Retrospective Chart Review of Antidepressant Use in Patients with Carcinoid Tumors
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With respect to the following presentation, there has been no relevant (direct or indirect) financial relationship between the party listed above (and/or spouse/partner) and any for-profit company in the past 24 months which could be considered a conflict of interest.
Learning Objectives

At the end of this talk, the attendee will be able to:

1. Describe the theoretical concerns for using antidepressants in carcinoid tumor

2. Compare the evidence for/against antidepressant safety in patients with carcinoid tumor
Clinical Vignette

- 54 year old man with secreting “carcinoid” tumor of the small intestine with metastasis to liver.
- Diagnosed 4 years ago.
- No past psychiatric history, progressively worsening mood.
- Paroxetine 20 mg daily started by oncologist.
“Carcinoid” Tumors

- Well-differentiated, low-grade neuroendocrine tumor
- Incidence: < 5 /100,000
- Median age of onset = 64 yrs
- Jejunum, Ileum, Appendix, Cecum
- Functional (secretory)
  - Serotonin
  - Others

Carcinoid Syndrome

- Diarrhea
- Flushing
- Sweating
- Wheezing
- Valvular disease

- Serotonin excess
- (maybe histamine and tachykinins too)
Serotonin Metabolism

L-Tryptophan

5-Hydroxy-Tryptophan (5-HTP)

5-Hydroxy-Tryptamine (5-HT)

5-Hydroxy-indole acetic acid (5-HIAA)

https://upload.wikimedia.org/wikipedia/commons/thumb/1/1c/Serotonin_biosynthesis.svg/2000px-Serotonin_biosynthesis.svg.png
Serotonin Metabolism

L-Tryptophan

5-Hydroxy-Tryptophan (5-HTP)

5-Hydroxy-Tryptamine (5-HT)

5-Hydroxy-indole acetic acid (5-HIAA)

Gut

Blood

CNS

L-Tryptophan

5-Hydroxy-Tryptophan (5-HTP)

5-Hydroxy-Tryptamine (5-HT)

5-Hydroxy-indole acetic acid (5-HIAA)
Serotonin Metabolism

L-Tryptophan → 5-HTP → 5-HT → 5-HIAA

Gut

Blood

CNS

L-Tryptophan

5-HTP

5-HT

5-HIAA
Depression in Carcinoid/NETs

- Major et al. (1973): N=22
  - 50% depression, clinical impression

- Soliday et al. (2004): N=182
  - 22% depression, HADS
Depression in Carcinoid/NETs

- Major et al. (1973): N=22
  - 50% depression, clinical impression

- Soliday et al. (2004): N=182
  - 22% depression, HADS

- Antidepressants may have a role in treating Carcinoid/NET
Antidepressants in Carcinoid/NET: The Problem

SERTRALINE, A SELECTIVE SEROTONIN REUPTAKE INHIBITOR, UNMASKING CARCINOID SYNDROME

Noyer, M.D., and Benjamin M. Schwartz, M.D.

Medicine and Obstetrics/Gynecology, Albert College of Medicine, Bronx, New York

CASE REPORT

A 56-year-old Hispanic woman was placed on sertraline (Zoloft) in June 1995 for depression of 2 yr duration. A purplish rash developed on her face, arms, and upper chest, as did intermittent cyanosis of her hands, nose, and legs; she also lost 27 kg. Every dose was followed by watery diarrhea. The skin changes and
SERTRALINE, A SELECTIVE SEROTONIN REUPTAKE INHIBITOR, UNMASKING CARCINOID SYNDROME

In summary, we present the case of a woman receiving an SSRI (sertraline) for depression who developed carcinoid syndrome with extra and psychiatric disturbance, both of which resolved after aminogluthethimide and octreotide were administered. We suggest that patients taking SSRIs who develop symptoms such as rash, diarrhea, or autonomic instability be suspected of having underlying carcinoid syndrome, especially if they are not also receiving a monoamine oxidase inhibitor.

A 56-year-old woman was referred to a dermatologist in June 1995 for depression of 2 yr duration. A purplish rash developed on her face, arms, and upper chest, as did intermittent cyanosis of her hands, nose, and legs; she also lost 27 kg. Every dose was followed by watery diarrhea. The skin changes and
Antidepressants in Carcinoid/NET: The Problem

Carcinoid Tumor, Selective Serotonin Reuptake Inhibitors, and Diarrhea

TO THE EDITOR: Selective serotonin reuptake inhibitor (SSRI) antidepressants are considered effective, easy to use, and well tolerated. Because of their fairly benign side effect profile and low degree of interaction with the metabolism of other medications, SSRIs are also frequently used in the treatment of depressive symptoms in patients with various physical illnesses.
Antidepressants in Carcinoid/NET: The Problem

Carcinoid
Serotonin Release

TO THE EDITOR:

Serotonin reuptake inhibitors are considered effective and well tolerated by most patients with carcinoid syndrome. A 56-year-old woman developed diarrhea and cyanosis of her hands and feet in June 1995 after starting low-dose sertraline. Her symptoms were initially responsive to increased serotonin reuptake inhibitor dose but worsened after her dose was followed by a severe diarrhea. The patient was admitted again in February 2005, this time with a 60-hour protracted ileus. Depression, associated with carcinoid tumors is relatively rare; nevertheless, it could develop, especially in rare cases of severe comorbidity with other illnesses, as in our patient. Our case suggests that SSRIs should be avoided in patients with carcinoid tumors because a severe dehydrating diarrhea may develop.

Zdeněk Šimbera, M.D.
Chocerady, Czech Republic
Antidepressants in Carcinoid/NET: The Problem

Noyer 1997

Simbera 2005

Furse 2008
Antidepressants in Carcinoid/NET: The Problem

In 1997, Noyer et al. first reported a case of a 56-year-old woman who developed carcinoid Syndrome in June 1995 for dyspepsia. She was found to have elevated serotonin levels and low dopamine metabolites. The patient was started on a low dose of fluoxetine, a selective serotonin reuptake inhibitor (SSRI), and her symptoms improved.

In 2000, Simberkoff et al. published a review of the literature on the use of SSRIs in carcinoid syndrome, highlighting the potential for these drugs to provoke carcinoid syndrome in patients who are taking them chronically. They emphasized the need for caution in prescribing SSRIs to patients with carcinoid syndrome.

In 2008, Furse et al. conducted a retrospective study of patients with carcinoid syndrome who were treated with SSRIs. They found that SSRIs could be associated with a higher incidence of carcinoid syndrome, and recommended that physicians should be aware of the need to avoid SSRIs in the treatment of carcinoid syndrome.

References:
Antidepressants in Carcinoid/NET: The Problem

- Noyer 1997
- Simbera 2005
- Furse 2008
Antidepressants in Carcinoid/NET: The Problem

- Noyer 1997
- Warner 2001
- Simbera 2005
- Soliday 2005b
- Soliday 2005a
- Russo 2005
- Williams 2005
- Macpherson 2009
- Furse 2008
- Lapi 2012
- Moran 2012
- Vybornykh 2005
- Dolenc 2005
- Kurklinsky 2011
- Moretti 2013

Authors:
- Murphy, 1998
- Warner, 2001
- Russo, 2005
- Macpherson, 2009
- Vybornykh, 2005
- Dolenc, 2005
- Kurklinsky, 2011
- Moretti, 2013
Conversely…

Selective Serotonin Reuptake Inhibitors and Patients With Carcinoid Tumor

MARK D. WILLIAMS, M.D.
TAMARA J. DOLENC, M.D.

Serotonin is targeted in the treatment of depression with selective serotonin reuptake inhibitors (SSRIs). In the side effects other than sedation were not mentioned for and the records of four of the five indicated improvement.

Psychosomatics 2005. 46(4): 370-372
Conversely...

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Carcinoid Tumor Type</th>
<th>Urinary 5-HIAA (mg/24 hours)</th>
<th>Carcinoid Syndrome</th>
<th>Carcinoid Tumor</th>
<th>Mood Disorder</th>
<th>Psychiatric Diagnoses</th>
<th>Antidepressant Treatment</th>
<th>Duration of Treatment</th>
<th>Mood Improvement</th>
<th>Side Effects</th>
<th>Somatostatin Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61</td>
<td>Male</td>
<td>Superficial nodules in stomach</td>
<td>3.9</td>
<td>No</td>
<td>57</td>
<td>20</td>
<td>Major depressive disorder, recurrent; generalized anxiety disorder</td>
<td>Sertraline, 50 mg/day</td>
<td>1 month</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
<td>Female</td>
<td>Terminal ileum, metastases to liver</td>
<td>121.0</td>
<td>Yes</td>
<td>56</td>
<td>30</td>
<td>Major depressive disorder, recurrent; social phobia</td>
<td>Paroxetine, 40 mg/day</td>
<td>4 years</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>56</td>
<td>Female</td>
<td>Right middle lung lobe</td>
<td>No data</td>
<td>No</td>
<td>51</td>
<td>46</td>
<td>Major depressive disorder, recurrent</td>
<td>Paroxetine, 40 mg/day</td>
<td>5 years</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>68</td>
<td>Male</td>
<td>Terminal ileum, metastases to liver, bones, pleura, carcinoid heart disease</td>
<td>4.5</td>
<td>No</td>
<td>46</td>
<td>63</td>
<td>Major depressive disorder, recurrent</td>
<td>Paroxetine, 20 mg/day</td>
<td>2 years</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>75</td>
<td>Male</td>
<td>Terminal ileum, hepatic metastases</td>
<td>5.6</td>
<td>No</td>
<td>68</td>
<td>25</td>
<td>Major depressive disorder, recurrent</td>
<td>Fluoxetine, 20 mg/day</td>
<td>10 weeks</td>
<td>Yes</td>
<td>Sedation</td>
<td>No</td>
</tr>
</tbody>
</table>

Psychosomatics 2005. 46(4): 370-372
Research Questions:

- Are they safe?
- Do they “precipitate” / “unmask” CS?
- Do they worsen CS or cause catastrophic events?
Methods

• Design:
  • Chart Review
  • All patients diagnosed with carcinoid tumor AND prescribed antidepressant (Jan 2008 – April 2015)

• Outcomes:
  • Duration of use
  • Was antidepressant stopped (yes/no)
  • Reason for stopping
  • Any serious events (carcinoid crisis, death)
## Results: Demographics

<table>
<thead>
<tr>
<th></th>
<th>CS+ N (%)</th>
<th>CS- N (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>16 (17.4%)</td>
<td>76 (82.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Age (years), Mean(SD)</strong></td>
<td>61.8 yr (14.9)</td>
<td>60.1 yr (10.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Gender: Female</strong></td>
<td>7 (43.8%)</td>
<td>50 (65.8)</td>
<td>0.087</td>
</tr>
<tr>
<td><strong>Tumor Location:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ileum</td>
<td>10 (62.5%)</td>
<td>8 (10.5%)</td>
<td></td>
</tr>
<tr>
<td>Duodenum</td>
<td>1 (6.3%)</td>
<td>5 (6.6%)</td>
<td></td>
</tr>
<tr>
<td>Appendix</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (25%)</td>
<td>2 (2.6%)</td>
<td></td>
</tr>
<tr>
<td>Jejunum</td>
<td>1 (6.3%)</td>
<td>1 (1.3%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastatses</td>
<td>16 (100%)</td>
<td>34 (44.7%)</td>
<td></td>
</tr>
</tbody>
</table>
### Results: Antidepressant Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>CS+ N (%)</th>
<th>CS- N (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Antidepressant</td>
<td>16 (100%)</td>
<td>72 (100%)</td>
<td></td>
</tr>
<tr>
<td>Serotonergic Antidepressant</td>
<td>15 (93.8%)</td>
<td>68 (89.5%)</td>
<td>.511</td>
</tr>
<tr>
<td>Multiple Antidepressants</td>
<td>4 (25%)</td>
<td>12 (15.8%)</td>
<td>.289</td>
</tr>
</tbody>
</table>

**Reason for Starting:**

<table>
<thead>
<tr>
<th>Reason</th>
<th>CS+ N (%)</th>
<th>CS- N (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression/Anxiety</td>
<td>13 (81.3%)</td>
<td>53 (69.7%)</td>
<td></td>
</tr>
<tr>
<td>Sleep</td>
<td>3 (18.8%)</td>
<td>6 (7.9%)</td>
<td></td>
</tr>
<tr>
<td>Other psychiatric symptom</td>
<td>4 (5.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatic Symptoms</td>
<td>3 (3.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking Cessation</td>
<td>5 (6.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unspecified</td>
<td>8 (10.5%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Results: Duration of Use

<table>
<thead>
<tr>
<th></th>
<th>CS+ N (%)</th>
<th>CS- N (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration of Use (months), MD (range)</strong></td>
<td>11.6 mo (0-121)</td>
<td>14.3 mo (0-172)</td>
<td>.641</td>
</tr>
<tr>
<td>Stopped for Any Reason</td>
<td>4 (25%)</td>
<td>27 (35.5%)</td>
<td>.308</td>
</tr>
<tr>
<td>Stopped within 1 month</td>
<td>3 (18.8%)</td>
<td>10 (13.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Reason for Stopping:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unspecified</td>
<td>1 (25%)</td>
<td>17 (63%)</td>
<td></td>
</tr>
<tr>
<td>Symptoms Resolved</td>
<td>2 (50%)</td>
<td>5 (18.5%)</td>
<td></td>
</tr>
<tr>
<td>Ineffective</td>
<td>2 (7.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delirium</td>
<td>2 (7.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side-Effects</td>
<td>1 (25%)*</td>
<td>1 (3.7%)**</td>
<td></td>
</tr>
</tbody>
</table>

*Unspecified side-effect  **Dizziness
## Results: Serious Events

<table>
<thead>
<tr>
<th>Serious Adverse Events</th>
<th>CS+ N (%)</th>
<th>CS- N (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoid Crisis</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>n/a</td>
</tr>
<tr>
<td>Conversion from CS- to CS+</td>
<td>n/a</td>
<td>0 (0%)</td>
<td>n/a</td>
</tr>
</tbody>
</table>
### Results: Antidepressants

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Carcinoid Syndrome Present (n=25)</th>
<th>Carcinoid Syndrome Absent (n=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>Dosage Range (mg)</td>
</tr>
<tr>
<td>SSRI</td>
<td>14 (56%)</td>
<td>55 (53.9%)</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>3 (12%)</td>
<td>20 (19.6%)</td>
</tr>
<tr>
<td>Sertraline</td>
<td>1 (4%)</td>
<td>20 (19.6%)</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>4 (16%)</td>
<td>6 (5.9%)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>3 (12%)</td>
<td>5 (3.9%)</td>
</tr>
<tr>
<td>Citalopram</td>
<td>2 (8%)</td>
<td>4 (3.9%)</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>NDRD</td>
<td>3 (12%)</td>
<td>20 (19.6%)</td>
</tr>
<tr>
<td>Bupropion</td>
<td>3 (12%)</td>
<td>20 (19.6%)</td>
</tr>
<tr>
<td>SNRI</td>
<td>3 (12%)</td>
<td>9 (8.8%)</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>1 (4%)</td>
<td>7 (6.9%)</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>2 (8%)</td>
<td>2 (2.0%)</td>
</tr>
<tr>
<td>SARI</td>
<td>3 (12%)</td>
<td>7 (6.9%)</td>
</tr>
<tr>
<td>Trazodone</td>
<td>3 (12%)</td>
<td>7 (6.9%)</td>
</tr>
<tr>
<td>TCA</td>
<td>2 (8%)</td>
<td>6 (5.9%)</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>1 (4%)</td>
<td>6 (5.9%)</td>
</tr>
<tr>
<td>Doxepin</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>NaSSA</td>
<td>5 (4.9%)</td>
<td></td>
</tr>
<tr>
<td>Mirtazapine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Legend:**
- SSRI = Serotonin Specific Reuptake Inhibitor
- NDRD = Norepinephrine-Dopamine Reuptake Inhibitor
- SNRI = Serotonin-Norepinephrine Reuptake Inhibitor
- SARI = Serotonin Antagonist and Reuptake Inhibitor
- TCA = Tricyclic Antidepressant
- NaSSA = Noradrenergic and Specific Serotonergic Antidepressant
Discussion

- Long duration of antidepressant use in 92 patients with NET/carcinoid tumors
- No documented carcinoid crisis
- No conversion of CS- patients to CS+ patients (i.e., no unmasking)
- No serious adverse effects
Original Article

Retrospective Review of Serotonergic Medication Tolerability in Patients With Neuroendocrine Tumors With Biochemically Proven Carcinoid Syndrome

Diana D. Shi, BA1; David P. Yuppa, MD1,2,3; Trevor Dutton, BA4; Lauren K. Brais, BA, MPH4; Sarah L. Minden, MD1,3; Ilana M. Braun, MD1,2,3; Matthew H. Kulke, MD, MMS2,3; Jennifer A. Chan, MD, MPH1,4; and Fremonta L. Meyer, MD1,2,3

Cancer, March 2017 (Published online Month 00, 2017)
DOI: 10.1002/cncr.30633
Limitations

- Retrospective design
  - Recall bias
  - Adequate documentation of symptoms
  - Lost to follow up
- Nomenclature changes
- Endpoints
  - Serious adverse events
  - Quality of Life
Conclusions

- Did not find evidence to support the claims that antidepressants must be avoided in carcinoid/NET

- Future research
  - Prospective Design
  - Tolerability
  - Efficacy
Questions

eisenberggrzeda@sunnybrook.ca
“Carcinoid” Tumors

INTRODUCTION — The term "carcinoid" is generally applied to well-differentiated neuroendocrine tumors originating in the digestive tract, lungs, or rare primary sites such as kidneys or ovaries. Use of the term carcinoid implies well-differentiated (low- to intermediate-grade) histology and is not traditionally used to describe high-grade or poorly differentiated neuroendocrine tumors (which are rare). In the digestive tract, carcinoid tumors may be sporadic or occur as part of the syndrome of multiple endocrine neoplasia (MEN) types 1 and 2. MEN type 1 patients have an increased risk of various tumors, including carcinoid tumors, pheochromocytomas, and hyperparathyroidism. It is estimated that about 20-30% of patients with gastrinomas have MEN type 1, which is also true for about 20% of patients with vipomas and 10% of patients with glucagonomas.
Carcinoid Tumors

- First described in 1907
- Slow growing tumor
- “carcinoid” = “cancer-like”
  - (benign)
- Malignant potential discovered in 1938
Carcinoid ➔ NET

- Neuroendocrine Tumors
  - Epithelial tumors
  - Endocrine / Neuroendocrine
  - Secretory

- 2.5 – 5 / 100,000 person-years
Carcinoid $\rightarrow$ NET

- Neuroendocrine Tumors
  - Epithelial tumors
  - Endocrine / Neuroendocrine
  - Secretory
- 2.5 – 5 / 100,000 person-years
- Anatomical Locations
  - Gastroenteropancreatic
  - Pulmonary
  - Other
Functional Status

- Functional = Secretory
- Non-Functional = Non-Secretory
- Secretory Products (amines/peptides)
  - Serotonin
  - Histamine
  - Kinins
  - Prostaglandins
  - VIP
  - ACTH
  - ...