A SYSTEMATIC LITERATURE REVIEW OF THE IMPACT OF 5-HT$_3$RA USE ON HEALTHCARE UTILIZATION IN PATIENTS WITH CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING IN THE UNITED STATES

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BACKGROUND

- Uncontrolled chemotherapy-induced nausea and vomiting (CINV) can lead to nutrient depletion, diminished function, disruption of chemotherapy, and increased costs.[1]
- Standard antiemetic therapy includes 5-hydroxytryptamine receptor antagonists (5-HT$_3$RAs) for CINV prophylaxis, with palonosetron recommended in NCCN,[1] MASCC,[2] and ASCO[3] guidelines as the preferred 5-HT$_3$RA for CINV prophylaxis with moderately emetogenic chemotherapy (MEC).
- Among all 5HT$_3$RAs, palonosetron is preferred in NCCN for highly emetogenic chemotherapy (HEC), and in MASCC for AC/EC chemotherapy when an NK1RA is not available.[1-2]
- There is evidence that using 5-HT$_3$RAs can reduce economic burden but no comprehensive review of the evidence is available.

OBJECTIVE

- This study aims to systematically review published literature on healthcare utilization associated with CINV prophylaxis with 5-HT$_3$RAs.

METHODS

Data Sources

- PubMed and 3 additional databases:
  - Database of Abstracts of Reviews of Effects (DARE)
  - NHS Economic Evaluation Database (NHS EED)
  - Health Technology Assessment Database (HTA)
- Four conferences: Academy of Managed Care Pharmacy (AMCP), American Society of Clinical Oncology (ASCO), International Society for Pharmacoeconomics and Outcomes (ISPOR), Multinational Association of Supportive Care in Cancer (MASCC)
- Bibliographies of included articles

Search Strategy

- Database searches were conducted during 7/2012 and conference years were 2010, 2011, and 2012.
- MeSH terms, subheadings, and key words used were: 5-HT$_3$RAs, dolasetron mesylate, granisetron, ondansetron, palonosetron, tropisetron, Anzemet®, Kytril®, Zofran®, Aloxi®, Navoban®, cost, cost analysis, economics, utilization, CINV, emesis, nausea, and vomiting.

Inclusion/Exclusion Criteria

- Studies published before 1997, not in English or not reporting data on human subjects, CINV, 5-HT$_3$RAs, pharmacological treatment, or cost/utilization were excluded. For duplicate studies, only the full-length articles (not the conference abstracts) were included in the review.

Outcomes

- Utilization: rescue medication, outpatient service, and inpatient service use.

RESULTS

Search Results and Description of Included Studies

Reference	Study Years	Study Design	OCEBM[4] (Jadad[5])	5-HT$_3$RA Studied	Indication for Chemotherapy	Chemo-therapy	Total N (by drug)	Observation Period (days)
Avritscher, 2010	97-02	CEA	2c	O, P	Br	MEC	707 (NR)	84
Feinberg, 2009	05-06	RETRO	2b	O, P	Br, Lu, CRC, other	LEC, HEC, MEC	3190 (P: 1636, O: 1554)	5
Feinberg, 2012	06-09	RETRO	2b	O, P	Lu	HEC, MEC	362 (P: 209, O: 153)	treatment + 7
Fox-Geiman, 2001	97-98	RCT	2b (3)	O, G	Pre-BMT	HEC	96 (Oral O: 32, Oral G: 32, IV O: 32)	9
Gralla, 1998		RCT	2b (4)	O, G	Lu, GI, other	HEC	1054 (G: 534, O: 520)	1
Grote, 2006		PRO	1b	P	Br, Ly, Lu, CRC, other	MEC	58 (P: 58)	5
Hatoum, 2012	05-08	RETRO	2b	P, (O, G, D)[A]	Br, Lu	HEC, MEC	11974 (P: 4060, Other: 7914)	180
Knoth, 2011a[B]	08-09	RETRO	2b	(P, O, G, D)[A]	Br, Lu, CRC	HEC, MEC	9558 (NR)	30
Knoth, 2011b[B]	08-09	RETRO	2b	P, (O, G, D)[A]	Br, Lu, CRC	HEC	1518 (P: 1184, Other: 334)	30
Knoth, 2011c[B]	08-09	RETRO	2b	P, (O, G, D)[A]	Br, Lu, CRC	MEC	4394 (P: 3061, Other: 1333)	30
Knoth, 2012a[B]	05-09	RETRO	2b	O, P, G, D		HEC, MEC	8812 (P: 3726, O: 3018, G: 1143, D: 925)	5
Knoth, 2012b[B]	08-09	RETRO	2b	O, P, G, D		HEC, MEC	5912 (P: 4245, Other: 1667)	30
Lin, 2010[B]	05-09	RETRO	2b	P, (O, G, D)[A]	Ly	HEC, MEC	2609 (P: 979, Other: 1630)	180
Mattiuzzi, 2010	05-08	RCT	2b (2)	O, P	Leukemia	MEC	143 (O: 47, P days 1-5: 48, P days 1,3,5: 48)	7
Schwartzberg, 2011	06-10	RETRO	2b	P, (O, G, D)[A]	Br, Ly, GI, Uro, other	HEC	4552 (P: 3574, Other: 978)	5
Yeh, 2011	06-08	RETRO	3b	O, P	Gy	HEC	53 (P: 34, O: 19)	7

[A] Aggregate data of indicated 5-HT$_3$RAs. [B] Conference presentation. [C] Oxford Center for Evidence-based Medicine Levels of Evidence. [D] Jadad score to assess quality of clinical trials. Study Design: cost-efficacy analysis (CEA); non-randomized prospective observational study (PRO); randomized control trial (RCT); retrospective cohort (RETRO). 5-HT$_3$RAs: ondansetron (O); palonosetron (P); granisetron (G); dolasetron (D). Indication: breast (Br); colorectal (CRC); gastrointestinal (GI); gynecological (Gy); lung (Lu); lymphoma (Ly); urogenital (Uro); pre-bone marrow transplant (Pre-BMT); other: other cancer/not specified. Chemotherapy: highly emetogenic chemotherapy (HEC); moderately emetogenic chemotherapy (MEC); low emetogenic chemotherapy (LEC). NR: not reported.

- Of the 434 identified records, 16 reporting utilization in the US were reviewed (excluded: 29 duplicates, 389 off-topic records).
- Studies varied significantly in designs, patients, 5-HT$_3$RA regimens, and definition of outcomes.

Rescue Medication Use (rate per cycle for all patients unless indicated)

Reference	5-HT$_3$RA Studied				
	O	P	G	D	Other[B]
Avritscher, 2010	61%[C]	56%[C]			
Feinberg, 2009	24%	67%			
Feinberg, 2012	83%	28%			
Fox-Geiman, 2001[A]	91%		85%		
Fox-Geiman, 2001[A]	79%				
Gralla, 1998	25%		31%		
Knoth, 2011b		7%			12%
Knoth, 2011c		16%			30%
Knoth, 2012a	11%	8%	20%	20%	
Knoth, 2012b	24%	14%	27%	31%	
Mattiuzzi, 2010[A]	11%	6%			
Mattiuzzi, 2010[A]		10%			
Schwartzberg, 2011		35%			35%

[A] Studies included multiple times indicate differences in drug administration. [B] Data included use of other 5-HT$_3$RAs (specific breakdown was not provided), unless otherwise noted. [C] Represents a model input. 5-HT$_3$RAs: ondansetron (O); palonosetron (P); granisetron (G); dolasetron (D).

- In 5 studies, fewer patients treated with palonosetron required rescue medication versus ondansetron users (56% vs. 61%, 28% vs. 83%, 8% vs. 11%, 14% vs. 24%, 6% vs. 11%)
- 2 studies found that palonosetron users had a lower rate of rescue medication use than patients using ondansetron, granisetron, or dolasetron (Knoth 2012a, Knoth 2012b).
- 7 of the 9 studies including palonosetron users found this group had lower rates of rescue medication use than the comparator 5-HT$_3$RA.
- Fox-Geiman (2001) reported relatively high rates of rescue medication use in ondansetron (91%, 79%) and granisetron (85%) users.

Outpatient and Inpatient Service Use (rate per cycle for all patients unless indicated)

Reference	5-HT$_3$RA Studied			Description
	O	P	Other[A]	
Outpatient				
Avritscher, 2010	10%[B]	5%[B]		office visit (patients with emesis)
Yeh, 2011	10%	8%		outpatient, related to CINV
Inpatient				
Avritscher, 2010	0.4%[B]	0.2%[B]		hospitalization (patients with emesis)
Feinberg, 2012	1%	1%		hospital re-admission related to CINV from day 1 to 7 days after last round of chemotherapy
Hatoum, 2012		4%	6%	hospitalization (breast cancer group)
Hatoum, 2012		10%	14%	hospitalization (lung cancer - carboplatin group)
Hatoum, 2012		16%	23%	hospitalization (lung cancer - cisplatin group)
Knoth, 2011a			6%	hospitalization among patients with CINV
Knoth, 2011a			1%	emergency room visit related to CINV for patients with CINV
Lin, 2010		7%	10%	emergency room/hospital admission events
Yeh, 2011	5%	0%		hospital re-admission related to CINV from day 1 to 7 days after last round of chemotherapy
Yeh, 2011	0%	0%		emergency room visit related to CINV for patients with CINV

[A] Data included use of other 5-HT$_3$RAs (specific breakdown was not provided by given paper), unless otherwise noted. [B] Represents a model input used by author.
5-HT$_3$RAs: ondansetron (O); palonosetron (P).

- 2 studies found palonosetron users required fewer outpatient services compared with ondansetron users (5% vs. 10%, 8% vs. 10%).
- 4 studies reported fewer patients treated with palonosetron (compared with ondansetron or other 5-HT$_3$RAs) required inpatient care (0.2% vs. 0.4%, 4% vs. 6%, 10% vs. 14%, 16% vs. 23%, 7% vs. 10%, 0% vs. 5%), while 2 studies reported similar use (1% vs. 1%, 0% vs. 0%).

LIMITATIONS

- Studies varied in designs, patients, 5-HT$_3$RA regimens, and definitions of outcomes. This heterogeneity prevented us from conducting meta-analysis.
- The majority of the studies indicating palonosetron users used fewer services than users of other 5-HT$_3$RAs were retrospective studies (8 of 10).

CONCLUSIONS

- CINV prophylaxis with palonosetron was shown to be associated with lower use of rescue medications, outpatient and inpatient services compared with ondansetron or other 5-HT$_3$RAs.
- Use of palonosetron as a standard CINV treatment may lead to reduced utilization of rescue medications and healthcare services.

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