BACKGROUND

- Octreotide long-acting repeatable (LAR) is FDA-approved for alleviating severe diarrhea or flushing associated with metastatic carcinoid tumors at doses ≥30mg every 4 weeks.  
- In clinical practice, octreotide LAR is sometimes prescribed at above-label doses, but evidence for this practice has not been systematically assessed.

OBJECTIVE

- We reviewed published literature on efficacy and safety of octreotide LAR at doses ≥30mg/month for treatment of neuroendocrine tumors (NENs).

METHODS

Data Sources
- Databases: PubMed and Cochrane Library
- Conference searches: American Society of Clinical Oncology (ASCO), European Neuroendocrine Tumor Society (ENETS), European Society for Medical Oncology (ESMO), North American Neuroendocrine Tumor Society (NANETS)
- Bibliographies of included articles

Search Strategy and Timeframe
- Database searches from 1998-2012 were conducted on 12/01/12. Conference years were 2000-2012.
- MeSH terms and key words used were: neuroendocrine tumors, neuroendocrine carcinoid, carcinoid tumor, carcinomas, neuroendocrine, carcinoid syndrome, octreotide, and sandozstatin.

Inclusion and Exclusion Criteria
- Studies published before 1998 or not reporting data on tumor adverse events or tumor progression were excluded.
- Tumor response: partial response or complete response in single or combination with other treatments were included.
- Studies with prospective or retrospective designs, randomized or non-randomized, patients, and the primary interventions were included.

RESULTS

Efficacy
- Efficacy was reported in 13 studies describing 260 subjects with doses ranging from 40mg/month to 30mg/3 weeks up to 120mg/month.  
- There appears to be a trend supporting the use of higher dose octreotide LAR to control symptoms and tumor progression, although the data on tumour improvement are limited by lack of quantitative measures of tumour severity and absence of formal quality of life analysis.

Reference
- Change in symptoms, disease markers, quality of life (QOL), tumor response, or survival with increased dose/Frequency of octreotide LAR

Table 1: Efficacy of octreotide LAR

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>Tumor Response</th>
<th>Tumor Progression</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthony 2011</td>
<td>20 studies</td>
<td>mean reduction in 46% and symptom control in 60%, flushing normalized in 75%, diarrhea normed in 70%, improved/enhanced in 30%, bronchospasm improved in 100%, hypoglycemia improved in 100%, pain improved in 47%</td>
<td>5%</td>
<td>nausea, vomiting, diarrhoea, abdominal pain, nausea, and vomiting and diarrhoea.</td>
</tr>
<tr>
<td>Vejle 2012</td>
<td>5 studies</td>
<td>mean response to high dose S-LAR in 57% of those with elevated HIAA, 50% with elevated CGA, 22% with elevated GSTR, 30% with those elevated markers responded to higher dose.</td>
<td>21%</td>
<td>nausea, vomiting, diarrhoea, abdominal pain, nausea, and vomiting and diarrhoea.</td>
</tr>
<tr>
<td>Bosset et al. 2010</td>
<td>8 studies</td>
<td>no significant difference observed with doses of 10mg/day, 30mg/3 weeks, and 60mg/2 weeks</td>
<td>25%</td>
<td>nausea, vomiting, abdominal pain, diarrhea, and flushing.</td>
</tr>
<tr>
<td>Markowski 2012</td>
<td>20 studies</td>
<td>tumor growth was controlled in 83.9% of subjects, and median time to progression in the total group was 11.3 months.</td>
<td>21%</td>
<td>nausea, vomiting, abdominal pain, diarrhea, and flushing.</td>
</tr>
<tr>
<td>Vejle 2001</td>
<td>20 studies</td>
<td>tumor response was noted at &quot;improvement&quot; of flushing, diarrhoea, and bronchospasm</td>
<td>20%</td>
<td>nausea, vomiting, abdominal pain, diarrhea, and flushing.</td>
</tr>
<tr>
<td>Woltering 2011</td>
<td>5 studies</td>
<td>symptoms improved in 60%, diarrhea improved in 62%</td>
<td>20%</td>
<td>nausea, vomiting, abdominal pain, diarrhea, and flushing.</td>
</tr>
<tr>
<td>Biersack 2013</td>
<td>5 studies</td>
<td>symptoms improved in 60% of patients, 27% in symptomatic patients with the best LAR group, and 32% in the S-LAR group.</td>
<td>20%</td>
<td>nausea, vomiting, abdominal pain, diarrhea, and flushing.</td>
</tr>
<tr>
<td>Wokoun 2005</td>
<td>5 studies</td>
<td>symptoms normalized in 38%, symptom control in 47% the study did not report results by doses of S-LAR</td>
<td>20%</td>
<td>nausea, vomiting, abdominal pain, diarrhea, and flushing.</td>
</tr>
<tr>
<td>Woltering 2006</td>
<td>5 studies</td>
<td>out of control flushing in 0% for 60mg, 51% in 30mg, and 7% in 10mg LAR group; out of control diarrhea in 10% for 20mg, 27.8% in 30mg, and 8% in 60mg S-LAR group; 1 subject in each of the groups had flushing (1 episode/week in 20mg, 7 episode/week in 30mg, 2 days/week in 60mg S-LAR).</td>
<td>20%</td>
<td>nausea, vomiting, abdominal pain, diarrhea, and flushing.</td>
</tr>
<tr>
<td>octreotide LAR (S-LAR)</td>
<td>10 studies</td>
<td>mean CGA 56.6 mg/mL in 20mg, 66.2 mg/mL in 30mg, and 65.2 mg/mL in 60mg S-LAR.</td>
<td>20%</td>
<td>nausea, vomiting, abdominal pain, diarrhea, and flushing.</td>
</tr>
</tbody>
</table>

Safety
- Safety was reported in 8 studies. Five supported the tolerability of higher dose octreotide LAR and 3 did not report results by dose, although study sample sizes may have been too small to identify rare events.

LIMITATIONS

- Included studies varied in designs, patients, and definition of outcomes, so heterogeneity of these data prevented us from conducting meta-analysis

CONCLUSIONS

- This was a comprehensive review and synthesis of global literature published in peer-reviewed journals and presented at a variety of international and national professional congresses.
- The review indicated that above-label doses of octreotide LAR for symptom and tumor control of NENs are being used frequently for management of NENs in clinical practice and that no excess toxicity has been observed.
- In most cases, the use of high-dose octreotide LAR [i.e., dose escalation] appears to be prescribed in those with increased symptoms or tumor progression on standard dose therapy.
- Expert opinion supports escalation of somatostatin analogs for patients with refractory hormonal symptoms.
- However, given the overall scarcity of published evidence on this topic, no conclusive statements can be made on the safety and efficacy of above-label dose and/or frequency of octreotide LAR in treatment of NENs.

References