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Antidepressants Appear Safe in Patients with Carcinoid Tumor: Results of A Restrospective Review

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Abstract

Introduction—Patients living with neuroendocrine tumors have high rates of depression, often necessitating antidepressants, including selective serotonin reuptake inhibitors (SSRI). Neuroendocrine tumors (NETs) secrete vasoactive substances, including serotonin, which contribute to the cluster of symptoms known as carcinoid syndrome (flushing and diarrhea). Controversy exists over whether or not antidepressants are safe in NET. We aimed to study the safety of antidepressant use in NET patients.

Methods—We conducted a retrospective chart review of patients with well differentiated NET who were also prescribed antidepressants from January 2008 through April 2015. The study took place at Memorial Sloan Kettering Cancer Center and was approved by the hospital's institutional review board.

Results—Ninety-two patients were included. There were 16 (17.4%) patients with carcinoid syndrome (10 ileum, 1 duodenum, 1 jejunum and 4 unknown primary); and 76 (82.6%) patients without (41 lung, 9 pancreas, 8 ileal, 5 duodenum, 5 appendix, 2 unknown primary, 1 jejunum and 5 other). Median duration of antidepressant prescription was 11.6 months (range, 0–121) among those with carcinoid syndrome (N=16) and 14.3 months (range, 0–172) among those without carcinoid syndrome (n=76). Antidepressants were stopped in 31 cases (33.7%), though the reason was not specified in the majority of cases (n=18;58%). None of the patients developed carcinoid syndrome while being prescribed antidepressants. No patients developed carcinoid crisis.

Conclusion—Our findings do not support previous authors' recommendations that SSRIs must be avoided in NET patients. Several classes of antidepressants appeared safe in NET patients with and without carcinoid syndrome.

Keywords

Neuroendocrine tumors; Malignant carcinoid syndrome; Antidepressive agents; Serotonin uptake inhibitors; Serotonin; Depression

Declaration of Interest: None

1. Introduction

Well-differentiated neuroendocrine tumors (NETs) are uncommon cancers most commonly originating in the aerodigestive tracts [1,2]. Traditional classification is based on embryonal origin (foregut, midgut, and hindgut) [3]. NETs can be further classified as functional (hormone secreting) and nonfunctional (non-hormone secreting). The symptom cluster known as carcinoid syndrome (CS) is associated mostly with midgut tumors located in the distal small intestine and proximal colon [4]. CS results from overproduction of serotonin and other vasoactive substances such as histamine, tachykinins, and prostaglandins that get secreted into the systemic circulation [5,6]. The relative contributions of each vasoactive substance involved in the syndrome are uncertain [5,6]. Typical symptoms include (a) episodic flushing involving the face neck and upper chest, which appears red and associated with a mild burning sensation which spontaneously resolves and, (b) secretory diarrhea that can vary from a few episodes to more than 30 a day, typically watery and non-bloody [4]. The diarrhea is usually unrelated to flushing episodes [4].

In the central nervous system (CNS), serotonin is involved in mood regulation [7]. Serotonin cannot cross the blood brain barrier, so CNS serotonin production depends on its precursor, tryptophan, crossing into the CNS [8]. In NET, tryptophan is shunted towards serotonin-producing NET cells, thus depriving the CNS of serotonin precursor [7]. This may explain the higher rates of depression in this population reported in some studies [9,10]. In cancer patients, antidepressants are a mainstay in treating depression [11,12], pain [13], and insomnia [14,15]. Serotonergic antidepressants (SA), such as the selective serotonin reuptake inhibitors (SSRIs), act by inhibiting serotonin reuptake in the synapse and thereby increasing the availability of serotonin in the CNS [16]. Many of the side-effects, however, result from serotonin receptor agonist activity in the gut, causing diarrhea and increased gastrointestinal motility [11]. Because of the overlap between these symptoms and the symptoms of CS, some authors have cautioned against the use of antidepressants in patients with NETs[17–19].

We sought to add to the small but growing literature on the safety of antidepressant therapy in patients with NETs with (CS+) and without (CS−) carcinoid syndrome. The primary outcome measures were duration of treatment of antidepressant therapy and frequency of treatment discontinuation. Secondary outcomes included reason for starting and stopping antidepressants, dosage ranges of antidepressants, and whether or not patients developed serotonin syndrome or carcinoid crisis during the study period.

2. Materials and Methods

2.1 Setting

We obtained an institutional review board waiver of authorization to review the records of patients with NETs at Memorial Sloan Kettering Cancer Center (New York, NY) who were prescribed anti-depressant therapy from January 1, 2008 through April 1st 2015.

2.2 Patient Identification

Patients were identified by searching the hospital's tumor registry for patients with NETs, which was then cross-referenced with hospital inpatient and outpatient pharmacy records for

presence of an antidepressant being prescribed. We searched for ICD-o codes that most overlapped with the historical “carcinoid tumor” nomenclature (e.g., well-differentiated tumors). Antidepressant search terms consisted of generic names for any antidepressant medication listed on the hospital formulary including all tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, norepinephrine-dopamine reuptake inhibitors, and others (e.g., trazodone, mirtazapine). Since antidepressants can be used for a variety of indications, the indication for starting a medication was not considered in the inclusion/exclusion criteria.

2.3 Chart Review

Electronic medical records (EMR), clinical histories and pathology were reviewed to confirm NET (by pathology reports) and antidepressant use (based on standardized medication list). Manual chart review was performed by one of five authors (AB, SE, FEF, MM, and RM), and independent review was performed (EIG) on 40% of cases to ensure quality. Any disagreements were resolved by group consensus. Initial training was provided to those abstracting data and a standardized data abstraction worksheet was used to improve methodologic consistency.

2.4 Inclusion/Exclusion Criteria

Participants were limited to adults aged 18–89 years old. Patients with a historical diagnosis of NET that had no evidence of disease at the time of initial presentation to our hospital were excluded. Poorly differentiated neuroendocrine carcinoma was not included in our study, in an attempt to overlap our NET sample as closely as possible with the now outdated term ‘carcinoid tumor’.

2.5 Data Elements

The hospital database was queried to obtain the following: (a) patient demographic data (age at the time of cancer diagnosis, gender); (b) cancer characteristics (tumor diagnosis, international classification of diseases-oncology histology and tumor site, and presence or absence of metastases at the time of diagnosis); (c) antidepressant characteristics (name, start and stop dates, dosage); (d) date of death; (e) date of first psychiatry visit, if applicable. Electronic notes linked to the hospital database were also queried for the search terms “serotonin syndrome”, “hypertensive urgency”, and “hypertensive crisis”. The two latter terms were included in the rare event that patients had been on MAO inhibitors

Manual chart review of home medication lists was used to abstract the following data: (a) name of antidepressant; (b) dose of antidepressant; (c) start date (considered to be the first date that a medication appeared in the home medication list); (d) date of last known antidepressant use. Last known antidepressant use was defined by one of the following: (a) antidepressant stopped (b) patient lost to follow up (defined as no entry in EMR > 3 months), (c) patient deceased (defined as date of death within 3 months of the last entry in EMR); (d) retrospective study completion (defined as date of study completion if within 3 months of the last entry in EMR). For consistency, the date of study completion was pre-

determined to be April 1st 2015. The total duration of antidepressant use was calculated as the number of days between first and last known antidepressant use.

Consultation notes and progress notes corresponding to the first and last known dates of antidepressant use were manually reviewed to abstract the following data: (a) reason for starting antidepressant (depression/anxiety, other psychiatric symptoms, insomnia, smoking cessation, somatic symptom (diarrhea or pain), and unspecified); (b) reason for stopping antidepressant (delirium, medication side-effects, symptom remission, lack of efficacy, and unspecified). Patient who were still prescribed antidepressants at the time of lost to follow-up, death, or study completion were given a designation of "antidepressant not stopped".

Carcinoid syndrome was defined by either (a) presence or absence of the phrase "carcinoid syndrome" in the attending electronic progress notes or (b) results of elevated biomarker measurements (urine 24-hour 5-HIAA). Electronic medical records were also reviewed for (a) presence or absence of somatostatin analogs (SSA), for example, octreotide or lanreotide); (b) presence or absence of phrases "serotonin syndrome", "carcinoid crisis" (c) presence or absence of metastases. Laboratory data from EMR was also manually reviewed for presence of biomarkers in case results had not been transcribed into oncology attending notes.

For patients taking multiple medications sequentially over time without interruption, the duration of antidepressant use was defined as the time from first date of use of the first antidepressant until the last date of use of the last antidepressant. The only exception was if antidepressants were stopped for > 1 month and then restarted. In these cases, only the longer of the two durations of use was reported.

2.6 Data Analysis

Measures of central tendency reported were either mean and standard deviation for normal distributions (age), or median and range for non-normal distributions (duration of antidepressant use). Other descriptive statistics (frequencies and percentages, ranges) were used to report all remaining categorical variables.

When observed differences were noted, tests for statistical significance were performed for certain variables. The Mann-Whitney U Test was used to determine statistical significance between the mean duration of antidepressant use between the CS+ and CS− groups because of unequal variance and samples sizes. Fisher's exact test was used test for differences in gender, rates of stopping antidepressants, rates of multiple antidepressants, and rates of SA use, between groups of CS+ and CS− patients. A p-value of .05 was used as the cutoff for statistical significance. All analyses were performed using IBM SPSS Inc., v22 (Chicago, IL, USA).

3. Results

The initial database search identified 116 cases for possible inclusion. Seventeen were excluded due to no evidence of disease at the time of initial presentation and 7 were excluded due to no antidepressant use based on manual chart review. A total of 92 patients

were included (16 CS+ and 76 CS−). Demographics and clinical characteristics are listed in table 1. Psychiatry consultation occurred in a minority of cases (n=19;27.1%). No instances of serotonin syndrome or hypertensive crisis were found.

The median duration of antidepressant use was 11.6 months (range, 0–121 months) in the CS+ group (n=16) and 14.3 months (range, 0–172 months) in the CS− group (n=76) (Table 1). Overall, antidepressants were stopped in 31 cases (33.7%), and in the majority of cases the reason for stopping was unspecified (n=18;58%). Among the CS+ group, antidepressant use of less than one month was found in 3 cases: one case was lost to follow up; two cases experienced symptom remission and no longer required antidepressants. Among the CS− group, antidepressant use of less than one month was found in 10 cases: 6 cases were lost to follow-up; two cases experienced symptom remission and no longer required antidepressants; one case reported dizziness warranting stopping antidepressant; one case had no specified reason for stopping antidepressant. No CS− patient developed CS at any point during the study period (n=0/76).

Overall, multiple antidepressants were prescribed in 16 cases (17.4%). Among patients prescribed multiple antidepressants, the majority were prescribed a combination of SA and non-SA in both CS+ (n=3;75%) and CS− (n=8;66.7%) subsets. Serotonergic antidepressants were prescribed in 83 cases (90.2%). In total, 127 antidepressants were prescribed to our sample of 92 patients, and the frequencies and dosage ranges of antidepressants are listed in table 2. The dosages listed represent the range of doses prescribed at the last known time of antidepressant use. No instances of monoamine oxidase inhibitor prescription were documented. No patients developed carcinoid crisis. Among the 18 patients prescribed SSA, 55.6% (n=10) of them stopped antidepressant use compared to 28.4% (n=21/74) of patients not prescribed a SSA (Chi-Square 4.79, df=1, p=.029).

4. Discussion

Despite being thought of as a rare disease[20], epidemiologic data from the past 50 years suggest that NETs are increasing in incidence and prevalence[1,21], and are now more common than esophageal, gastric, pancreatic, and hepatobiliary cancers[1]. Because NETs are often slow growing and survival durations are often long, the burden of illness—including high rates of depression and low quality of life—are significant. Accordingly, antidepressant use may become a mainstay of whole-person care for NET patients, yet research has found that antidepressants may be under-prescribed among NET patient populations[22].

The safety of SAs in patients with the carcinoid syndrome was first called into question following publication of a case report by Noyer et al. in 1997 [17], in which antidepressant use “unmasked” CS (and thus unmasked a NET) in a patient not previously known to have a NET. It is worth noting that Noyer et al., did not explicitly caution against using SSRIs in patients with NETs, although subsequent authors would cite their results as such. It would be 8 more years until Williams et al. [8] responded by presenting a series of 5 patients with NET, one of whom had CS, and all of whom were safely prescribed antidepressants for durations ranging from 1 month to 5 years. The authors argued that it was premature to completely discount the use of SSRIs in patients with NETs. Since then, a second case report described

"unmasking" of a NET [18], and a third case reported that antidepressants caused CS in a patient with known NET but without prior CS [19]. In the last two publications, the authors explicitly cautioned against the use of SSRIs in patients with NETs [18,19].

Recently, Shi et al [23] conducted a retrospective chart review of biochemically-proven neuroendocrine patients who initiated treatment with serotonergic antidepressants following a diagnosis of NET tumor. They included 52 patients in their study, all of whom had elevated levels of urinary 5-HIAA. Within their sample, less than < 10% of them developed the constellation of CS symptoms, and no patients developed carcinoid crisis or other medical emergencies due to initiation of antidepressant treatment.

Our study revealed several important findings about the safety of antidepressants in patients with well differentiated NETs. First, we found a modest number of patients with CS who were prescribed antidepressants for long durations. The median duration of antidepressant use was one year, with a maximum duration of 10 years in a CS+ patient and 14 years in a CS− patient. The majority of CS+ did not stop antidepressants at any point during the study, and among those who did, CS was never reported to be the reason for stopping. Second, no patients developed a carcinoid crisis and no patients required dose reduction of their antidepressant medication. Third, no CS− patients developed CS following the administration of antidepressants. It is worth noting that among the CS+ patients, 75% of those who stopped antidepressant use did so within one month. Conversely, among CS− patients, only 37% of those who stopped antidepressant use did so within one month. Our small sample size limits our ability to interpret these findings and future studies should try replicate this finding.

The majority of patients in our sample were prescribed SAs, which, even among the general population, can cause gastrointestinal side effects [8]. Interestingly, only few patients were prescribed non-SAs (e.g., bupropion), which do not act on the serotonergic system and therefore carry less risk of diarrhea in general [24]. The reasons for this finding are not clear and future research should examine the safety profile of non-SAs versus SAs in this population. SSAs function by blocking the hormone activity associated with the secretory products of NETs and may be prescribed to reduce the symptom burden of NETs[6]. Accordingly, we expected that patients prescribed SSAs would better tolerate antidepressant use and would thus have a lower rate of stopping antidepressant use. Our finding that patients who were prescribed SSAs were more likely to discontinue antidepressant use was unexpected and could be explained by the possibility of SSAs acting as a proxy for significantly worse symptom burden in our sample, or, may have reflected clinicians' discomfort with using serotonergic agents in patients with carcinoid syndrome. The question of whether SSAs may allow for improved tolerability of antidepressants in NET patients[8,23] is still an important one, and should be explored in larger, prospective studies.

There are limitations to our study. Firstly, despite the large overall sample size, the size of the CS+ subset was small (n=16), and this subset of patients may be most at risk for worsening CS symptoms following antidepressant use. Secondly, inherent to this population is also the possibility of a selection bias, since oncologists may avoid prescribing antidepressants to patients with carcinoid syndrome or a history of carcinoid crisis. Other

forms of bias may have been introduced by the limited date range (2008 onwards) or because of the retrospective nature of the study design. For example, oncology attending notes may not have documented the presence or absence of CS, medication lists may not have been accurately updated, patients may not have accurately recalled all medications that they were prescribed, medication nonadherence may not have been reported, and indications for starting and stopping antidepressants were often unspecified. Bias may have also been introduced because the nomenclature of carcinoid and neuroendocrine tumors has changed over the sampling period, however, we attempted to circumvent this by searching for a variety of histological codes and ICD codes relating to carcinoid histology. Still, some tumors however, classified by different ICD codes may have been missed. Lastly, the study design did not allow us to explore several key issues, for example, whether carcinoid tumor symptoms worsened following the onset of antidepressant use, and whether the outcomes were different for patients who started antidepressant use after NET diagnosis compared to before the diagnosis. Prospective studies with systematic symptom monitoring may provide valuable information regarding this issue. In addition, future studies should also measure and trend urinary 5-HIAA levels following initiation of antidepressant use to monitor for adverse outcomes and to study whether this biomarker can be used to predict tolerability of antidepressants in this patient population.

5. Conclusion

With the growing incidence and prevalence of NETs, the use of antidepressants may have an increasing role in the whole-person care of patients with NETs. Until now, guidance on the safety of antidepressants in NETs (and CS, specifically) has been largely lacking. Our findings do not support the conclusions drawn by previous authors that SSRIs should be avoided in NET patients. In fact, many classes of antidepressants appeared to be safe in NET patients, both with and without CS. One notable exception is the class of monoamine oxidase inhibitors, since no instances of their use were found in our sample. Our findings echo the results of Shi et al., who demonstrated safety of antidepressant use in a large number of patients with biochemically-proven carcinoid syndrome [23]. As with antidepressant use in all patients, NET patients should be monitored for worsening of symptoms, and referral to psychiatrists with expertise in treating cancer patients may be helpful. Future research should examine the efficacy of antidepressants in this patient population.

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Abbreviations

NET	neuroendocrine tumors

CS	carcinoid syndrome
CNS	central nervous system
SA	serotonergic antidepressant
SSRI	selective serotonin reuptake inhibitor
EMR	electronic medical record
SSA	somatostatin analog

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Table 1

Patient Demographics And Antidepressant Variables

	Group		
	Carcinoid Syndrome Present *n* (%)	**Carcinoid Syndrome Absent *n* (%)**	**p-value**
Total	16 (17.4%)	76 (82.6%)	
Age (years), *M*(SD)	61.8 yr (14.9)	60.1 yr (10.9)	
Gender			
Male	9 (56.3%)	26 (34.2%)	p=.087 [a]
Female	7 (43.8%)	50 (65.8%)	
Tumor Location			
Lung		41 (53.9%)	
Pancreas		9 (11.8%)	
Ileum	10 (62.5%)	8 (10.5%)	
Duodenum	1 (6.3%)	5 (6.6%)	
Appendix		5 (6.6%)	
Unknown Primary	4 (25%)	2 (2.6%)	
Jejunum	1 (6.3%)	1 (1.3%)	
Other		5 (6.6%)	
Illness Features			
Metastases	16 (100%)	34 (44.7%)	
Somatostatin Analog	14 (87.5%)	4 (5.3%)	
Biomarker Positive	12 (75%)	0 (0%)	
Duration of Antidepressant Use (range) (months), *Md*	11.6 mo. (0–121)	14.3 mo. (0–172)	p=.641 [b]
Reason for starting antidepressant			
Depression/Anxiety	13 (81.3%)	53 (69.7%)	
Sleep	3 (18.8%)	6 (7.9%)	
Other psych symptom		4 (5.3%)	
Somatic Symptoms		3 (3.9%)	
Smoking Cessation		2 (2.6%)	
Unspecified		8 (10.5%)	
Reason for stopping antidepressant			
Unspecified	1 (25%)	17 (63.0%)	
Remission	2 (50%)	5 (18.5%)	
Ineffective		2 (7.4%)	
Delirium		2 (7.4%)	
Side-effects	1 (25%)	1 (3.7%)	
Antidepressant Variables			
Serotonergic Antidepressant	15 (93.8%)	68 (89.5%)	p=.511 [c]
Multiple Antidepressants	4 (25%)	12 (15.8%)	p=.289 [d]
Stopped for Any Reason	4 (25%)	27 (35.5%)	p=.308 [e]

[a] Fisher's exact test $\chi^2(1)=2.724$;

[b] Mann-Whitney U Test (normal distribution was not assumed);

[c] Fisher's exact test $\chi^2(1)=.274$;

[d] Fisher's exact test $\chi^2(1)=.780$;

[e] Fisher's exact test $\chi^2(1)=.656$

M = Mean, *Md* = Median

Demographic variables, illness variables, and antidepressant variables of patients with and without carcinoid syndrome.

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Table 2

Frequencies and dose ranges of antidepressants used by patients with and without carcinoid syndrome.

	Group			
	Carcinoid Syndrome Present (*n*=25)		**Carcinoid Syndrome Absent (*n*=102)**	
Antidepressant	***n* (%)**	**Dosage Range (mg)**	***n* (%)**	**Dosage Range (mg)**
SSRI	14 (56%)		55 (53.9%)	
Escitalopram	3 (12%)	10 – 30 mg	20 (19.6%)	5 – 30 mg
Sertraline	1 (4%)	50 – 100 mg	20 (19.6%)	25 – 200 mg
Paroxetine	4 (16%)	10 – 40 mg	5 (4.9%)	10 – 40 mg
Fluoxetine	3 (12%)	20 – 40 mg	6 (5.9%)	20 – 40 mg
Citalopram	2 (8%)	20 mg	4 (3.9%)	10 – 40 mg
Fluvoxamine	1 (4%)	150 mg		
NDRI	3 (12%)		20 (19.6%)	
Bupropion	3 (12%)	300 mg	20 (19.6%)	150 – 450 mg
SNRI	3 (12%)		9 (8.8%)	
Venlafaxine	1 (4%)	75 mg	7 (6.9%)	75 – 300 mg
Duloxetine	2 (8%)	20 – 60 mg	2 (2.0%)	20 – 60 mg
SARI	3 (12%)		7 (6.9%)	
Trazodone	3 (12%)	25 – 50 mg	7 (6.9%)	25 – 100 mg
TCA	2 (8%)		6 (5.9%)	
Amitriptyline	1 (4%)	25 mg	6 (5.9%)	10 – 150 mg
Doxepin	1 (4%)	25 mg		25 mg
NaSSA			5 (4.9%)	
Mirtazapine			5 (4.9%)	7.5 – 15 mg

SSRI = Serotonin Specific Reuptake Inhibitor, NDRI = Norepinephrine-Dopamine Reuptake Inhibitor, SNRI = Serotonin-Norepinephrine Reuptake Inhibitor, SARI = Serotonin Antagonist and Reuptake Inhibitor (SARI), TCA = Tricyclic Antidepressant, NaSSA = Noradrenergic and Specific Serotonergic Antidepressant

Frequencies and dose ranges of antidepressants used by patients with and without carcinoid syndrome. The sample size of 127 reflects that some patients received more than one antidepressant.