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Association of 5-HIAA and Mortality in Neuroendocrine Tumor Patients: A Systematic Review and Meta-Analysis

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Vijay N. Joish[1], Sandip Shah[2], Helen (Dong) Shao[2], Chad McKee[1], Pablo Lapuerta[1], Jerome Zacks[3]

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Full ePoster

Figure 1. PRISMA

Table 1. Studies

Figure 2. Forest

Figure 3. Model

Background

- Excessive secretion of serotonin by neuroendocrine tumors (NET) has been associated with tumor burden, fibrosis, and intermediate outcomes such as development of carcinoid heart disease (CaHD) and progression of CaHD[1,2]
- There is a lack of studies clearly defining the relationship between 5-hydroxyindoleacetic acid (5-HIAA), a marker of serotonin, and long-term outcomes such as mortality in patients with NETs[3,4]

We conducted a systematic review and meta-analysis to investigate the association between 5-HIAA and all-cause mortality in NET patients

Methods

- A systematic literature search was performed for studies published in English between 2007-2017 and indexed in PubMed, Embase, or secondary sources
- Clinical and observational studies in patients with NETs reporting 24-hour urinary 5-HIAA (mg/24 h) and mortality were included
- Mortality was converted to rates per person-years (number of patients by months of study follow-up, divided by 12) and log-transformed to normalize the data
- A restricted maximum likelihood (REML) meta-regression model, which controls for study size and dispersion, was used to estimate the relationship between 5-HIAA and 1-year mortality

References

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Disclosures

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VNJ, CM (former), PL are employees of Lexicon Pharmaceuticals, Inc.
SS, HDS (former) are employees of MKTXS who received funding from Lexicon Pharmaceuticals, Inc. for this work.
JZ has received research support from Lexicon Pharmaceuticals, Inc.

Results

Systematic Literature Review

- 1,715 records were screened, 307 of which underwent full-text review
- 36 studies reporting urinary 5-HIAA and mortality were assessed for eligibility in the meta-analysis, of which 12 studies (with 14 treatment arms) were included (**Figure 1**)
- The 12 included studies reported results for 755 NET patients contributing 3,442 person-years (**Table 1**)

Figure 1. PRISMA flow diagram of screened and included studies

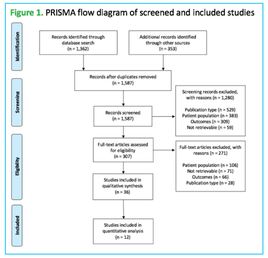


Table 1. Study population and clinical characteristics contributing to the analysis

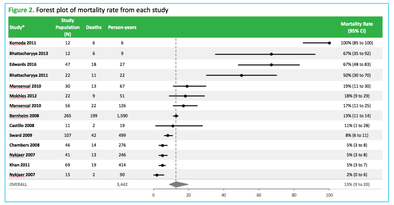
Study*	Study Population (N)	Follow-Up (months)	Person-years	Deaths, n	Mean 5-HIAA (mg/24h)
Bernheim 2008	265	72	1,590	199	183.0
Bhattacharyya 2011	22	12	22	11	150.0
Bhattacharyya 2013	12	8.5	9	6	139.8
Castillo 2008	11	21	19	2	251.0
Chambers 2008	46	72	276	14	60.7
Edwards 2016	47	7	27	18	168.0
Khan 2011	69	72	414	19	71.0
Komoda 2011	12	6	6	6	157.5
Mansencal 2010	30	27	67	13	358.0
Mansencal 2010	56	27	126	22	251.0
Mokhles 2012	22	28	51	9	186.0
Nykjaer 2007	15	72	90	2	4.0
Nykjaer 2007	41	72	246	13	32.5
Swand 2009	107	56	499	42	76.5

*Some studies included specific subgroups of NET patients, for example with CS or CaHD.

5-HIAA and Mortality

- Mean 5-HIAA across all studies was 149.2 mg/24 h (range, 4.0 to 358.0; **Table 1**); the reference range is 2 to 7 mg/24 h[5]
  - Mean 5-HIAA was 43.4 mg/24 h in studies not reporting CS or CaHD specifically; 161.0 mg/24 h in CS patients, and 199.2 mg/24h in CaHD patients
- The overall annual mortality rate was 13% (95% CI, 9% to 20%) across studies from the random effects model (**Figure 2**)
  - Overall mortality was 5.6% in studies not reporting CS or CaHD specifically; 8.2% in CS patients, and 27.8% in CaHD patients

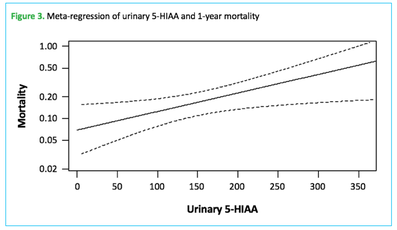
Figure 2. Forest plot of mortality rate from each study



Meta-Regression Analysis: 5-HIAA and Mortality

- For every 10-unit increase in 5-HIAA, the meta-regression model yielded an 11.8% (95% CI, 8.96 to 17.0) increase in 1-year mortality (**Figure 3**)
  - This association remained significant after controlling for underlying subgroup conditions (NET only, CS, CaHD; $P = 0.007$)

Figure 3. Meta-regression of urinary 5-HIAA and 1-year mortality



Conclusions

- In NET patients, elevated 5-HIAA levels are predictive of all-cause mortality within 1 year
- Reducing serotonin may lead to better long-term outcomes for NET patients

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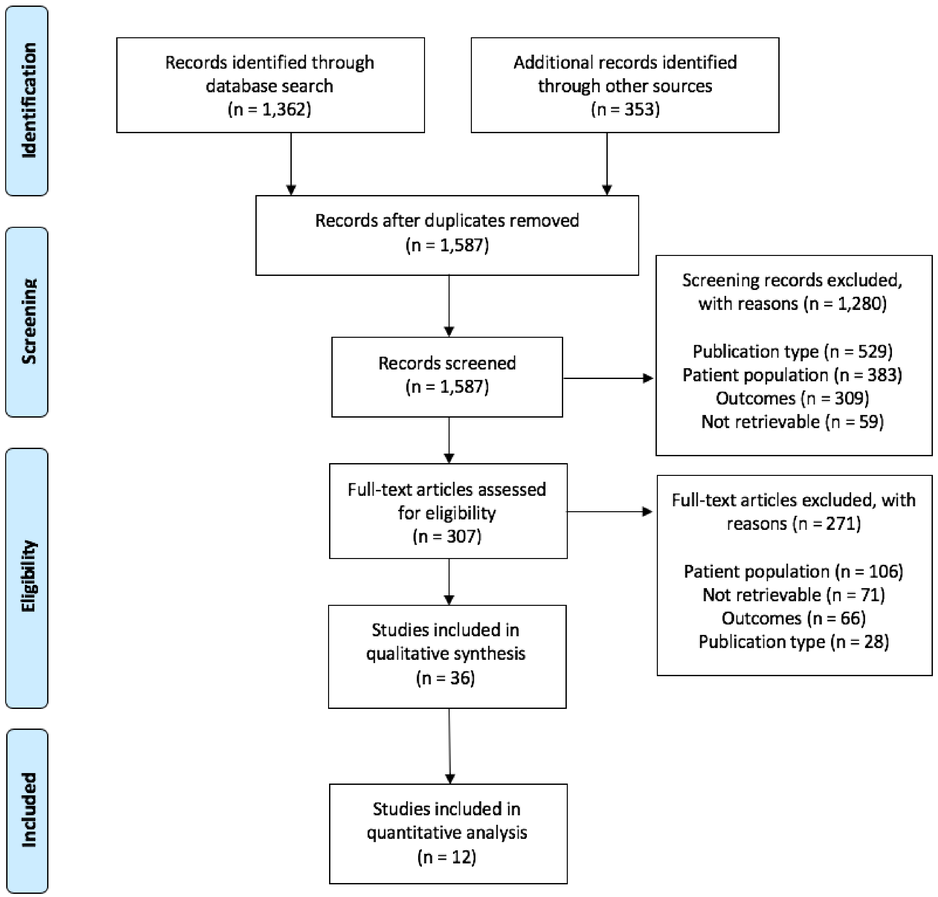

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References of Included Studies

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Figure 2. Forest plot of mortality rate from each study

Study*	Study Population (N)	Deaths	Person-years	Mortality Rate (95% CI)
Komoda 2011	12	6	6	100% (85 to 100)
Bhattacharyya 2013	12	6	9	67% (35 to 92)
Edwards 2016	47	18	27	67% (48 to 83)
Bhattacharyya 2011	22	11	22	50% (30 to 70)
Mansencal 2010	30	13	67	19% (11 to 30)
Mokhles 2012	22	9	51	18% (9 to 29)
Mansencal 2010	56	22	126	17% (11 to 25)
Bernheim 2008	265	199	1,590	13% (11 to 14)
Castillo 2008	11	2	19	11% (1 to 28)
Sward 2009	107	42	499	8% (6 to 11)
Chambers 2008	46	14	276	5% (3 to 8)
Nykjaer 2007	41	13	246	5% (3 to 8)
Khan 2011	69	19	414	5% (3 to 7)
Nykjaer 2007	15	2	90	2% (0 to 6)
OVERALL			3,442	13% (9 to 20)

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