# Randomised Clinical Trial: The Effect of Baclofen in Patients With Gastro-Oesophageal Reflux

## A Randomised Prospective Study

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## Abstract and Introduction

### Abstract

**Background** Baclofen, a $GABA_B$ agonist, has been shown to reduce transient lower oesophageal sphincter relaxations (TLESRs), a major cause of gastro-oesophageal reflux disease (GERD).
**Aim** To examine the effect and tolerability of baclofen in GERD patients over a **2-week period.**
**Methods** **Forty-three GERD patients** with abnormal 24-h pH tests were prospectively randomised to receive baclofen or placebo in a double-blind fashion for 2 weeks. Oesophageal manometry, 24-h pH monitoring, and a standard questionnaire was administered, before and after treatment.
**Results** Thirty-four patients completed the study. In the baclofen group there were significant decreases in 24-h pH score **(*P* = 0.020)**, percent of upright reflux episodes (*P* = 0.016), percent total time pH <4 (*P* = 0.003), number of reflux episodes (*P* = 0.018), number of reflux episodes longer than 5 min (*P* = 0.016), number of postprandial reflux episodes (*P* = 0.045), and percentage of time pH <4 (*P* = 0.003). No significant changes in reflux parameters were noted in the placebo group. Patients receiving baclofen had significantly less belching (*P* = 0.038), regurgitation (*P* = 0.036) and overall symptom score (*P* = 0.004) whereas placebo patients had less heartburn (*P* = 0.001), chest pain (*P* = 0.002), regurgitation (*P* = 0.017) and overall symptom score (*P* = 0.000). However, there were no significant differences in changes of reflux parameters or symptoms when comparing the two groups. Drowsiness did not limit baclofen use.
**Conclusions** Baclofen was associated with a significant decrease in percent upright reflux by 24-h pH monitoring and a significant improvement in belching, regurgitation and overall symptom score. Baclofen may be more effective in patients with predominantly upright reflux and belching.

### Introduction

Gastro-oesophageal reflux disease (GERD) affects up to 20% of the Western population.[1] Acid suppression has been the mainstay of therapy for GERD over time, with proton pump inhibitors being the treatment of choice. However, despite potent antacid therapies, symptoms can persist in up to 30% of GERD patients.[2] Mechanisms of GERD include incompetence of the lower oesophageal sphincter (LES), decreased oesophageal clearance, impaired resistance of the

oesophageal mucosa, and increased transient lower oesophageal sphincter relaxations (TLESRs). Of these, TLESRs have been shown to be a major cause of reflux in healthy patients and in those with GERD.[3-5] In this light, $GABA_B$ agonists have emerged as an alternative target for GERD treatment in those patients who have failed antacid therapy.

The $GABA_B$ receptors are expressed in neurons of the motor nucleus of the vagal nerve and nucleus tract solitarious, and play a central role in TLESRs, while peripheral activation of $GABA_B$ receptors inhibit distension related TLESRs.[6] Baclofen (4-amino-2(p-chlorophenyl)-butanoic acid), a selective $GABA_B$ receptor agonist, has not only been used traditionally as a muscle relaxant for many years, but has also been shown to reduce TLESRs in both animals and in humans.[7,11] Clinical studies of its short term or single dose use have demonstrated its effectiveness in reducing the number of TLESRs, and likewise reducing the number of reflux events.[12,17] Data are limited regarding long-term use of baclofen, however, with one study showing an improvement of GERD symptoms over 1 month.[15]

Although baclofen offers an option to inhibit both acid and non-acid reflux, and thus an option for treatment of refractory GERD, there has been concern of its centrally acting side effects (drowsiness), limiting its use. Arbaclofen placarbil, a pro-drug isomer of baclofen, has been found to show short-term improvement of GERD symptoms in two studies with good tolerability; however, in a more recent phase II study no significant benefit was seen in GERD symptoms compared to placebo.[18-20] Lesogaberan (AZD3355) and AZD9343, baclofen analogues, have been developed as $GABA_B$ agonists to likewise reduce TLESRs without centrally acting side effects, and have been found to decrease reflux episodes in some studies when used as adjunctive therapy to PPIs.[21] To date, however, other than baclofen, no other $GABA_B$ agonists are FDA approved, and their use remains limited in the research setting.

Given the paucity of alternative treatment options to antacids for GERD, this study was done to further evaluate the clinical effectiveness of baclofen on GERD and GERD related symptoms as well as to assess its tolerability in light of previously reported side effects.Continue Reading

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