Summary statement of the proposal for deletion

Antacids are oral medicines to relieve heartburn, sour stomach, or acid indigestion. They work by neutralizing excess stomach acid. They mainly consist of aluminum, calcium or magnesium salts. Some antacids, such as aluminum carbonate and aluminum hydroxide, may be prescribed with a low-phosphate diet to treat hyperphosphatemia and/or to prevent the formation of some kinds of kidney stones. These medicines are widely available without a prescription. Long term use of these formulations may cause or exacerbate renal insufficiency (especially in patients with renal insufficiency) and metabolic alkalosis.

Despite lack of systematic data on efficacy of these medicines, they have been used for decades in management of dyspepsia and the gastroesophageal reflux disease (GERD). However, currently most up to date clinical guidelines recommend use of proton-pump inhibitor (PPI) medicines or histamine H$_2$ receptor antagonists for suppression of gastric acid secretion to control symptoms and prevent complications of dyspepsia and GERD.

With widespread availability and demonstrated efficacy and safety of PPIs and histamine H$_2$ receptor antagonists these medicines (especially PPIs) are the recommended first line antisecretary therapy in dyspepsia. Today antacids have no place in current and updated clinical guidelines for management of dyspepsia with or without H. Pylori, GERD and peptic ulcer disease.

Therefore due to:

- lack of comparative efficacy data
- availability of alternative efficient and cost effective medicines (H$_2$ receptor antagonists and PPIs)
- evidence of non superiority over placebo
- comparatively higher probability of side effects and drug interactions
- lack of universal formulation/preparation

antacids are not "essential" medicines and could be removed from WHO model list of essential medicines.
**Summary of evidences**

*Pharmacology and Clinical applications of Antacids (1-2)*

Antacids are weak bases that react with gastric hydrochloride acid to form a salt and water. After a meal approximately 45 mEq/h of hydrochloride acid is secreted. A single dose of 156 mEq of antacid given 1 hour after a meal neutralizes the acid for up to 2 hours. However, the acid neutralization capacity among different formulation of antacids is highly variable. Formulations containing magnesium hydroxide or aluminum hydroxide are among the most commonly marketed antacids. Usual dose is about 10-20 ml 4 times a day.

The clinical use of antacids is based on their ability to increase the pH of gastric secretions. With usual doses, antacids could maintain gastric pH above 4–5. Antacids, in decreasing order of their ability to neutralize a given amount of acid, are calcium carbonate, sodium bicarbonate, magnesium salts, and aluminum salts. Magnesium hydroxide and aluminum hydroxide are the most potent magnesium and aluminum salts. Magnesium oxide has essentially the same acid neutralizing effect as magnesium hydroxide.

Sodium bicarbonate rapidly reacts with hydrochloric acid to form sodium chloride, carbon dioxide, and water; excess bicarbonate that does not neutralize gastric acid rapidly empties into the small intestine and is absorbed. Mild metabolic alkalosis occurs; in patients with normal renal function, the kidneys excrete the excess sodium and bicarbonate ions and the urine becomes alkaline. Antacids other than sodium bicarbonate generally do not cause metabolic alkalosis, because the cation formed in the stomach is minimally absorbed and regains a basic anion in the small intestine.

Calcium carbonate is slowly solubilized in the stomach and reacts with hydrochloric acid to form calcium chloride, carbon dioxide, and water. About 90% of the calcium chloride formed is converted to insoluble calcium salts (mainly calcium carbonate and to a lesser extent calcium phosphate) and calcium soaps in the small intestine and is not absorbed. When calcium carbonate is administered orally, a limited amount of calcium and intestinal bicarbonate are absorbed and hypercalcemia may occur. In some patients, metabolic alkalosis and the milk-alkali syndrome may occur. Calcium is excreted by the kidneys and hypercalcemia frequently occurs in patients receiving calcium carbonate.

Aluminum hydroxide or oxide is slowly solubilized in the stomach and reacts with hydrochloric acid to form aluminum chloride and water. In addition to forming aluminum chloride, dihydroxyaluminum sodium carbonate and aluminum carbonate form carbon dioxide, and aluminum phosphate forms phosphoric acid. About 17–30% of the aluminum chloride formed is absorbed and is rapidly excreted by the kidneys in patients with normal renal function. Aluminum-containing antacids (except aluminum phosphate) also combine with dietary phosphate in the intestine forming insoluble, nonabsorbable aluminum phosphate which is excreted in the feces. If phosphate intake is limited in patients with normal renal function, aluminum antacids (except aluminum phosphate) decrease phosphate absorption and hypophosphatemia and hypophosphaturia may occur; calcium absorption is increased.

Magnesium hydroxide rapidly reacts with hydrochloric acid to form magnesium chloride and water. About 15–30% of the magnesium chloride formed is absorbed and is rapidly excreted by the kidneys in patients with normal renal function. Any magnesium hydroxide that is not converted to magnesium chloride in the stomach is presumably subsequently changed in the small intestine to soluble but poorly absorbed salts. Magnesium hydroxide binds bile salts in vitro, but to a much lesser
extent than does aluminum hydroxide. Magnesium-containing antacids have a laxative action.

Antacid-induced increases in gastric pH inhibit the proteolytic action of pepsin, an effect which is particularly important in patients with peptic ulcer disease. The optimum pH for pepsin activity is 1.5–2.5 and progressive inhibition occurs as gastric pH increases; above pH 4, the proteolytic activity of pepsin is minimal.

Antacids do not coat the lining of peptic ulcers or the GI mucosa. Although some antacids, such as aluminum hydroxide, have astringent and demulcent actions, these effects are probably not important in the treatment of peptic ulcers. With larger doses than those used for the antacid effect, magnesium hydroxide (magnesia) and magnesium oxide antacids produce a laxative effect.

Antacids have been used for decades, mainly as OTC medicines, in the treatment of patients with dyspepsia and acid peptic disorders. Long term use of these formulations may cause or exacerbate renal insufficiency (especially in patients with renal insufficiency) and metabolic alkalosis (1-2). All antacids may affect absorption of other medications by binding to the drug and reducing its absorption or by increasing intragastric pH so that the drug’s dissolution or solubility is altered. Antacids through drug interactions, reduction of bioavailability of oral medicines and affecting their pharmacokinetics’ properties have the potential to cause therapy failures (3-4).

However, antacids were the mainstay of treatment for acid peptic disorders until the advent of H₂ receptor antagonists and proton pump inhibitors (5-9).

**Lack of evidence of efficacy on use of antacids in Dyspepsia (10-12)**

Although antacids are commonly used to relieve symptoms of dyspepsia, evidence for this use is lacking. Evidence from randomized controlled trials (RCTs) found antacids to be similar to placebo in relieving symptoms of gastroesophageal reflux (when given over 2 weeks) and non-ulcer dyspepsia (NUD) (when given over 6 weeks). The National Institute for Health and Clinical Excellence (NICE) does not recommend long-term, frequent, and continuous use of antacid in people with NUD. This is based on limited evidence that found antacids to be no more effective than placebo in reducing NUD symptoms. This is supported by a subsequent Cochrane review (10).

However in cases of proven NUD, NICE advises patients "that antacids only relieve symptoms in the short term rather than preventing them and that self-treatment with an antacid for immediate relief of symptoms may be continued if the person finds this helpful". And that "long-term, frequent, and continuous use of antacid is inappropriate" (12).

**Antacids vs. placebo:**

In a review published in Cochran Database (10) reported that antacids (one trial evaluating 109 participants; RRR -2%; 95% CI -36% to 24%) were not statistically significantly superior to placebo in managing dyspepsia. The NICE recommendation is based on an assessment of two RCTs which found antacids to be no more effective than placebo in treating NUD. One RCT (n = 109 adults) found no difference in improvement (in terms of dyspepsia symptoms reported as a dichotomous outcome) between antacids (37% of people were improved) and placebo (38% were improved) after 6 weeks of treatment (risk difference −1, 95% CI −19 to 17). The risk ratio for symptoms persisting unchanged or worse in the antacid group was 1.02 (95% CI 0.76 to 1.36). Another trial (n = 108) found no difference in pain score reduction (on a continuous dyspepsia scale) between the placebo and antacid groups (31% versus
36% reduction, respectively). The mean reduction comparing antacid and placebo was 5% (95% CI –13 to 23).

A systematic review (11) (search date: up to 2002) and a subsequent Cochrane review (search date: up to January 2006) did not identify any new evidence. In both reviews, only one trial met inclusion criteria. Both reviews concluded that antacids were not significantly better than placebo in those with NUD.

A systematic review (search dates: 1972–2005) identified four RCTs (that met inclusion criteria) which compared antacids with placebo. A meta-analysis of the four pooled trials (n = 1155) found a trend but no statistical difference between antacids and placebo in producing subjective improvement in adults after 2 weeks of therapy. These trials (treatment= 578, placebo= 577) with a mean Jadad score 3.5 (range: 2–5) met the inclusion and exclusion criteria. They evaluated subjective improvement (defined as rating of treatment as ‘good/excellent’ or global assessment of ‘better/much better’) after 2 weeks to 4 weeks of therapy. The combined absolute benefit increase of antacid treatment over placebo was 8% (95% CI: 0–16%, P= 0.06). The combined relative benefit increase was 0.11 (95% CI: 0.03–0.20). The NNT was 13 (95% CI: 6–250).

A systematic review (search date up to 2002) identified one RCT (that met inclusion criteria) which evaluated the effectiveness of antacids in non-ulcer dyspepsia. This double-blind RCT (n = 222 adults) compared an antacid, an H2-receptor antagonist, and placebo in people with NUD after 6 weeks of treatment. Treatment with an antacid (n = 54) was not significantly better than placebo (n = 54): relative risk reduction –2% (95% CI 24 to 36%).

**Long term use of Antacids**

According to NHS recommendation long-term, frequent and continuous use of antacids is inappropriate for people with NUD because evidence for the use of antacids in NUD is poor and indicates that antacids are no more effective than placebo in relieving symptoms (12).
Short list of Resources

6. Cohen H; Latin American consensus on gastroesophageal reflux disease: an update on therapy; gastroenterologia Hepatologia; 33; 135-147; 2010.
9. Mejia A and Kraft WK; Acid peptic diseases: pharmacological approach to treatment; Expert review of clinical pharmacology; 2; 295-314; 2009.
http://www.cks.nhs.uk/dyspepsia_proven_non_ulcer