Gastroesophageal reflux disease (GERD) is a common disorder that affects up to 20% of the population worldwide. The classic symptoms of GERD, which include heartburn and acid regurgitation, are troublesome and have a substantial negative impact on patients' health-related quality of life. Consequently, effective treatment to provide enduring control of GERD symptoms is necessary.

Acid-suppressive therapy currently forms the mainstay of treatment for GERD and proton pump inhibitors (PPIs) are the treatment-of-choice in this regard. However, GERD symptoms often persist despite PPI therapy in a considerable number of patients. Recent survey data, for example, indicate that approximately 50% of patients diagnosed with GERD continued to experience symptoms despite PPI treatment, and around one-quarter (22%) of PPI users report taking additional over-the-counter (OTC) medicines to control their symptoms.

Possible reasons for a lack of effect with PPI therapy include inadequate dosing and/or poor compliance (possibly resulting from lack of efficacy), pharmacokinetic characteristics (such as poor oral bioavailability or rapid metabolism due to genetic polymorphisms or cytochrome P450 induction), and incorrect diagnosis. Acid-suppressive therapy currently forms the mainstay of treatment for GERD and proton pump inhibitors (PPIs) are the treatment-of-choice in this regard. However, GERD symptoms often persist despite PPI therapy in a considerable number of patients. Recent survey data, for example, indicate that approximately 50% of patients diagnosed with GERD continued to experience symptoms despite PPI treatment, and around one-quarter (22%) of PPI users report taking additional over-the-counter (OTC) medicines to control their symptoms.

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reflux at the gastroesophageal junction\textsuperscript{11}. The LES is a 3-4 cm region of circular smooth muscle that is maintained at high resting basal pressure (>10 mm Hg) via neural, myogenic and hormonal input\textsuperscript{12}. Transport of esophageal contents into the stomach occurs with neurally mediated relaxation of the LES, and concurrent partial inhibition of CD activity; the CD usually contracts with respiration. The retrograde flow of gastric contents is prevented by LES contraction\textsuperscript{11}. Basal LES pressure of at least 3 mm Hg is required to prevent gastric reflux\textsuperscript{13}.

Low tonic basal LES pressure was previously a favored mechanism to explain the pathogenesis of GERD\textsuperscript{14}. However, this theory was largely based on flawed measurements of LES function, and it is now established that reflux episodes can occur in patients with normal LES pressure. Moreover, the poor clinical performance of agents supposedly acting on LES pressure, such as the 5-HT\textsubscript{4} partial receptor agonists cisapride and tegaserod, and motilides such as erythromycin, provides further evidence that low tonic LES pressure is not a major mechanism in the pathogenesis of GERD\textsuperscript{10}. For example, a randomized, double-blind study in healthy volunteers found no significant differences between tegaserod and placebo in terms of the number of acid and weakly acidic or weakly alkaline reflux episodes, bolus transit time or distal esophageal contraction amplitude\textsuperscript{15}. Similarly, Champion et al. reported that “standard” doses of erythromycin had no relevant effects on esophageal function or acid reflux parameters in patients with GERD\textsuperscript{16}.

More recently, transient LES relaxation (TLESR) has been identified as an important factor in the pathophysiology of GERD (Figure 1)\textsuperscript{17}. TLESR is characterized by rapid LES relaxation in the absence of swallowing or esophageal peristalsis\textsuperscript{18-20}. Neural control of TLESR is via a vago-vagal reflex initiated in response to gastric distension by activation of mechanosensitive vagal afferent neurons that terminate in the dorsal vagal complex of the brainstem\textsuperscript{12,19}. Efferent vagal nerve signals stimulate the release of nitric oxide, pituitary adenylate cyclase activating peptide, and vasoactive intestinal peptide from enteric neurons, resulting in smooth muscle relaxation\textsuperscript{12,17}. The efferent neural pathway in TLESR is thought to be the same as that for swallow-induced LES relaxation, only more intense and prolonged; TLESR are of greater magnitude and duration than the LES relaxation occurring during swallowing. Additionally, extragastric factors may influence the rate and occurrence of TLESR. Increased TLESR occurs with mechanical stimulation of the pharynx, hyperglycemia, duodenal nutrient infusions, intracolonic lactose, and bronchoconstriction (in asthmatics). Conversely, TLESR is inhibited during sleep or anesthesia, indicating higher central nervous system (CNS) activity, and in response to supine posture, and cold stress\textsuperscript{12,17}.

TLESR is a normal physiologic response to postprandial gastric distension and the rate of TLESR increases after meals in healthy volunteers\textsuperscript{1,22}. Some studies have shown a similar rate and incidence of TLESR among healthy individuals and GERD patients\textsuperscript{14,18,23}; however, other stud-

![Figure 1. Transient relaxation of the lower esophageal sphincter (TLESR) and associated motility events. Events in boldface denote defining features of TLESR; the other changes are common but not obligatory components of a TLESR. Reproduced with permission\textsuperscript{17}.](image-url)
ies indicate an increased prevalence of TLESR among those with GERD. In particular, GERD patients may experience more instances of TLESR in the supine position that are associated with acid reflux. Since acid secretion is unchanged in GERD patients, possible reasons for the higher likelihood of reflux during a TLESR in those with GERD include altered distribution of gastric juices or a larger opening of the gastroesophageal junction during relaxation.

The role of TLESR versus other mechanical factors such as low or absent tonic basal LES pressure, straining and swallowing varies between endoscopy-positive and endoscopy-negative GERD patients. Non-TLESR mechanisms may be equally or more important among patients with endoscopy-positive GERD in the presence of hiatal hernia, in which the position of the gastric receptors with the lowest threshold for initiation of TLESR has shifted proximally. However, data are controversial and further clarification of the role of non-TLESR mechanisms is required.

### Pharmacologic Targets for Reflux Inhibition

Theoretically, pharmacologic modification of both the frequency and quality (i.e., degree and duration) of TLESR can be achieved anywhere along the pathway from gastric mechanoreceptors to the smooth muscle cells of the LES. However, observations that drugs with TLESR-modifying activity do not affect swallow-induced LES relaxation suggest that these agents act on the afferent, rather than efferent, pathway. A site of action in the brain also seems possible in some cases. Targets for pharmacologic TLESR modification therapy have emerged based on preclinical evidence and include nitric oxide synthase inhibitors, cholecystokinin receptor 1 (CCK1) antagonists, metabotropic glutamate receptor 5 (mGluR5) antagonists, and γ-aminobutyric acid (GABA) type B receptor (GABAB) agonists. Among these, only mGluR5 receptor antagonists and GABAB receptor agonists have shown positive results in proof-of-concept studies in the clinical setting, as described in the following section.

### Clinical Findings on Reflux Inhibitors

**ADX10059**

ADX10059 is an orally available small molecule that acts as a negative allosteric modulator of mGluR5 receptors. In a single-blind, placebo-controlled, proof-of-concept study in 24 GERD patients, single doses of ADX10059 reduced acid reflux (as measured by pHmetry) and improved GERD symptoms. Compared with placebo, ADX10059 250 mg three times daily was not only associated with significantly lower percentages of time with esophageal pH < 4 over 24 hours (and at night) but also fewer symptomatic acid reflux episodes (Figure 2). The duration of such episodes was also shorter with ADX10059; this was a somewhat surprising finding as there is no evidence or theoretical basis that TLESRs that occur during partial pharmacological inhibition are not identical to those seen in control conditions. The administration of ADX10059 was associated with a very high rate of side effects, including dizziness and nausea, which indicates the need to discover new modulators of mGluR5 receptors in order to improve tolerability.

**Baclofen**

Baclofen is a selective GABAB receptor agonist with well established efficacy in the treat-
ment of spasticity. Numerous studies, in adult healthy volunteers and patients with GERD (including children), indicate that this agent reduces the number of TLESR and improves GERD symptoms (Table II)\textsuperscript{32-40}. In adult healthy volunteers, for example, a single dose of oral baclofen significantly decreased the incidence of TLESR (by up to 64\%) and increased basal LES pressure (by up to 40\%)\textsuperscript{32,37}. This effect was confirmed in adult GERD patients, in whom a single 40 mg dose inhibited up to 40\% of instances of TLESR\textsuperscript{34,35}. Baclofen also reduced the occurrence of acid reflux episodes and decreased acid exposure in adult GERD patients after administration of a single 40 mg dose\textsuperscript{33,35,38} or multiple doses of 10-20 mg three or four times daily\textsuperscript{36}. In pediatric GERD patients, a single dose of baclofen 0.5 mg/kg provided 51\% inhibition of TLESR\textsuperscript{40} and administration of baclofen 0.7 mg/kg once daily for 1 week reduced acid reflux episodes by 39\%\textsuperscript{39}.

Add-on treatment with baclofen appears to be effective in patients with GERD symptoms despite PPI therapy. Indeed, the addition of baclofen 20 mg three times daily reduced the cumulative severity score for 14 GERD symptoms from 10.3 to 5.8 ($P < 0.01$) in patients with persistent GERD symptoms while treated with omeprazole (Table II)\textsuperscript{41}. This evidence suggests a potential role for add-on treatment with a GABA\textsubscript{B} receptor agonist in patients who experience GERD symptoms despite PPI therapy.

However, the utility of baclofen in the management of GERD is limited by the requirement for frequent dosing, due to its short half-life (3-4 hours), and poor tolerability with a high rate of CNS side effects such as sedation and dizziness. This is explained by the ability of baclofen to enter the CNS and act on the high concentrations of GABA\textsubscript{B} receptors in the brain\textsuperscript{17}.

**XP19986, AZD9343 and AZD3355**

Efforts to overcome tolerability issues associated with baclofen have resulted in the development of agents such as XP19986, an investigational prodrug of R-baclofen. In a dose-ranging, placebo-controlled study in GERD patients, XP19986 significantly reduced the number of reflux episodes ($P \leq 0.05$ vs. placebo) and showed a similar rate of side effects to placebo\textsuperscript{42}. However, it remains to be shown that XP19986 has an acceptable tolerability profile during long-term use. Indeed, while the main advantage of XP19986 is related to improved pharmacokinetics, there is little reason to expect it to substantially differ from baclofen with respect to CNS side effects.

Research has also focused on the development of GABA\textsubscript{B} receptor agonists with primarily peripheral, rather than central, activity. Promising preclinical results have been obtained with two such agents, AZD9343 and AZD3355. AZD9343 showed low permeation into the CNS in rats and, in dogs, it dose-dependently inhibit-
## Table II. Clinical studies of baclofen in adult healthy volunteers or GERD patients.

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose</th>
<th>LES outcomes</th>
<th>Acid-related outcomes</th>
<th>GERD symptoms outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>% Inhibition of TLESR</td>
<td>Increase in % basal LES tone</td>
<td>% Inhibition of reflux episodes</td>
</tr>
<tr>
<td>Healthy volunteers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lidums et al.32</td>
<td>40 mg SD</td>
<td>61***</td>
<td>19**</td>
<td>60*</td>
</tr>
<tr>
<td>Ciccaglione et al.36</td>
<td>40 mg SD</td>
<td>NA</td>
<td>NA</td>
<td>57**</td>
</tr>
<tr>
<td>Lee et al.37</td>
<td>40 mg SD</td>
<td>64*</td>
<td>40*</td>
<td>None</td>
</tr>
<tr>
<td>Vela et al.38</td>
<td>40 mg SD</td>
<td>NA</td>
<td>NA</td>
<td>76*</td>
</tr>
<tr>
<td>GERD patients (including children)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cange et al.33</td>
<td>40 mg SD</td>
<td>NA</td>
<td>NA</td>
<td>48***</td>
</tr>
<tr>
<td>van Herwaarden et al.34</td>
<td>40 mg SD</td>
<td>34***</td>
<td>6 (ns)</td>
<td>42*</td>
</tr>
<tr>
<td>Zhang et al.35</td>
<td>40 mg SD</td>
<td>40**</td>
<td>41*</td>
<td>43*</td>
</tr>
<tr>
<td>Ciccaglione et al.36</td>
<td>40 mg SD</td>
<td>NA</td>
<td>NA</td>
<td>51**</td>
</tr>
<tr>
<td>Koe et al.41</td>
<td>5 mg tid increasing to 20 mg tid at steady-state</td>
<td>NA</td>
<td>NA</td>
<td>Bile reflux: 48*; Acid reflux: None</td>
</tr>
<tr>
<td>Koek et al.41</td>
<td>5 mg tid increasing to 20 mg tid at steady-state</td>
<td>NA</td>
<td>NA</td>
<td>69*</td>
</tr>
<tr>
<td>Vela et al.38</td>
<td>40 mg SD</td>
<td>NA</td>
<td>NA</td>
<td>39*</td>
</tr>
<tr>
<td>Kawai et al.39</td>
<td>0.7 mg/kg od × 1w</td>
<td>NA</td>
<td>NA</td>
<td>Reduced emesis in 6/8 patients</td>
</tr>
<tr>
<td>Omari et al.40</td>
<td>0.5 mg/kg SD</td>
<td>51*</td>
<td>None</td>
<td>59*</td>
</tr>
</tbody>
</table>

*P ≤ 0.05; **P ≤ 0.001; ***P ≤ 0.0001 vs placebo. NA = not assessed; ns = not significant; SD = single dose; tid = three times daily; od = once daily; qid = four times daily.
ed TLESR\textsuperscript{43}. Similarly, AZD3355 has also been shown to have low CNS activity in rats and mice\textsuperscript{44}. In dogs, the latter agent demonstrated dose-dependent inhibition of TLESR\textsuperscript{44} and reduced esophageal acid exposure time\textsuperscript{45}. The potentially better tolerability of these agents versus baclofen makes them promising new therapies for reflux inhibition in patients who experience GERD symptoms despite PPI therapy. Results from clinical studies of these agents are therefore awaited with interest.

\section*{Conclusions}

It is apparent that, despite the success of PPIs, there is a significant unmet medical need in GERD. The role of TLESR as an important factor behind reflux has prompted the discovery of several targets for TLESR inhibition, but most have a low utility for pharmacologic therapy of GERD. To date, only GABA\textsubscript{B} agonists and mGluR5 antagonists have shown positive proof of concept in the clinical setting, and further studies are clearly required to investigate the promising utility of such agents for patients who suffer from GERD symptoms despite PPI therapy.

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