QUESTION 39
A 60-year-old man complains of recurrent episodes of watery diarrhoea four years after excision of an abdominal tumour. Somatostatin receptor scintigraphy is performed and is shown below.

![Image of somatostatin receptor scintigraphy]

Which one of the following would be most effective in managing his symptoms?
A. Interferon.
B. Octreotide.
C. Loperamide.
D. Streptozotocin.
E. Cholestyramine.

Somatostatin-receptor scintigraphy — Many pancreatic endocrine tumors have high concentrations of somatostatin receptors and can therefore be imaged with a radiolabeled form of the somatostatin analogue octreotide (111-indium pentetreotide) (OctreoScan). This technique has proven particularly effective for visualizing gastrinomas, glucagonomas, nonfunctioning pancreatic tumors, and carcinoid tumors. It has the advantage of instantaneous whole body scanning, which also allows detection of distant metastases. MRI appears to have even greater sensitivity for detection of liver metastases compared with planar or SPECT somatostatin receptor scintigraphy.

Gastroenteropancreatic neuroendocrine tumours
- Patients with metastatic gastroenteropancreatic neuroendocrine tumors often become symptomatic from hormonal hypersecretion rather than from tumor bulk.
- Secretion of serotonin and other vasoactive substances into the systemic circulation results in the carcinoid syndrome.
Symptoms of the carcinoid syndrome, as well as other hormonal syndromes resulting from peptide hormone hypersecretion by pancreatic endocrine tumors, can often be well controlled with somatostatin analogs and/or interferon-alfa (IFNa).

Somatostatin is a 14-amino acid peptide that inhibits the secretion of a broad range of hormones. It acts by binding to somatostatin receptors, which are expressed on the majority of neuroendocrine tumors.

Somatostatin analogs = octreotide. Long-acting octreotide is typically initiated at a dose of 20 mg IM after a brief trial of the short-acting formulation, with gradual escalation of the dose as needed for optimal control of symptoms. Patients may, in addition, use additional short-acting octreotide for breakthrough symptoms.

Octreotide side effects. About one-third of patients have nausea, abdominal discomfort, bloating, loose stools, and fat malabsorption during the first several weeks of therapy, after which time, symptoms tend to subside. Mild glucose intolerance rarely occurs, due to transient inhibition of insulin secretion. More importantly, octreotide reduces postprandial gallbladder contractility and delays gallbladder emptying, and up to 25 percent of patients develop asymptomatic cholesterol gallstones or sludge within the first 18 months of therapy.

IFNa with and without octreotide — The ability of interferon-alfa (IFNa) to stimulate T-cell function and to control the secretion of tumor products led to its initial use in patients with the carcinoid syndrome. Low-dose IFNa alone improves symptoms of hormonal hypersecretion in 40 to 50 percent of patients with either carcinoid or pancreatic neuroendocrine tumors, induces tumor stabilization in 20 to 40 percent, and achieves objective tumor regression in up to 15 percent.

Combined therapy with IFNa and somatostatin analogs is reported to control symptoms in patients with the carcinoid syndrome who are resistant to somatostatin analogs alone.

Summary — Somatostatin analogs and IFNa appear to be of greatest utility for control of symptoms related to hormone hypersecretion. The use of these agents in asymptomatic patients is controversial because of the low rates of objective tumor regression. Symptomatic patients are generally initiated on short-acting octreotide with rapid transition to the long acting formulation, and subsequent titration of dose to optimize symptom control. A trial of combined therapy could be considered for patients who have poorly controlled or recurrent symptoms while on octreotide alone.

Streptozocin combinations — The antitumor activity of combinations of streptozocin with 5-FU and/or doxorubicin for patients with advanced carcinoid remains controversial.
### Gut guidelines

**Table 3** Clinical features of pancreatic neuroendocrine tumours

<table>
<thead>
<tr>
<th>Tumour</th>
<th>Symptoms</th>
<th>Malignancy</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulinoma</td>
<td>Confusion, sweating, dizziness, weakness, unconsciousness, relief with eating</td>
<td>10% of patients develop metastases</td>
<td>Complete resection cures most patients</td>
</tr>
<tr>
<td>Gastrinoma</td>
<td>Zollinger-Ellison syndrome of severe peptic ulceration and diarrhoea</td>
<td>Metastases develop in 60% of patients; likelihood correlated with size of primary</td>
<td>Complete resection results in 10 year survival of 90%; less likely if large primary</td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>Necrolytic migratory erythema, weight loss, diabetes mellitus, stomatitis, diarrhoea</td>
<td>Metastases develop in 60% or more patients</td>
<td>More favourable with complete resection; prolonged even with liver metastases</td>
</tr>
<tr>
<td>VIPoma</td>
<td>Werner-Morrison syndrome of profuse watery diarrhoea with marked hypokalaemia</td>
<td>Metastases develop in up to 70% of patients; majority found at presentation</td>
<td>Complete resection with five year survival of 95%; with metastases, 60%</td>
</tr>
<tr>
<td>Somatostatinoma</td>
<td>Cholelithiasis; weight loss; diarrhoea and steatorrhoea. Diabetes mellitus</td>
<td>Metastases likely in about 50% of patients</td>
<td>Complete resection associated with five year survival of 95%; with metastases, 60%</td>
</tr>
<tr>
<td>Non-syndromic pancreatic neuroendocrine tumour</td>
<td>Symptoms from pancreatic mass and/or liver metastases</td>
<td>Metastases develop in up to 50% of patients</td>
<td>Complete resection associated with five year survival of at least 50%</td>
</tr>
</tbody>
</table>

**Table 5** Sensitivities (%) of the various imaging modalities for locating specific neuroendocrine tumours

<table>
<thead>
<tr>
<th>Modality</th>
<th>Primary carcinoid tumour</th>
<th>Carcinoid liver metastases</th>
<th>Primary gastrinoma</th>
<th>Gastrinoma metastases</th>
<th>Liver metastases</th>
<th>Primary insulinoma*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound</td>
<td>46</td>
<td>83</td>
<td>23</td>
<td>50</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>64</td>
<td>88</td>
<td>38–75</td>
<td>54–88</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>56</td>
<td>85</td>
<td>22–90</td>
<td>63–90</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>SSRS</td>
<td>80</td>
<td>90</td>
<td>72</td>
<td>97</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>EUS</td>
<td>80 gastric</td>
<td>90–100</td>
<td>93</td>
<td>95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angio+Ca Stim</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
CT, computed tomography; MRI, magnetic resonance imaging; SSRS, somatostatin receptor scintigraphy; EUS, endoscopic ultrasound; Angio+Ca Stim, angiography with calcium stimulation.

*Metastatic insulinoma is rare; no data available.

All of the above sensitivities for detecting tumour are further enhanced by intraoperative ultrasound.

**Recommendations (therapy)**

- The extent of the tumour, its metastases, and secretory profile should be determined as far as possible before planning treatment (grade C).
- Surgery should be offered to patients who are fit and have limited disease—primary with or without regional lymph nodes (grade C).
- Surgery should be considered in those with liver metastases and potentially resectable disease (grade D).
- Where abdominal surgery is undertaken and long term treatment with SMS analogues is likely, cholecystectomy should be considered.
- For patients who are not fit for surgery, the aim of treatment is to improve and maintain an optimal quality of life (grade D).
- The choice of treatment depends on the symptoms, stage of disease, degree of uptake of radionuclide, and histological features of the tumour (grade C).
- Treatment choices for non-resectable disease include SMS analogues, biotherapy, radionuclides, ablation therapies, and chemotherapy (grade C).
- External beam radiotherapy may relieve bone pain from metastases (grade C).
- Chemotherapy may be used for inoperable or metastatic pancreatic and bronchial tumours, or poorly differentiated NETs (grade B).

**9.4 Symptomatic treatment**

There are a number of treatment options available for patients displaying symptoms due to hormones/peptides secreted by a secretory tumour. These include somatostatin analogues, proton pump inhibitors for gastrinomas, and diazoxide for insulinomas, which are indicated in patients with secretory tumours and distressing symptoms from peptide production. They could be commenced immediately in patients with inoperable disease or preoperatively in patients who have operable disease (liver resection with or without resection of the primary).

The only proven hormonal management of NETs is administration of somastostatin analogues. Somatostatin is a brain-gut peptide that inhibits the release of many hormones and can impair some exocrine functions. Somatostatin receptors are present in the vast majority (70–95%) of NETs but only in about half of insulinomas, and less in poorly differentiated NETs and somatostatinoma. Somatostatin analogues bind principally to receptor subtypes 2 and 5.

Somatostatin analogues inhibit the release of various peptide hormones in the gut, pancreas, and pituitary, antagonise growth factor effects on tumour cells, and at very high dosage may induce apoptosis. The elimination half life of the natural hormone somatostatin is only a few minutes, making it of no value in routine therapy. Octreotide has a half life of several hours, making intermittent therapy possible. This drug is administered by subcutaneous injection starting at 50–100 µg twice or three times a day to a maximum daily dose of 1500 µg. More recently, analogues with sustained release from depot injections have been synthesised and these are given every 2–4 weeks. These drugs, lanreotide (fortnightly injection), Sandostatin LAR (monthly), and Lanreotide Autogel (also monthly), have shown significant improvement in the quality of life of patients and have
as good or better efficacy compared with short acting octreotide.\textsuperscript{121-123} Patients may be stabilised with octreotide (short acting) for 10–28 days before converting them to long acting somatostatin analogues. Escalation of dose is often needed over time. Biochemical response rates (inhibition of hormone production) are seen in 30–70\% of patients with symptomatic control in the majority of patients; tumour growth may stabilise and rarely shrinkage of tumour may occur. In instances of stress (for example, anaesthesia, surgical operations (see above), hepatic artery embolisation), patients with the carcinoid syndrome or even with the tumour but without syndrome should have increased coverage by somatostatin analogues, preferably short acting octreotide by intravenous administration (50 µg/h). This extra cover should be administered 12 hours before, during, and 48 hours after the procedure to prevent a cardiovascular carcinoid crises.\textsuperscript{79}

Few side effects from somatostatin analogues have been reported and they include fat malabsorption, gall stones and gall bladder dysfunction, vitamin A and D malabsorption, headaches, diarrhoea, dizziness, and hypo- and hyperglycaemia. Monitoring of circulating and, where relevant, urinary hormone levels should be undertaken during periods of treatment. Patients should also have the regular relevant imaging.