Agents that modify serotonergic function have therapeutic potential for the treatment of visceral hypersensitivity, either through a direct effect on perception or through modulation of visceral tone or motility. Administration of selective serotonin reuptake inhibitors reduces oesophageal sensitivity to distension but not gastric sensitivity to distension. 5-HT ligands may also influence gastric mechanosensitivity by altering tone. Although the exact role of 5-HT receptors in the control of gastrointestinal functions remains unknown, 5-HT is generally considered to be the main candidate involved in the modulation of motor and sensory function from the gastrointestinal tract. Hence serotonergic modulation of upper gut sensitivity appears to be promising for the development of novel approaches to the treatment of functional disorders of the upper gastrointestinal tract.

SUMMARY
Agents that modify serotonergic function have therapeutic potential for the treatment of visceral hypersensitivity, either through a direct effect on perception or through modulation of visceral tone or motility. Administration of selective serotonin reuptake inhibitors (SSRIs) reduces oesophageal sensitivity to distension but not gastric sensitivity to distension. Administration of amitriptyline to patients with functional dyspepsia has no effect on sensitivity to gastric distension but may provide symptomatic benefit. The 5-HT₄ antagonist ondansetron partly reverses sensitisation to gastric distension during duodenal lipid infusion. 5-HT ligands may also influence gastric mechanosensitivity by altering tone. Cisapride, a 5-HT₄ agonist/weak 5-HT₂ antagonist induces a small degree of gastric contraction in the fasting state but postprandially it markedly enhances gastric accommodation. Similarly, the SSRI paroxetine enhances relaxation in response to a liquid meal and may provide symptomatic benefit for patients with impaired gastric accommodation. The 5-HT₄ receptor agonist sumatriptan activates intrinsic inhibitory neurones in the stomach. The resulting gastric inhibition has been shown to reduce postprandial symptoms in patients with functional dyspepsia caused by hypersensitivity. Buspirone, a 5-HT₁₆ agonist, reduces cholinergic tone to the stomach, thereby increasing the threshold for discomfort and reducing the severity of dyspeptic symptoms.
5-HT RECEPTORS AND 5-HT RECEPTOR LIGANDS
Several 5-HT receptor subtypes have been identified in the gastrointestinal tract. These are located in nerves or on smooth muscle cells where they mediate a number of different actions (fig 1). Although a growing number of 5-HT receptor agonists and antagonists are available, only a limited number of selective ligands are suitable for human studies (table 1).

Enteric neurones resemble central serotonergic neurones in terms of their response to 5-HT reuptake inhibitors. SSRI prolong the availability of physiologically released 5-HT and thereby enhance the effects of 5-HT released synaptically from neurones located centrally as well as those originating at the level of the ENS (fig 2). These agents have to be used to study involvement of 5-HT in gastrointestinal sensorimotor function in humans.

Non-SSRIs such as the tricyclic antidepressants have received a relatively high level of attention whereas the effects of SSRIs on gastrointestinal function and their role in the treatment of functional gastrointestinal disorders remains largely unexplored.

SEROTONERGIC MODULATION OF OESOPHAGEAL SENSITIVITY
Conflicting results have been reported concerning the ability of 5-HT to modify oesophageal sensitivity. According to one study, administration of the tricyclic antidepressant amitriptyline, a non-SSRI, failed to alter thresholds for perception, discomfort, and pain induced by oesophageal balloon distension. However, in another study, the tricyclic antidepressant imipramine reduced the pain threshold, but not the perception threshold, during balloon distension in healthy volunteers but the difference was small.

Recently, we demonstrated that administration of the SSRI citalopram significantly lowered mechano- and chemosensitivity in healthy subjects. The action of citalopram occurred without alteration of basal oesophageal motility. Although this finding supports the involvement of 5-HT in the modulation of oesophageal sensitivity, it does not provide information about whether a central or peripheral mechanism of action is involved.

Motility abnormalities and hypersensitivity to acid, cholinergic agents, and intraluminal distension stimuli are pathophysiological abnormalities found in patients with non-cardiac chest pain. The results of a relatively small study

Table 1 Overview of 5-HT receptors and their ligands

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Selective agonist</th>
<th>Selective antagonist</th>
<th>Non-selective agonist</th>
<th>Non-selective antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>8-OH-DPAT</td>
<td>WAY 100365</td>
<td></td>
<td>Buspirone</td>
</tr>
<tr>
<td>1B</td>
<td>Sumatriptan</td>
<td>GR 55562</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1D</td>
<td>Sumatriptan</td>
<td>BRL 15572</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1F</td>
<td>LY 334370</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2A</td>
<td>αMe-5-HT</td>
<td>Ketanserin</td>
<td>Mianserin</td>
<td></td>
</tr>
<tr>
<td>2B</td>
<td>αMe-5-HT</td>
<td>BV 723C86</td>
<td>Cyproheptadine</td>
<td></td>
</tr>
<tr>
<td>2C</td>
<td>αMe-5-HT</td>
<td>Mesulergine</td>
<td>Cyproheptadine</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>SR 57227</td>
<td>Olanzapine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>BIM UB</td>
<td>GR 113908</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Those suitable for use in humans are italicised.
Serotonergic modulation of visceral sensation

Influence on perception to gastric distension
SSRIs do not appear to affect sensitivity to gastric distension. Likewise, preliminary studies using the non-selective antagonists of 5-HT₃ and 5-HT₄ receptor subtypes cyproheptadine and mianserin were also unable to affect the mechanical induced gastric sensation in humans (unpublished observations). In a small group of patients, the non-selective SSRI amitriptyline provided symptomatic benefit in the absence of a change in gastric sensitivity to distention.

Studies in animals suggest that 5-HT₄ receptors are putative excitatory mediators in visceral sensory pathways, and thus 5-HT₄ antagonists may reduce the level of perception to visceral distension. However, in human studies this effect has only been observed in the lower part of the gastrointestinal tract. The selective 5-HT₄ antagonists alserotonin and ondansetron do not appear to have any significant effects on sensitivity to gastric distension. These observations suggest that gastric mechanosensitivity is not mediated through release of 5-HT in humans. However, this does not preclude an action of 5-HT ligands on sensitivity to mechanical distension.

Influence on fasting and postprandial gastric tone
The main determinant of gastric mechanosensitivity is gastric tone. A subset of patients with functional dyspepsia have been shown to have insufficient accommodation (decrease in gastric tone) after a meal. It is possible therefore that serotonergic ligands, which influence fasting and postprandial gastric tone, may also affect sensitivity to gastric distension.

Short pretreatment with the SSRI paroxetine has been shown to enhance gastric accommodation to a meal in healthy volunteers in the absence of any effect on fasting gastric compliance. These observations suggest that 5-HT release is involved in the control of the accommodation reflex and therefore in the modulation of visceral sensation during the postprandial state. In support of this hypothesis, 5-HT₄, 5-HT₃, 5-HT₁A, and 5-HT, receptors have all been identified on myenteric neurones in the guinea pig stomach.

Pretreatment with 5-HT₄ receptor antagonists was found to have no influence on fasting or postprandial gastric tone in healthy volunteers. However, activation of 5-HT₂ receptors, believed to be located presynaptically on nerve terminals of enteric cholinergic interneurones and motor neurones (fig 1), has been shown to enhance the release of acetylcholine from cholinergic nerve endings, resulting in increased contractility.

Prokinetic benzamides, such as cisapride, act as 5-HT₄ receptor agonists. Their gastrokinetic properties are thought to originate from their ability to stimulate 5-HT₄ receptors on cholinergic nerve terminals. In humans, pretreatment with cisapride has been shown to shift gastric volume-pressure relationships towards higher pressures for the same distending volume. This effect was associated with lowered discomfort thresholds during gastric distension. Surprisingly, cisapride has also been shown to enhance gastric accommodation to a meal.

The effect of 5-HT in a subset of myenteric neurones is known to evoke a slow depolarising response. This effect is mediated by the so-called 5-HT₁₇ receptors which are predominantly located on inhibitory motor neurones of the gastric myenteric plexus (fig 1). Recent studies have identified sumatriptan as a 5-HT₁₇ receptor agonist which interacts with nitrergic myenteric neurones in the guinea pig stomach and which induces gastric relaxation in cats and humans. In acute studies, sumatriptan has been shown to enhance the intragastric volumes needed to induce perception and discomfort in fasted healthy volunteers, and to normalise meal induced relaxation and improve symptoms of early satiety in patients with impaired postprandial accommodation.

A subset of patients with functional dyspepsia have hypersensitivity to gastric distension accompanied by more prevalent symptoms of pain, belching, and weight loss. Sumatriptan was found to decrease sensitivity to distension in patients with hypersensitivity to gastric distension. It also improved symptoms that followed eating a standardised meal, possibly by decreasing the level of activation of tension mechanoreceptors.

The non-selective 5-HT₃, receptor agonist buspirone is thought to decrease gastric tone and increase the distension induced volume thresholds in healthy volunteers, thereby mimicking some of the effects of sumatriptan. In a placebo controlled, double blind, randomised, crossover study, buspirone was shown to be superior to placebo at improving gastric accommodation in patients with functional dyspepsia. Based on these findings, SSRIs, 5-HT₄ receptor agonists, 5-HT₁A receptor agonists, and 5-HT₁D receptor agonists all appear to have beneficial effects in patients with functional dyspepsia and impaired accommodation. The 5-HT₁A and 5-HT₁D receptor agonists may have additional therapeutic potential for the treatment of gastric visceral hypersensitivity. The effect of these agents on visceral sensitivity appears to be associated with a change in gastric tone.

SEROTONERGIC MODULATION OF DUODENAL SENSITIVITY
Upper gastrointestinal viscero-visceral reflexes are predominantly mediated through vagal afferents and triggered physiologically by intestinal mechanical stimuli and by the presence of duodenal nutrients. Several observations suggest the involvement of 5-HT in the control of duodenogastric reflexes.

In animals, low intensity non-painful duodenal distension inhibits gastric motility. This response is abolished by low doses of granisetron administered peripherally but not centrally, suggesting a peripheral site of action for this 5-HT₃ antagonist. In humans, ondansetron reduces the sensation of nausea provoked by the combined stimuli of intraduodenal lipid infusion and gastric distension. As the drug does not alter gastric tone or sensitivity, it probably acts at duodenal vagal afferents.
A recent study demonstrated reduction in dyspepsia symptoms in patients treated with the 5-HT3 receptor antagonist.

CONCLUSION
Serotonergic modulation of upper gut sensitivity appears promising for the development of novel approaches to the treatment of functional disorders of the upper gastrointestinal tract.

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REFERENCES