitment figures for clinical trials.

*H pylori* eradication in Parkinson’s disease  
Randomised controlled trials and clinical controlled trials (non-randomised).

**Types of participants**  
All adults with a diagnosis of Parkinson’s disease using validated criteria who test positive for *H pylori*.

**Types of interventions**  
Standard triple antibiotic therapy to eradicate *H pylori*.

**Types of outcome measures**  
Change in Parkinson’s disease symptoms using validated scales and measurement tools including ‘on/off time’, Unified Parkinson’s Disease Rating Scale (UPDRS), quality of life. Any adverse events of antibiotic treatment will also be noted. Measures of levodopa absorption.
Search methods for identification of studies

We searched the following electronic databases: MEDLINE, EMBASE, PsycINFO, CINAHL, BNI (from the NLH), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2009, issue 3), and NHS Centre for Reviews and Dissemination (CRD) databases (Health Technology Assessment (HTA) and Database of Abstracts of Reviews of Effects (DARE)). All databases were searched from inception and searches were updated on 25th May 2011.

In addition, we checked reference lists of reviews and retrieved articles for additional studies. We searched trial registers for ongoing clinical trials. We performed citation searches on key articles and handsearched conference proceedings from the 6th to 13th International Conferences of Parkinson’s Disease and Movement Disorders (years 2000 to 2009) for additional relevant articles. We contacted authors where necessary for additional information. The search strategy developed for MEDLINE is presented in Appendix 1. Searches were tailored to other bibliographic databases.

Data collection and analysis

Selection of studies

From the searches, one author (KR) reviewed the title and abstract of each paper and retrieved potentially relevant references. Following this initial screening, two review authors (KR, RS) independently selected studies to be included in the review using predetermined inclusion criteria. In all cases disagreements about any study inclusion were resolved by consensus and a third review author was consulted if disagreement persisted (YBS).

Data extraction and management

Two review authors (KR, RS or SP) extracted data independently using a proforma and contacted chief investigators to provide additional relevant information if necessary. We extracted details of the study design, participant characteristics, study setting, intervention, dropouts, outcome data including details of outcome assessment, adverse effects and methodological quality from each of the included studies. We also extracted data on recruitment to clinical trials to estimate the prevalence of Helicobacter pylori in Parkinson’s disease. We extracted information from other studies identified from the searching reporting the prevalence of Helicobacter pylori in Parkinson’s disease. We resolved disagreements about extracted data by consensus.

Assessment of risk of bias in included studies

All studies that met the inclusion criteria for the Helicobacter pylori eradication review were randomised controlled trials. We assessed methodological quality in terms of the randomisation procedure, concealment of allocation, blind assessment of outcomes and losses to follow up. We did not use the ‘Risk of bias’ tables and study quality is described in the text.

Further studies identified to determine the prevalence of Helicobacter pylori in Parkinson’s disease patients used survey methods and were not formally assessed for methodological quality.

Measures of treatment effect

We report information on the prevalence of Helicobacter pylori in Parkinson’s disease descriptively.

It was not appropriate to pool the data from individual studies of Helicobacter pylori eradication, as one study is still ongoing, and the two completed trials included in the review had different objectives and reported different outcomes. We therefore report the results descriptively.

Assessment of heterogeneity

We conducted no formal statistical pooling but we considered differences in the participants and interventions to be possible explanations for heterogeneity between studies.

Subgroup analysis and investigation of heterogeneity

Stratified analyses were not possible due to the small number of studies included in the review.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

Searching the electronic databases yielded 114 references. Two relevant studies were found by handsearching Movement Disorders abstracts, and one ongoing trial was found in a trial register. Eight studies went forward for formal inclusion/exclusion for the review of Helicobacter pylori eradication in Parkinson’s disease. Three studies (4 reports) met the inclusion criteria. Three further studies were identified as providing information on the prevalence of Helicobacter pylori in Parkinson’s disease.
Included studies

Full details of the studies included in the review of *H pylori* eradication in Parkinson's disease are shown in the Characteristics of included studies table.

Excluded studies

We excluded four studies from the review of *H pylori* eradication in Parkinson's disease. Reasons for exclusion are presented in the Characteristics of excluded studies table.

Risk of bias in included studies

We assessed the methodological quality of the included trials by means of the method of randomisation and allocation concealment, blinding, and losses to follow up. In the two completed RCTs, the method of randomisation and allocation concealment was clear and adequate in one trial (Pierantozzi 2006) and unclear in the other (Bjarnason 2005). For both trials, the authors stated that both patients and outcome assessors were blind to allocation. Losses to follow up occurred exclusively in the intervention groups in both trials. Loss to follow up due to non-compliance was 10% in both trials. In addition, adverse effects resulted in a further 20% loss to follow up in the Bjarnason trial (Bjarnason 2005, see section on adverse effects below).

For the ongoing trial, there are few details of methodological quality to date (Szumski 2008) with the exception that the authors state the trial will be double-blind.

Effects of interventions

Prevalence of *H pylori* infection in Parkinson's disease

Through literature searching for all studies of *H pylori* in Parkinson's disease, we found four studies reporting estimates of the prevalence of *H pylori* in this patient group.

The first study by Dobbs et al (Dobbs 2000) examined serum *H pylori* anti-urease-IgG antibody levels in 105 patients with idiopathic Parkinson's disease and 210 without Parkinson's disease from the same location in the UK. Overall, they found 48% of patients with Parkinson's to be seropositive and 40% of the controls. The authors found an age-dependent increase in *H pylori* infection in the control group (< 72.5 years 32%, ≥ 72.5 years 54%) but not in Parkinson's disease patients (< 72.5 years 52%, ≥ 72.5 years 44%). This differential age trend was not due to differences in social class. The antibody titre in women was 76.3% (61.5, 94.7) of that in males irrespective of age or disease status. Patients with Parkinson's disease were more likely to be seropositive (OR 2.0; 95% CI 1.0 to 2.2, P < 0.04) before 72.5 years of age.

The second study by Tsuboi and Yamada (Tsuboi 2008) examined serum *H pylori* antibody in 51 patients with Parkinson's disease in Japan (19 men, 32 women, mean age 67 (SD 7.4) years, disease duration 6.3 (3.9) years, Hoehn and Yahr stage 2.2 (1.0)). The overall prevalence of *H pylori* infection in Parkinson's disease patients was 57%. *H pylori* infection was not related to BMI, serum lipids or UPDRS part III scores, but the disease progression rate assessed by UPDRS motor score/disease duration (years) was worse in the *H pylori* infected group than the non-infected group (P = 0.04).

The authors concluded that *H pylori* infection may worsen clinical progression of motor signs in Parkinson's patients.

The third study (Wlodarek 2003) examined the prevalence of *H pylori* infection in 58 Parkinson's disease patients from Poland and 26 of their spouses using the 13C urea breath test. Thirty-four (59%) Parkinson's patients were *H pylori*-positive, a similar percentage to their spouses. The authors comment that the prevalence of *H pylori* in the general population in Poland is high (estimates range from 60% to 95%).

The fourth study by Pierantozzi (Pierantozzi 2006) is a RCT of *H pylori* eradication from Italy, included in the section below. For the trial, 79 patients meeting Parkinson's disease brain bank criteria and on levodopa monotherapy with motor fluctuations were screened for *H pylori* infection. Forty-eight patients were negative using non-invasive tests (serology, stool sample), and two further patients were negative following upper gastrointestinal endoscopy. Twenty-nine of 79 or 36.7% Parkinson's disease patients were *H pylori*-positive.

An ongoing RCT (Szumski 2008) examining the effects of *H pylori* eradication on motor fluctuations in Parkinson's disease aims also to identify the frequency of *H pylori* in Parkinson's using standard laboratory assays. The study is based in the USA. The trial started in January 2008 and results are expected in 2010.

*H pylori* eradication in Parkinson's disease

Two RCTs and one ongoing RCT met the inclusion criteria. One RCT (Pierantozzi 2006) and the ongoing RCT (Szumski 2008) examined the effects of *H pylori* eradication on the absorption of levodopa and motor symptoms. The other RCT (Bjarnason 2005) examined the effects of *H pylori* eradication on motor symptoms independently of the effect on levodopa absorption (use of levodopa was an exclusion criteria in this trial).

The ongoing trial (Szumski 2008) is yet to report preliminary findings, so data from this study will be incorporated in an update of this review. The purpose of the trial is to determine whether treatment of *H pylori* improves treatment effectiveness in patients with Parkinson's disease and motor fluctuations. Patients recruited have to be on levodopa therapy with demonstrable medication efficacy but with a ‘wearing off’ phenomenon present between levodopa doses, and be positive for *H pylori* IgG antibody by serum ELISA. It is a placebo-controlled, double-blind, parallel-group randomised trial using standard triple antibiotic therapy for *H pylori* eradication.
tion. The primary outcome is total daily ‘off time’ (measured by patient symptom diaries) and secondary outcomes are UPDRS total scores and UPDRS motor scores ‘on’ and ‘off’, quality of life (PDQ-39) and side effects profile.

The two completed trials have different objectives and report different outcomes, so results are presented descriptively. Pierantozzi et al (Pierantozzi 2006) reports a RCT in a group of 34 H pylori infected patients (confirmed by endoscopy) with Parkinson's disease on levodopa monotherapy with motor fluctuations. The purpose of the trial was to examine the effect of H pylori eradication on levodopa absorption and motor symptoms. The intervention was standard triple antibiotic therapy for H pylori eradication; the comparison group was the antioxidant allopurinol. The purpose of using an anti-oxidant in the comparison group of this trial was to determine whether a negative effect of H pylori infection on levodopa absorption was due to oxidative stress (Pietroistuti 2008). Allopurinol was accepted as a surrogate placebo according to our inclusion criteria as in this trial, and in another (Salim 1993), it was shown to have no effect on H pylori eradication. The serum levodopa concentration area under the curve for both the 0 to 4 hours protocol and 0 to 11 hours protocol (daily plasma levodopa concentration time curve) was significantly higher in the antibiotic group in comparison with the antioxidant group at both short-term (one week) and longer-term (three months) follow up. The global clinical score (the sum of all rated UPDRS motor scores) was significantly lower in the antibiotic group at one week and three months (global clinical score (range from 1 to 1620). At three months the score was 333.5 (32.9) in the antibiotic group versus 619.7 (80.5) in the anti-oxidant group for the 0 to 11 hours protocol). The total ‘on time’ duration was significantly longer in the antibiotic than the antioxidant group both at one week and three months (total ‘on time’ duration (hours) at three months was 10.6 (0.8) in the antibiotic group versus 2.8 (1.4) in the antioxidant group for the 0 to 11 hours protocol).

The objective of the Bjarnason study (Bjarnason 2005) was to obtain proof-of-principle that infection with H pylori contributes to idiopathic parkinsonism. It was a randomised, placebo-controlled, double-blind efficacy study of H pylori eradication on the time course of motor symptoms in Parkinson's disease. Patients included in the trial were H pylori-positive (confirmed by endoscopy) and did not use levodopa. The intervention was standard triple antibiotic therapy for H pylori eradication. Follow up was at one year when de-blinding occurred and patients on placebo were offered open-active treatment. Follow up is planned for five years post-eradication. The primary outcome measure was mean stride length at free walking speed which was assessed every six weeks. Secondary outcome measures were measures of rigidity and postural instability. The planned sample size was 56 patients but recruitment was halted at 31 because two patients had marked deterioration in their mean stride length with eradication failure. Interim analyses were performed on the 20 patients who had reached de-blinding at one year. Two further patients had marked deterioration in symptoms with eradication failure after de-blinding (see adverse effects section below). The authors found a significant increase in the estimated change in mean stride length with H pylori eradication compared to placebo (59 mm; 95% CI 18 to 100 versus -10 mm; 95% CI -54 to 34), mean torque to flex (a measure of rigidity) and percentage body sway. The authors conclude that their results point to a direct or surrogate role of H pylori infection in the pathogenesis of idiopathic Parkinson's disease.

Adverse effects of H pylori eradication

Bjarnason's trial (Bjarnason 2005) reports marked deterioration of Parkinson's disease symptoms with H pylori eradication failure in four patients. The mean time course for stride length (their primary outcome) in those patients where eradication failed was -243 mm/year (95% CI -427 to -60) versus 45 mm/year (95% CI -10 to 100) where eradication had been successful. The authors decided to halt recruitment for the trial following these adverse effects.

Eradication failure occurred in two patients in the Pierantozzi trial (Pierantozzi 2006). In these patients, the global clinical score and ‘on time’ did not improve as they did in all other patients who had successful H pylori eradication between follow up at one week and three months. However, there was no evidence of a marked deterioration of symptoms as reported by the Bjarnason trial.

Discussion

Very few studies met the inclusion criteria for this review. Four studies reported the prevalence of H pylori infection in Parkinson's disease patients, and two completed and one ongoing clinical trial examined H pylori eradication in Parkinson's disease.

Estimates for the prevalence of H pylori infection in the general population vary considerably by region and increase with increasing age (Graham 1991; Raghunath 2003). Estimates in patients with Parkinson's disease from the four studies identified from our searching range from 37% (Pierantozzi 2006) to 59% (Wlodarek 2003), demonstrating that levels in this patient population are broadly similar to those in the general population. Each study was conducted in a different country and as prevalence rates vary by region it is difficult to compare the studies directly. The largest study reporting prevalence rates in Parkinson's disease patients was from the UK and found 48% to be H pylori-positive (Dobbs 2000). Results from the ongoing clinical trial will provide further information on the prevalence of H pylori in Parkinson's disease (Szumski 2008).

One completed (Pierantozzi 2006) and one ongoing (Szumski 2008) clinical trial address the effects of H pylori eradication on the absorption of levodopa and motor symptoms in Parkinson's disease. The completed trial showed significant improvements in
levodopa absorption and motor symptoms (using the global clinical scale) with \textit{H pylori} eradication (Pierantozzi 2006). This trial also found a benefit of ‘on time’ of nearly eight hours with eradication (for their 0 to 11 hours protocol) which is very large and would be clinically significant for patients if confirmed in large-scale trials. The authors chose to use the anti-oxidant allopurinol as their comparison group rather than placebo. The reason for this was to explore further the mechanism by which \textit{H pylori} infection interferes with levodopa absorption. The authors hypothesised that this could be mediated by the increased local oxidative stress linked to \textit{H pylori} infection (Pietroiusti 2008). Allopurinol does not eradicate \textit{H pylori} but may antagonise its oxidant effects. The authors found no beneficial effect of allopurinol and concluded that the adverse effect of \textit{H pylori} infection on levodopa absorption was probably not mediated by oxidative stress (Pietroiusti 2008). Given that allopurinol has no effect on \textit{H pylori} infection on levodopa absorption was probably not mediated by oxidative stress (Pietroiusti 2008). None of the included studies reported adverse effects associated with antibiotic treatment, but one reported worsening of Parkinson’s disease symptoms associated with eradication failure (Bjarnason 2005). Eradication failure was not associated with a worsening of symptoms in the other completed trial (Pierantozzi 2006).

We await the results of the ongoing trial with interest where further information will be available on \textit{H pylori} prevalence in Parkinson’s disease, the effects of \textit{H pylori} eradication on levodopa absorption and motor symptoms, and any adverse effects. These results will be incorporated in an update of this review.

\section*{Authors’ Conclusions}
\subsection*{Implications for Practice}
At present no recommendations can be made regarding widespread screening for \textit{H pylori} infection and \textit{H pylori} eradication in Parkinson’s disease patients. There is limited evidence to suggest that \textit{H pylori} eradication improves the absorption of levodopa and improves motor symptoms. Results from an ongoing trial will add to this evidence base (Szumski 2008). The potential benefits of \textit{H pylori} eradication need to be balanced against the costs of screening and treatment.

\subsection*{Implications for Research}
Results to date suggest that the prevalence of \textit{H pylori} infection in Parkinson’s disease is broadly similar to that in the general population. Further information will come from the recruitment figures for the ongoing trial of \textit{H pylori} eradication (Szumski 2008). Only three trials met the inclusion criteria for \textit{H pylori} eradication in Parkinson’s disease. One of these is still to report their results and the completed trials had different objectives and outcomes. There is a need for well-conducted RCTs with standard outcome measures for motor symptoms, incorporating costs of screening and treatment, and also potential adverse effects associated with eradication failure.

\section*{Acknowledgements}
We would like to thank Dr Pietroiusti for providing the data from the figures for the Pierantozzi 2006 trial and Lucyna Kwasniewska, Scientist, Campden BRI, for translating a study from Polish to English.
References to studies included in this review

Bjarnason 2005 [published data only]

Pierantozzi 2006 [published and unpublished data]

Szumski 2008 [unpublished data only]

References to studies excluded from this review

Borgohain 2008 [published data only]

Lee 2008 [published data only]

Pierantozzi 2001 [published data only]

Pierantozzi 2001a [published data only]

Additional references

Dobbs 2000

Fabbrini 1987

Graham 1991

Graham 1992

Hardoff 2001

Kurlan 1988

Lahner 2009

Lyte 2010

Niehues 2009

Pietroiusti 2008
Raghunath 2003

Salim 1993

Tsubo 2008

Wlodarek 2003

* Indicates the major publication for the study
### Characteristics of included studies  
**[ordered by study ID]**

#### Bjarnason 2005

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised controlled trial of parallel-group design. Double-blind, placebo controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Patients diagnosed with definite idiopathic Parkinson's disease and <em>H pylori</em> positive, confirmed by endoscopy. Exclusion criteria were: use of levodopa, secondary parkinsonism, other progressive disorders affecting physical ability, clinical depression or dementia, other specific neurological condition, cardiovascular or respiratory symptoms during normal activities, UK MRC muscle strength score of &lt; 4/5, concurrent therapy with drugs which might be antidopinergic, or with hypnotics or sedatives, recent change in life situation, serious pathology such as ulcer or neoplasm at endoscopy. Analysis carried out on 10 patients randomised to <em>H pylori</em> eradication (mean age 59 (38 to 80) years, 22.2% men), and 11 patients randomised to placebo (mean age 62 (41 to 83), 72.7% men)</td>
</tr>
<tr>
<td>Interventions</td>
<td>Standard triple antibiotic therapy for <em>H pylori</em> eradication: omeprazole 20 mg, clarithromycin 500 mg and amoxicillin 1 g, twice daily for 1 week. The placebo was matched to the capsules/tablets of the active drugs. Compliance was checked by telephone</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Follow-up at 1 year. Assessments made every 6 weeks and the change over the course of the year was reported for each outcome. The primary outcome was mean stride length (a measure of hypokinesia). Secondary outcomes were measures of rigidity (torque extension/flexion, mean torque to extend, mean torque to flex) and postural instability (body sway, mean foot separation)</td>
</tr>
<tr>
<td>Notes</td>
<td>The objectives of this trial and outcome measures are very different from those of the other 2 trials included in this review</td>
</tr>
</tbody>
</table>

#### Pierantozzi 2006

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised controlled trial of parallel-group design. Double-blind. Comparison group is antioxidant therapy (considered a surrogate placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Patients diagnosed with idiopathic Parkinson's disease using UK brain bank criteria, on levodopa monotherapy and showing motor fluctuations or wearing off phenomenon. <em>H pylori</em> positive by serology and stool testing and confirmed by endoscopy. Exclusion criteria: no gastric diseases, no concomitant neurologic disease, no use of anti-Parkinson drugs excepting levodopa, no use of drugs potentially affecting gastrointestinal (GI) motility and integrity, negative history of gastric lesions and surgery. 36 patients included, Hoehn &amp; Yahr stage 2 to 3, mean duration of PD 7.2 (1.9) years. 19 patients randomised to antibiotics (mean age 64.9 (9.6) years, 47% men) and 17 patients randomised to antioxidant therapy (mean age 66.3 (6.9) years, 47% men)</td>
</tr>
<tr>
<td>Interventions</td>
<td>Standard triple antibiotic therapy for <em>H pylori</em> eradication: omeprazole 20 mg, clarithromycin 500 mg and amoxicillin 1 g, for 1 week. Antioxidant therapy - allopurinol 100 mg for 15 days</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Follow up at 1 week and 3 months. Outcomes include measures of levodopa absorption (serum levodopa concentration area under the curve (AUC), time to maximum plasma levodopa concentration), and motor symptoms (global clinical score - total UPDRS III motor scores)</td>
</tr>
</tbody>
</table>
Notes
The antioxidant allopurinol was accepted as a surrogate placebo in our inclusion criteria, as in this trial, and in another (Salim 1993), it was shown to have no effect on H pylori eradication.

Szumski 2008
Methods
Randomised controlled trial of parallel-group design. Double-blind, placebo-controlled. Ongoing trial

Participants
Patients diagnosed with idiopathic Parkinson's disease, Hoehn &Yahr stage 2 to 4 in the 'off' state. Levodopa therapy required. Stable therapy with demonstrable efficacy but with wearing off phenomenon between levodopa doses. Positive for H pylori IgG antibodies by serum ELISA. Exclusion criteria are: other neurologic disease, current abdominal pain, unexplained nausea/vomiting or GI bleeding, history of gastric cancer, peptic or duodenal ulcer or other gastric or duodenal lesions, history of previous gastric surgery, history of previous brain surgery for PD, family history of gastric cancer, prior treatment for H pylori, recent use of proton-pump inhibitor, amoxicillin or clarithromycin, allergy or sensitivity to antibiotics, use of drugs affecting gastric motility, inability to participate in the morning in an “off” state, inability to communicate in English and pregnancy

Interventions
Standard triple antibiotic therapy (clarithromycin, amoxicillin and omeprazole) for H pylori eradication

Outcomes
Primary outcome is total daily “off” time according to patients symptom diaries. Secondary outcome measures are UPDRS total scores and UPDRS part III (motor) scores “on” and “off”, quality of life (PDQ-39) and side effects

Notes
Ongoing trial. Results are expected in 2010.

GI: gastrointestinal; MRC: Medical Research Council; PD: Parkinson's disease; PDQ-39: Parkinson's Disease Questionnaire; UPDRS: Unified Parkinson's Disease Rating Scale

Characteristics of excluded studies [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borgohain 2008</td>
<td>This study is not a randomised controlled trial or controlled clinical trial. It is a before and after study and so is therefore excluded from this review</td>
</tr>
<tr>
<td>Lee 2008</td>
<td>This study is not a randomised controlled trial or controlled clinical trial. It is a before and after study and so is therefore excluded from this review</td>
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<td>Pierantozzi 2001</td>
<td>This study is not a randomised controlled trial or controlled clinical trial. It is a before and after study and so is therefore excluded from this review</td>
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<tr>
<td>Pierantozzi 2001a</td>
<td>This study is not a randomised controlled trial or controlled clinical trial. It is a before and after study and so is therefore excluded from this review</td>
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</table>
DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. MEDLINE search strategy
1) exp HELICOBACTER PYLORI/ OR exp HELICOBACTER INFECTIONS/
2) Pylori.ti,ab
3) Helicobacter*.ti,ab
4) (H AND Pylori).ti,ab
5) 1 OR 2 OR 3 OR 4
6) exp PARKINSON DISEASE/
7) (Parkinsons AND disease).ti,ab
8) Parkinson*.ti,ab
9) 6 OR 7 OR 8
10) 5 AND 9

HISTORY

Protocol first published: Issue 4, 2010
Review first published: Issue 11, 2011

CONTRIBUTIONS OF AUTHORS

All authors contributed to the protocol development. Karen Rees ran the searches and screened the results of the searching for potential studies for inclusion. Karen Rees and Rebecca Stowe or Smitaa Patel assessed studies for inclusion, abstracted data and assessed quality of the included studies. Karen Rees performed the analyses and wrote the review. All authors contributed to discussions regarding the results and made comments and revisions to the final draft.

DECLARATIONS OF INTEREST

None
SOURCES OF SUPPORT

Internal sources

• Parkinson’s Disease Society, UK.
• Birmingham Clinical Trials Unit, University of Birmingham, UK.

External sources

• No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

It was our intention to pool the studies statistically and to perform stratified analyses to explore the impact of case definition, disease severity and method and assessment of H pylori eradication. It was also our intention to undertake funnel plots and tests of asymmetry to assess possible publication bias. None of these analyses were possible due to the lack of trials included in the review.

INDEX TERMS

Medical Subject Headings (MeSH)

*Helicobacter pylori; Anti-Bacterial Agents [*therapeutic use]; Antiparkinson Agents [pharmacokinetics; *therapeutic use]; Helicobacter Infections [*drug therapy; epidemiology]; Levodopa [pharmacokinetics; *therapeutic use]; Parkinson Disease [*drug therapy; metabolism]; Randomized Controlled Trials as Topic

MeSH check words

Humans