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Journal

Antimicrobial Agents and Chemotherapy, 57(12)

ISSN

0066-4804

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Publication Date

2013-12-01

DOI

10.1128/aac.00921-13

Peer reviewed

AAC Journals.ASM.org

Comparative Evaluation of Serotonin Toxicity among Veterans Affairs Patients Receiving Linezolid and Vancomycin

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Despite the theoretical risk of serotonin toxicity (ST) with linezolid, "real-world" clinical evaluations of the risk of ST in patients receiving linezolid have been limited to case reports and noncomparator studies. An observational, matched-cohort study was conducted to evaluate the risk of ST among hospitalized patients who received linezolid or vancomycin at the Upstate New York Veterans Affairs Healthcare Network (Veterans Integrated Service Network 2 [VISN-2]). Matching criteria included VISN-2 hospital, hospital ward, prior hospital length of stay, age, and baseline platelet counts. The patients' electronic medical records were evaluated for symptoms consistent with ST and the Hunter serotonin toxicity criteria (HSTC) using an intensive, natural word search algorithm. The study included 251 matched pairs. Demographics and comorbidities were similar between groups. Over half of the study population received at least one concurrent medication with serotonergic activity. Receipt of agents with serotonergic activity was more pronounced in the vancomycin group, and the higher frequency was due to concomitant antihistamine and antiemetic use. Antidepressant use, including selective serotonin reuptake inhibitors (SSRIs), was similar between groups. No patients in either group were found to meet the criteria using the word search algorithm for ST. Fewer linezolid patients than vancomycin patients met the HSTC overall (3.2% versus 8.8%) and when stratified by receipt of a concurrent serotonergic agent (4.3% versus 12.4%). Of the patients meeting the HSTC, most had past or present comorbidities that may have contributed to or overlapped the HSTC. This study of hospitalized patients revealed comparably low frequencies of adverse events potentially related to ST among patients who received linezolid or vancomycin.

Serotonin toxicity (ST), also often referred to as serotonin syndrome, is characterized by a triad of symptoms, including mental status changes, neuromuscular abnormalities, and autonomic hyperactivity. In addition to these symptoms, the patient must also have a temporal history of exposure to a drug known to have serotonergic properties. Signs and symptoms of ST appear anywhere from 1 h to several days after exposure to serotonergic agents (SAs), and clinical manifestations of ST range from barely perceptible to lethal (1, 2). As a weak inhibitor of monoamine oxidase, linezolid has the theoretical potential to cause ST, especially when used in combination with adrenergic and SAs (1, 3, 4). This precaution is reflected in the current linezolid package insert, which states that, "spontaneous reports of serotonin toxicity with co-administration of linezolid and serotonergic agents have been reported" and "where administration of linezolid and concomitant serotonergic agents is clinically appropriate, patients should be closely observed for signs and symptoms of serotonin syndrome" (5).

Despite this risk, few comparative studies have evaluated the association between the use of linezolid and ST among patients concurrently receiving linezolid and medications with adrenergic and serotonergic activity (4, 6–17). To date, published postmarketing evaluations of the risk of ST in patients receiving concomitant linezolid and other serotonergic medications have been limited primarily to case reports and small retrospective studies without comparator groups (4, 6–17). While case reports and noncomparator cohort studies provide a glimpse into the causal relationship between drug exposure and effect, it is impossible to quantify the prevalence of the finding or the magnitude of the effect caused by a specific agent or a combination of agents. The most robust analysis to date is a comparison of ST between linezolid and comparators across 20 phase III and IV comparator-controlled clinical studies by Butterfield et al. (18). In their review of the adverse event databases from those studies, which included 10,484 patients (5,426 treated with linezolid and 5,058 treated with comparators), Butterfield and colleagues (18) did not find enough evidence to conclude that linezolid-induced ST was different from that induced by comparators. No patients who received linezolid or the study comparator had an adverse event identified as ST. Furthermore, that analysis revealed comparably low proportions of potential ST in patients receiving linezolid and comparators when applying either the Sternbach criteria or Hunter serotonin toxicity criteria (HSTC) for diagnosis of ST; the Sternbach criteria and the HSTC are the two best-described criteria for defining ST in clinical practice (1, 2).

Although these findings are reassuring, several considerations should be noted when interpreting these results. First, those authors relied on the adverse event databases from the original clinical trials. Because they were unable to access to the patients' original medical records, the positive and negative predictive values of the findings could not be assessed. Second, the adverse effect profiles of patients enrolled in clinical trials may not be fully reflective of the diverse patient populations who use the drugs in clinical practice. Therefore, comparative, patient-level analyses in the clinical arena are still needed to ascertain the "real-world" risk of ST, especially among patients receiving concomitant SAs. This

Received 1 May 2013 Returned for modification 29 May 2013
Accepted 6 September 2013
Published ahead of print 16 September 2013
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doi:10.1128/AAC.00921-13

TABLE 1 Medications reported to cause ST[a]

Concomitant SA[b]
Amphetamines and derivatives
Dextroamphetamine
Methamphetamine
Fenfluramine
Dexfenfluramine
Phentermine
Analgesics
Codeine
Dextropropoxyphene (propoxyphene)
Fentanyl
Meperidine
Pentazocine
Tramadol
Methotrimeprazine
Antidepressants (MAOI)
Isocarboxazide
Moclobemide
Phenelzine
Tranylcypromine
Pargyline
Antidepressants (SSRI)
Citalopram
Fluoxetine
Fluvoxamine
Paroxetine
Sertraline
Escitalopram
Antidepressants (TCA)
Amitriptyline
Clomipramine
Desipramine
Doxepin
Imipramine
Nortriptyline
Trimipramine
Maprotiline
Antidepressants (other)
Buspirone
Bupropion
Duloxetine
Mirtazapine
Nefazodone
Venlafaxine
Trazodone
Antiemetics
5-HT3 antagonists (dolasetron, granisetron, ondansetron)
Droperidol
Metoclopramide
Antiepileptics
Carbamazepine
Valproate
Antihistamines
Brompheniramine
Chlorpheniramine
Diphenhydramine
Antiparkinsonians
Amantadine
Bromocriptine
Levodopa
Selegiline
Antipsychotics
Clozapine
Risperidone
Ziprasodone
Olanzapine
Quetiapine
Illicit drugs
Cocaine
Lysergic acid diethylamide
Ecstasy (MDMA)
Mescaline
Migraine
Dihydroergotamine
5-HT1 agonists (naratriptan, rizatriptan, sumatriptan, zolmitriptan)
Weight loss
Sibutramine
Fenfluramine
Other
Dextromethorphan
5-Hydroxytryptophan
L-Tryptophan
Lithium
Reserpine
St. John's wort
Tetrabenazine

[a] See references 4, 17, and 18.
[b] MAOI, monoamine oxidase inhibitor; 5-HT3, 5-hydroxytryptamine; MDMA, 3,4-methylenedioxy-*N*-methylamphetamine.

analysis sought to fill this void in the literature by comparing the incidence of ST among hospitalized Veterans Affairs (VA) patients who received linezolid or vancomycin.

(This study was presented, in part, as a platform presentation at the 2012 IDWeek, a joint meeting of the IDSA, SHEA, HIVMA, and PIDS [19].)

MATERIALS AND METHODS

Study design and population. A matched-cohort study was performed among hospitalized patients at the New York VA Health Care Network, or Veterans Integrated Service Network 2 (VISN-2), from January 2005 until February 2008. Patients on linezolid therapy for at least 1 day were matched 1:1 to those on vancomycin for at least 2 days. We purposefully made the entry criteria for vancomycin ≥2 days to avoid matching linezolid patients to patients who received vancomycin for only <24 h; there was a considerable number of "one-time" orders for vancomycin over the study period. We selected to include patients who received at least 1 day of linezolid treatment, since ST after the receipt of one dose of linezolid has been reported (20). Matching criteria were (i) location at the start of therapy (intensive care unit [ICU] or non-ICU), (ii) admission hospital within VISN-2 (Albany, Bath, Buffalo, Canandaigua, or Syracuse, NY), (iii) length of stay (LOS) prior to initiation of therapy ± 7 days, (iv) age (<50, 50 to 70, or >70 years), and (v) baseline platelet counts (≤100,000

TABLE 2 Verbatim and surrogate word searches for HSTC

Verbatim or exact term(s)	Surrogate terms
Spontaneous clonus	Clonus, myoclonus, twitching, muscle twitch, muscle twitching, rigidity
Inducible clonus and agitation or diaphoresis	Clonus, myoclonus, twitching, muscle twitch, muscle twitching, rigidity, and agitation, restless, restlessness, akathesia, hostility, psychomotor agitation, anxious, or diaphoresis, hyperhidrosis, diaphoretic, sweating, cold sweat, flushed face
Ocular clonus and agitation or diaphoresis	Ocular clonus, nystagmus, eye twitching, drooping eye, and agitation, restless, restlessness, akathesia, hostility, psychomotor agitation, anxious, or diaphoresis, hyperhidrosis, diaphoretic, sweating, cold sweat, flushed face
Tremor and hyperreflexia	Tremor, hyperkinesia, shakiness, and hyperreflexia, jerking
Hypertonic and temp of >38°C and ocular clonus or inducible clonus	Hypertonic, hypertonia, muscle rigidity, rigid, rigidity, spasm, spasticity, jaw trismus, and fever, hyperthermia, pyrexia, drug fever, intermittent fever, body temp increased, temp elevation, and ocular clonus, nystagmus, eye twitching, drooping eye, or clonus, myoclonus, twitching, muscle twitch, muscle twitching, rigidity

or >100,000 cells/mm^3). A random-number generator was used to select a patient match for the study in the event that multiple patients met the matching criteria.

Methods and procedure for collection of patient data. The pharmacy generated a list of patients from VISN-2 facilities who received linezolid or vancomycin. Clinical data for each patient who received linezolid or vancomycin across VISN-2 were obtained from the VISN-2 computerized patient record system (CPRS). The following data were collected: demographics, comorbidities (21), hospitalization history, antibiotic therapy, disease severity (22, 23), concomitant medications, microbiologic data, source of infection, and laboratory data.

The dose, route of administration, and duration of therapy for linezolid or vancomycin were recorded. All other medication usage was captured from 35 days prior to the start of linezolid or vancomycin therapy to 7 days after treatment discontinuation. Patients were reviewed for concomitant receipt of medications with serotonergic activity, and these included amphetamines and derivatives, analgesics, antidepressants (selective serotonin reuptake inhibitors [SSRIs], monoamine oxidase inhibitors, tricyclic antidepressants [TCAs], and others), antiemetics, antiepileptics, antihistamines, antiparkinsonians, antipsychotics, illicit drugs, migraine medications, weight loss drugs, and other miscellaneous agents (Table 1) (1, 4, 17, 18).

The severity of illness at the initiation of therapy was captured by using the Acute Physiology and Chronic Health Evaluation II (APACHE-II) score (22), based on the patient's worst physiologic score within the first 24 h of linezolid or vancomycin therapy. Laboratory values, complete blood count data, microbiologic culture data, and susceptibility data were recorded from 5 days prior to the initiation of linezolid or vancomycin therapy to 3 days after the discontinuation of therapy. The indication for treatment was categorized as bloodstream, urinary tract, skin and skin structure/osteoarticular, intra-abdominal, respiratory, or other/unknown infection. If a patient had multiple indications for therapy, the indication with the highest risk for mortality was used to classify the source of infection (24).

Outcomes. Patients who received linezolid or vancomycin were evaluated for clinical signs of ST by using an intensive word search algorithm for ST and the HSTC (1), which are the most well-described criteria for defining ST in clinical practice. The safety analysis was performed in a stepwise manner using a natural word search algorithm similar to the one reported by Butterfield et al. (18). We searched for adverse event terms starting 1 week prior to the initiation of linezolid or vancomycin until 1 week after discontinuation of either treatment to ensure that no cases of ST on therapy were missed due to mischarting of clinical data. The progress notes section from the patients' electronic medical records were first searched for the adverse event terms serotonin toxicity, serotonin syndrome, serotonin storm, hyperserotonemia, serotonergic syndrome, serotonin toxidrome, serotonergic, serotonin crisis, serotonin episode, and neuroleptic malignant syndrome and using a search string for all terms containing "serotonin." Next, the patients' electronic progress notes were searched for verbatim or exact terms of the HSTC during the same time frame (Table 2). A similar search was then done by utilizing synonyms or surrogate terms for the HSTC terms (1). Surrogate terms for HSTC were included due to the likelihood that a clinician may characterize a symptom specified in the criteria by a different term in the patients' electronic medical records. In addition, misspellings and abbreviations were included for all word search algorithms to minimize the likelihood of missing a potential ST case. For patients identified by either the exact or surrogate word search algorithm, a treatment-blinded review was performed to ensure that the adverse event criteria had been met during therapy with linezolid or vancomycin or within 1 week of therapy completion. Only cases that occurred during therapy with vancomycin or linezolid were considered. For the HSTC that involved >1 clinical symptom for meeting the criteria (e.g., ocular clonus and agitation or diaphoresis), symptoms had to occur within 2 days of each other while on therapy or within 7 days of completion of the study drug. The time period of 7 days posttreatment was a conservative estimate of the time that an event could be attributed to either agent (18).

Data analysis plan. For the bivariate analyses comparing linezolid and vancomycin, categorical variables were compared by using the Mantel-Haenszel test for pair-matched data (McNemar's test), and continuous variables were compared by using the paired *t* test or the Wilcoxon matched-pairs test. The relationships between clinical and demographic characteristics and the occurrence of ST were compared by using Fisher's exact test for categorical variables and the Student *t* and Mann-Whitney U tests for continuous and ordinal variables, respectively.

To assess for the presence of effect measure modification, treatment-ST relationships were stratified by receipt of any SA, receipt of an antidepressant, and receipt of SSRIs. The 95% confidence intervals (CIs) were used to determine the heterogeneity/homogeneity of stratum-specific effect measures in each stratified analysis.

Since this was a matched-pair cohort study, conditional log-binomial regression was used to determine if treatment was independently associated with ST after adjustment for potential confounding variables (25). Treatment interaction terms identified in the stratified analyses and all variables associated ($P < 0.2$) with ST and treatment were entered into the model. A manual backward approach was used to delineate the best-fitting or most parsimonious model. Potential confounding variables were retained in the final model if the resulting risk ratio (RR) for the treatment group changed by >10% in the absence of the confounder. All calculations were computed by using SAS version 9.3 (SAS, Cary, NC) and SPSS version 11.5 (SPSS, Chicago, IL).

RESULTS

During the study period, 298 hospitalized patients received linezolid for at least 1 day. Of these 298 patients, we were able to find

TABLE 3 Bivariate comparisons of baseline clinical covariates and concomitant receipt of SAs between patients who received linezolid and those who received vancomycin and the presence and absence of ST determined by HSTC[j]

Parameter	Treatment				ST			
	Value for group				Value for group			
	Linezolid ($n = 251$)	Vancomycin ($n = 251$)	RR (95% CI)	*P* value	Presence of ST ($n = 30$)	Absence of ST ($n = 472$)	RR (95% CI)	*P* value
Matching criteria								
No. (%) of patients								
Age category (yr)				1.00				0.29
<50	17 (6.8)	17 (6.8)			4 (13.3)	30 (6.4)		
50–75	140 (55.8)	140 (55.8)			17 (56.7)	263 (55.7)		
>75	94 (37.5)	94 (37.5)			9 (30.0)	179 (37.9)		
Hospital				1.0				0.19
Albany	54 (21.5)	54 (21.5)			6 (20.0)	102 (21.6)		
Bath	35 (13.9)	35 (13.9)			1 (3.3)	69 (14.6)		
Buffalo	94 (37.5)	94 (37.5)			10 (33.3)	178 (37.7)		
Canandaigua	1 (0.4)	1 (0.4)			0 (0)	2 (0.4)		
Syracuse	67 (26.7)	67 (26.7)			13 (43.3)	121 (25.6)		
Hospital ward at initiation of therapy			1.00	1.0				0.002
ICU	52 (20.7)	52 (20.7)			13 (43.3)	91 (19.3)	2.93 (1.47–5.83)	
Non-ICU	199 (79.3)	199 (79.3)			17 (56.7)	381 (80.7)		
Baseline platelet count			1.0	1.0				0.34
<100,000 cells/mm^3	15 (6.0)	15 (6.0)			3 (10.0)	27 (5.7)	0.57 (0.18–1.78)	
>100,000 cells/mm^3	236 (94.0)	236 (94.0)			27 (90.0)	445 (94.3)		
Median LOS prior to therapy (days) (IQR)	7 (3–16)	3 (1–12)		<0.001	6 (2–26)	5 (1–14)		0.59
Clinical covariates and demographics								
Mean age (yr) (SD)	68.5 (12.4)	68.6 (13.3)	NA	0.89	66.1 (13.3)	68.7 (12.8)	NA	0.28
No. (%) of male patients	243 (96.8)	244 (97.2)	1.00 (0.97–1.03)	0.80	28 (93.3)	459 (97.2)	0.43 (0.11–1.65)	0.22
Mean wt (kg) (SD)	84.7 (24.6)	86.3 (24.3)	NA	0.47	80.2 (19.8)	85.8 (24.6)	NA	0.22
Mean creatinine clearance (ml/min) (SD)	57.1 (29.7)	57.8 (26.9)	NA	0.76	63.4 (32.2)	57.0 (28.0)	NA	0.23
Mean APACHE-II score (SD)	12.4 (6.3)	13.1 (6.1)	NA	0.17	13.4 (7.3)	12.7 (6.1)	NA	0.58
Median baseline platelet counts ([10^3 cells/mm^3) (IQR)	278 (211–373)	243 (190–298)	NA	<0.001	254 (189–301)	265 (196–342)	NA	0.74
Median duration of therapy (days) (IQR)	10 (6–15)	7 (4–12)	NA	0.02	9 (5–14)	8 (5–15)	NA	0.84
Median no. of comorbidities (IQR)	2 (1–4)	3 (2–4)	NA	0.06	2 (1–3)	3 (2–4)	NA	0.69
No. (%) of patients with								
Diabetes	98 (39.0)	111 (44.2)	0.88 (0.71–1.09)	0.25	12 (40.0)	197 (41.7)	0.93 (0.46–1.90)	0.85
Heart failure	52 (20.7)	46 (18.3)	1.13 (0.80–1.60)	0.49	6 (20.0)	92 (19.5)	1.03 (0.43–2.45)	0.95
Chronic obstructive pulmonary disease	64 (25.5)	75 (29.9)	0.85 (0.65–1.12)	0.26	5 (16.7)	134 (28.4)	0.52 (0.20–1.34)	0.16
Hypertension	167 (66.5)	161 (64.1)	1.04 (0.91–1.18)	0.85	19 (63.3)	309 (65.5)	0.92 (0.45–1.88)	0.81
History of CVA or stroke	24 (9.6)	30 (12.0)	0.80 (0.49–1.31)	0.38	3 (10.0)	51 (10.8)	0.92 (0.29–2.94)	1.00
Hepatic dysfunction	16 (6.4)	19 (7.6)	0.84 (0.44–1.60)	0.60	3 (10.0)	32 (6.8)	1.48 (0.47–4.65)	0.47
Alcoholism	17 (6.8)	29 (11.6)	0.59 (0.33–1.04)	0.06	2 (6.7)	44 (9.3)	0.71 (0.17–2.88)	1.00
Receipt of chronic dialysis	14 (5.6)	12 (4.8)	1.17 (0.54–2.52)	0.70	3 (10.0)	23 (4.9)	2.03 (0.66–6.27)	0.20
Decubitus ulcers	42 (16.7)	29 (11.6)	1.45 (0.92–2.28)	0.11	2 (6.7)	69 (14.6)	0.43 (0.11–1.78)	0.29
Malignancy	66 (26.3)	74 (29.6)	0.89 (0.67–1.19)	0.43	8 (26.7)	132 (28.0)	0.94 (0.43–2.06)	0.88
HIV infection	4 (1.6)	1 (0.4)	4.00 (0.45–35.79)	0.18	0 (0)	5 (1.1)	NA	1.00
History of transplant	3 (1.2)	2 (0.8)	1.50 (0.25–8.98)	0.65	0 (0)	5 (1.1)	NA	1.00
Immunosuppressive drugs	35 (13.9)	21 (8.4)	1.67 (0.99–2.81)	0.05	3 (10.0)	53 (11.2)	0.88 (0.28–2.82)	1.00
Surgery requiring >48 h of hospitalization in preceding 30 days	86 (34.3)	79 (31.5)	1.09 (0.85–1.40)	0.50	8 (26.7)	157 (33.3)	0.74 (0.34–1.63)	0.46
Previous hospitalization of >72 h in preceding 180 days	148 (59.0)	112 (44.6)	1.32 (1.11–1.57)	0.002	13 (43.3)	247 (52.3)	0.71 (0.35–1.43)	0.34
Antecedent antibiotic exposure in preceding 30 days	166 (66.1)	161 (64.1)	1.03 (0.90–1.18)	0.65	17 (56.7)	310 (65.7)	0.70 (0.35–1.41)	0.32
No. (%) of patients with pathogen isolated								
MRSA	91 (36.3)	72 (28.7)	1.26 (0.99–1.60)	0.05	7 (23.3)	156 (33.1)	0.63 (0.28–1.44)	0.27
MSSA	19 (7.6)	15 (6.0)	1.27 (0.64–2.49)	0.49	3 (10.0)	31 (6.6)	1.53 (0.49–4.79)	0.47
CoNS	27 (10.8)	34 (13.5)	0.79 (0.50–1.25)	0.32	3 (10.0)	58 (12.3)	0.80 (0.25–2.57)	1.00
Enterococcus spp.	121 (48.2)	52 (20.7)	2.33 (1.79–3.03)	<0.001	10 (33.3)	163 (34.5)	0.95 (0.46–1.99)	0.89
No. (%) of patients with source of infection								
Bloodstream	60 (23.9)	35 (13.9)	1.71 (1.19–2.47)	0.003	9 (30.0)	86 (18.2)	1.84 (0.87–3.88)	0.11
Respiratory	41 (16.3)	72 (28.7)	0.57 (0.41–0.80)	<0.001	8 (26.7)	105 (22.2)	1.25 (0.57–2.74)	0.57
Skin/bone	92 (36.7)	85 (33.9)	1.08 (0.87–1.35)	0.48	6 (20.0)	171 (36.2)	0.47 (0.19–1.10)	0.07
Urinary tract	37 (14.7)	15 (6.0)	2.47 (1.44–4.23)	<0.001	2 (6.7)	50 (10.6)	0.62 (0.15–2.52)	0.76
Intra-abdominal	16 (6.4)	11 (4.4)	1.45 (0.69–3.04)	0.32	3 (10.0)	24 (5.1)	1.95 (0.63–6.04)	0.21
Other/unknown	5 (2.0)	33 (13.1)	0.15 (0.06–0.38)	<0.001	2 (6.7)	36 (7.6)	0.87 (0.22–3.52)	1.00

(Continued on following page)

TABLE 3 (Continued)

Parameter	Treatment				ST			
	Value for group				Value for group			
	Linezolid ($n = 251$)	Vancomycin ($n = 251$)	RR (95% CI)	*P* value	Presence of ST ($n = 30$)	Absence of ST ($n = 472$)	RR (95% CI)	*P* value
No. (%) of patients with receipt of concomitant SA								
Any SA	140 (55.8)	170 (67.7)	0.82 (0.71–0.95)	0.007	27 (90.0)	283 (60.0)	5.57 (1.71–18.12)	0.001
Antidepressant (any)	83 (33.1)	86 (34.4)	0.97 (0.74–1.25)	0.79	12 (40.0)	157 (33.3)	1.31 (0.65–2.66)	0.45
SSRIs[a]	49 (19.5)	47 (18.7)	1.04 (0.72–1.51)	0.83	9 (30.0)	87 (18.4)	1.81 (0.86–3.83)	0.12
TCA[b]	8 (3.2)	8 (3.2)	1.00 (0.40–2.50)	1.00	2 (6.7)	14 (3.0)	2.17 (0.57–8.33)	0.25
Other[c]	38 (15.1)	45 (17.9)	0.84 (0.57–1.26)	0.41	6 (20.0)	77 (16.3)	1.26 (0.53–2.99)	0.60
Analgesics[d]	73 (29.1)	50 (19.9)	1.46 (1.08–1.97)	0.01	9 (30.0)	114 (24.2)	1.32 (0.62–2.81)	0.47
Antiemetics[e]	1 (0.4)	55 (21.9)	0.02 (0.003–0.13)	<0.001	8 (26.7)	48 (10.2)	2.90 (1.35–6.19)	0.005
Antiepileptics[f]	0 (0)	5 (2.0)	NA	0.03	2 (6.7)	3 (0.6)	7.1 (2.29–22.03)	0.03
Antihistamines[g]	0 (0)	46 (18.3)	NA	<0.001	4 (13.3)	42 (8.9)	1.53 (0.56–4.18)	0.34
Antiparkinsonians[h]	3 (1.2)	9 (3.6)	0.33 (0.09–1.23)	0.08	3 (10.0)	9 (1.9)	4.54 (1.59–12.92)	0.03
Antipsychotics[i]	7 (2.8)	12 (4.8)	0.58 (0.23–1.48)	0.25	4 (13.3)	15 (3.2)	3.91 (1.52–10.09)	0.02

[a] Citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, and escitalopram.
[b] Amitriptyline, clomipramine, desipramine, doxepine, imipramine, nortriptyline, trimipramine, and maprotiline.
[c] Buspirone, bupropion, duloxetine, mirtazapine, nefazodone, venlafaxine, and trazodone.
[d] Codeine, dextropropoxyphene (propoxyphene), fentanyl, meperidine, pentazocine, tramadol, and methotrimeprazine.
[e] 5-HT3 antagonists (dolasetron, granisetron, and ondansetron), droperidol, and metoclopramide.
[f] Carbamazepine and valproate.
[g] Brompheniramine, chlorpheniramine, and diphenhydramine.
[h] Amantadine, bromocriptine, levodopa, and selegiline.
[i] Clozapine, quetiapine, risperidone, ziprasodone, and olanzapine.
[j] Abbreviations: CVA, cerebrovascular accident; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; CoNS, coagulase-negative *Staphylococcus* spp.; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants; IQR, interquartile range; NA, not applicable.

vancomycin matches for 251 patients from a cohort of 2,408 patients on vancomycin therapy for ≥48 h. We were unable to find matches for 47 linezolid patients due to the lack of a match based on the following criteria: baseline platelet counts ($n = 20$) and prior length of stay ± 7 days ($n = 27$). A comparison of matching variables and concurrent receipt of SAs is shown in Table 3. Although we were able to successfully "caliper" match each linezolid patient to a vancomycin patient by prior length of stay ± 7 days, the median prior length of stay was longer ($P < 0.05$) for the linezolid group than for the vancomycin group. All other matching criteria were identical between groups.

The groups were relatively similar across key baseline covariates (Table 3). However, several differences at a *P* value of <0.2 were observed. Patients who received linezolid were more likely ($P < 0.2$) to be hospitalized in the past 180 days, have decubitus ulcers, receive immunosuppressive agents, have a higher mean baseline platelet count, have an infection due to methicillin-resistant *Staphylococcus aureus* (MRSA) or *Enterococcus* spp., and have a bloodstream or urinary tract infection. Time at risk, reflected by a longer median duration of therapy, was also higher for the linezolid group than for the vancomycin group. Vancomycin was received, on average, for 10 ± 9.7 days. In contrast, the total mean (standard deviation) time of linezolid treatment was 13.3 (12.1) days; the mean (standard deviation) times of oral and intravenous use were 8.5 (11.6) and 4.8 (8.0) days, respectively. Patients who received vancomycin had a higher frequency of alcoholism, a higher median number of comorbidities, and a higher frequency of respiratory tract infections. Concomitant receipt of agents with serotonergic activity was also more pronounced in the vancomycin treatment group. The higher frequency of SA use was driven primarily by antihistamines and antiemetics. Antidepressant use, including SSRIs and TCAs, was similar between groups. More patients in the vancomycin group received ≥2 agents with serotonergic activity than in the linezolid group (32.7% and 16.3%, respectively; *P* value of <0.001). The difference in the receipt of ≥2 SAs between treatment groups was due to the receipt of antihistamines and antiemetics. If only the receipt of agents with serotonergic activity other than antihistamines and antiemetics was considered, nearly identical proportions of patients in the vancomycin group relative to those in the linezolid group received ≥2 SAs (16.7% and 15.9%, respectively; *P* value of 0.8). Receipt of ≥2 antidepressants occurred in 6.8% of both treatment groups.

Overall, there were no reports of ST by any of the exact or surrogate word searches in either treatment group. Results of the HSTC word search algorithm are displayed in Fig. 1. In total, 30 (6%) patients met HSTC by either the exact or surrogate word search. Eight (3.2%) linezolid patients and 22 (8.8%) vancomycin patients met HSTC (relative risk [RR] = 0.36; 95% CI, 0.17 to 0.79; $P = 0.007$). Results of the stratified analyses (concomitant receipt of an agent with serotonergic activity) are provided in Tables 4 to 6. For patients who did not receive a concomitant SA, similar proportions of patients in the linezolid and vancomycin groups were found to meet the definition of ST by the HSTC word search algorithm. Among those who received at least one SA, 4.3% of linezolid patients met the HSTC, while 12.3% of vancomycin patients met the HSTC by any word search algorithm. Of the 310 patients who received at least one SA, both members of a treatment pair received an SA in 93 instances. Among these 93 pairs, the risk of meeting the HSTC was lower among linezolid patients than among vancomycin patients (RR = 0.31; 95% CI, 0.11 to 0.88). When stratified by concurrent receipt of antidepressants and SSRIs, a higher proportion of vancomycin patients than linezolid patients met the HSTC across all resultant strata. Of the 169 patients who received at least one antidepressant, both members of a treatment pair received an antidepressant in 22 instances. The risk of meeting the HSTC was lower among linezolid patients than among vancomycin patients among these concordant cases (RR = 0.33; 95% CI, 0.07 to 1.65). Tables 7 (patients on linezolid) and 8

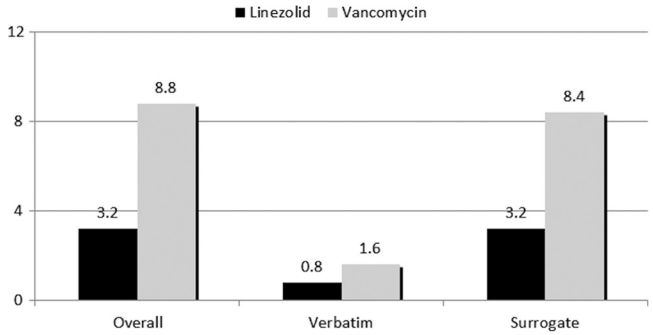

FIG 1 Comparison of incidences of HSTC between patients who received linezolid and patients who received vancomycin. Note that verbatim and surrogate HSTC classifications are not mutually exclusive. Of the 30 patients who met the HSTC, 5 met criteria based on both word search algorithms, 24 satisfied only the surrogate search algorithm, and 1 met the criteria based only on the verbatim word search algorithm.

(patients on vancomycin) list the clinical characteristics of patients meeting the HSTC by either the exact or surrogate word search. Most patients meeting the HSTC had past or present comorbidities which may have contributed to, or overlapped, the reported adverse events.

Bivariate comparisons between clinical covariates and the occurrence of ST by HSTC are shown in Table 3. Variables found to be associated with ST by HSTC at a P value of <0.2 included hospital, residence in ICU, baseline platelet count, necessity of chronic dialysis, receipt of a medication with serotonergic activity, and receipt of SSRIs, antiemetics, antiepileptics, antiparkinsonians, and antipsychotics. Of these variables, only baseline platelet counts, receipt of any SA, and receipt of an antiemetic varied between treatment groups. In the conditional log-binomial regression, an association between linezolid and ST by HSTC remained (RR = 0.45; 95% CI, 0.19 to 1.07; $P = 0.07$) after adjustment for concurrent receipt of at least one SA (inclusion of a concurrent SA in the model was the only variable to change the RR by 10%).

DISCUSSION

Based on a lack of real-world comparator data on the risk of ST with linezolid, especially in patients receiving concomitant SAs (4, 6–17), the intent of this study was to delineate the risk of ST associated with linezolid relative to that associated with vancomycin among hospitalized patients. We selected vancomycin as the comparator since it is used for similar indications in clinical practice, and it is not known to cause ST (26, 27). We opted to perform this study within VISN-2 because hospitalized VA patients have a higher frequency of conditions which elevate the risk for drug-induced ST (1). Most notably, VA patients tend to receive more medications with serotonergic activity than other hospitalized patient populations (http://www.va.gov/vetdata/). In our study, more than half of the patients were receiving a medication with serotonergic activity, and many of them were on an antidepressant. An additional advantage of studying VA patients is that the VA system is a closed health care system. All patient data, both inpatient and outpatient records across the entire VA network, exist in a readily searchable electronic database. This feature is ideal when applying a natural search algorithm like the one used in this study and, most importantly, minimizes several types of information bias, including missing cases, incomplete case ascertainment due to loss to follow-up, outcome misclassification, and inconsistent charting practices.

By applying an intensive natural word search algorithm to the electronic medical records of this matched cohort, we were unable to find any notable differences in the risk of ST between agents. No cases of ST in the exact and surrogate ST word search algorithms were noted. A larger number of patients met the HSTC in the vancomycin group than in the linezolid group, and the differences were more pronounced among patients receiving medications with serotonergic activity. Upon closer inspection of these patients, it is unlikely that any of these patients actually experienced ST (Tables 7 and 8). One of the defining characteristics of ST by HSTC is clonus. As part of our natural word search algorithm, we used "rigidity" as a surrogate for clonus. This resulted in many patients, particularly in the vancomycin group, being classified as having ST by HTSC. Many patients who met HSTC by rigidity in the vancomycin group had longstanding conditions (e.g., Parkinson's disease) independent of their drug assignment, and this resulted in positive HSTC classifications. If one excludes rigidity

TABLE 4 Comparison of HSTC between linezolid and vancomycin stratified by receipt of any SA

Criterion	No. (%) of patients			
	SA[a]		No SA	
	Linezolid ($n = 140$)	Vancomycin ($n = 170$)	Linezolid ($n = 111$)	Vancomycin ($n = 81$)
HSTC	6 (4.3)	21 (12.4)	2 (1.8)	1 (1.2)
Verbatim	2 (1.4)	4 (2.4)	0 (0)	0 (0)
Surrogate	6 (4.3)	19 (11.2)	2 (1.8)	1 (1.2)

[a] Of the 310 patients who received at least one SA, both members of a treatment pair received an SA in 93 instances. Among these 93 pairs, the risk of meeting the HSTC was lower among linezolid patients (RR = 0.31; 95% CI, 0.11 to 0.88).

TABLE 5 Comparison of HSTC between linezolid and vancomycin stratified by receipt of an antidepressant

Criterion	No. (%) of patients			
	Antidepressant[a]		No antidepressant	
	Linezolid ($n = 83$)	Vancomycin ($n = 86$)	Linezolid ($n = 168$)	Vancomycin ($n = 165$)
HSTC	3 (3.6)	9 (10.5)	5 (3.0)	13 (7.9)
Verbatim	2 (2.4)	1 (1.2)	0 (0)	3 (1.8)
Surrogate	3 (3.6)	8 (9.3)	5 (3.0)	12 (7.3)

[a] Of the 169 patients who received at least one antidepressant, both members of a pair received an antidepressant in 22 instances. Among these 22 pairs, the risk of meeting the HSTC was lower among linezolid patients (RR = 0.33; 95% CI, 0.07 to 1.65).

TABLE 6 Comparison of HSTC between linezolid and vancomycin stratified by receipt of a selective serotonin reuptake inhibitor

Criterion	No. (%) of patients			
	SSRI		No SSRI	
	Linezolid ($n = 49$)	Vancomycin ($n = 47$)	Linezolid ($n = 202$)	Vancomycin ($n = 204$)
HSTC	3 (6.1)	6 (12.8)	5 (2.5)	16 (7.8)
Verbatim	2 (4.1)	1 (2.1)	0 (0)	3 (1.5)
Surrogate	3 (6.1)	5 (10.6)	5 (2.5)	15 (7.4)

TABLE 7 Clinical characteristics of patients administered linezolid who met the HSTC by either the exact or surrogate word search[a]

Age of patient (yr)	Source(s) of infection	Duration of therapy (days)	Time to start of therapy after admission (days)	Concurrent SA(s) (days of use)	Criterion met	ST term(s) (day[s] of therapy when noted)	Clinical description
46	UTI	6	5	Paroxetine (−180–EOT), cocaine (chronic)	HE/HS	Clonus (1), myoclonus (1)	Patient admitted with cocaine and alcohol-related seizures; symmetrical clonus was present bilaterally 3 days prior to start of linezolid and continued through day 1 of therapy
80	SSTI	14	7	Citalopram (chronic), phenytoin (−7–EOT)	HE/HS	Myoclonus (1, 2, 4, 6), twitching (4–8), tremor (5–6), jerking (1, 2, 4, 5, 7, 11), nystagmus (4), eye twitching (5), drooping face (4), diaphoretic (14)	Patient arrived from nursing home experiencing seizures; symptoms were present at admission and were intermittent throughout hospital stay
81	SSTI	11	330	Citalopram (−14–EOT)	HS	Rigidity (4, 5, 9)	Patient with history of dementia and multiple episodes of UTIs; patient had a complicated and prolonged hospital course; on multiple days of linezolid therapy, the medicine resident described his neck as rigid; there was no mention of rigidity in other medical notes
61	i.v. CRBSI	5	3	Levodopa (−3–EOT)	HE/HS	Spontaneous clonus (2), clonus (2), agitation (1–2), diaphoretic (3)	Patient with longstanding Parkinson's disease and non-Hodgkin's lymphoma; a nursing note stated that the patient had hyperreactive movements with clonus in upper extremities; clonic movements, agitation, and diaphoresis were also noted in a medical resident's note
72	Lower respiratory tract infection	7	9	Fentanyl (−9–EOT)	HS	Twitching (7), agitation (7), diaphoresis (6)	Patient admitted with acute pancreatitis, complicated by severe acidosis, hypotension, renal failure, and ventilatory failure; on day 7 of linezolid treatment, a 30-s episode of twitching was noted during HD; this was also observed at 2 previous HD sessions; twitching was attributed to multiorgan failure and electrolyte abnormalities; agitation and diaphoresis in response to withdrawal of sedation medications were also in nursing notes
74	Abdominal wall postoperative infection	5	27	Fentanyl (−1–EOT)	HS	Rigidity (5)	Patient admitted for repair of ruptured abdominal aortic aneurysm; patient had complicated hospital course with multiple stays in ICU; on day 5 of linezolid treatment, abdomen was noted to be rigid and distended by the vascular surgeon; this was the only mention of rigidity; patient expired on day 5 of linezolid treatment after care was withdrawn
58	i.v. CRBSI	12	38	None	HS	Rigidity (12), anxiousness (14)	Patient with advanced cutaneous T-cell lymphoma; while receiving methotrexate and prednisone, he was diagnosed with an acute abdomen (perforated viscus); rigidity of abdomen was noted upon PE and associated with perforated viscus
83	i.v. CRBSI and UTI	7	17	None	HS	Rigidity (7)	Patient with advanced Alzheimer's disease who was admitted from nursing home with dehydration and decreased activity; on day 7 of linezolid, the kinesiotherapy note stated that his tone was rigid; this was the only mention of rigidity

[a] Abbreviations: HD, hemodialysis; HS, Hunter surrogate; HE, Hunter exact; i.v. CRBSI, intravenous catheter-related bloodstream infection; PE, physical evaluation; SSTI, skin/soft tissue infection; UTI, urinary tract infection; EOT, end of treatment.

TABLE 8 Clinical characteristics of patients on vancomycin who met the HSTC by either an exact or surrogate word search[a]

Age of patient (yr)	Source of infection	Duration of therapy (days)	Time to start of therapy after admission (days)	Concurrent SA(s) (days of use)	Criterion met	ST term(s) (day[s] of therapy when noted)	Clinical description
59	i.v. CRBSI due to CNS and *Enterococcus* spp.	4	166	Citalopram (−90–EOT)	HE	Clonus (longstanding), hypertonia (longstanding), fever (1)	Patient with longstanding history of worsening, spastic quadriplegia; clonus and hypertonia were noted upon PE throughout his hospitalization; patient was febrile on day 166 of hospitalization, and his fever was attributed to an i.v. catheter-related infection
72	i.v. CRBSI due to MRSA	17	3	Metoclopramide (−1–EOT)	HE/HS	Tremor (4, 10–14), hyperreflexia (11)	Patient with extensive past medical history (diabetes, CAD, PVD, stage 5 chronic kidney disease on HD, hypothyroidism, hypertension); permacatheter became infected with MRSA on day 3 of hospitalization, and vancomycin treatment was started; on neurology note, patient was noted to have hyperreflexia, and this was attributed to his severe diabetic neuropathy; tremors were attributed to vertebral stenosis
68	i.v. CRBSI	7	23	Fentanyl (−14–EOT)	HS	Rigidity (4), agitation (2)	Patient with ischemic cardiomyopathy and GI bleeding; complicated hospital course in ICU, with acute renal and respiratory failure; patient expired on day 7 of vancomycin therapy; while in ICU, patient experienced intermittent agitation, including biting on endotracheal tube, relieved by midazolam; abdominal rigidity was noted upon PE on day 4 of therapy
58	Lower respiratory tract infection	16	33	Fluoxetine (−35–EOT)	HS	Rigidity (15)	Patient with history of hypertension, hyperlipidemia, diabetes, congestive heart failure/ischemic cardiomyopathy, coronary artery disease, and hiatal hernia; also ICD placement; on day 15 of therapy, the patient experienced rigidity off the ward, and this was the only mention of rigidity; patient expired the following day
62	i.v. CRBSI	5	7	Fentanyl (−7–EOT), amitriptyline (−7–1)	HS	Twitching (2), agitation (1–5), restlessness (2–5)	Male with right parieto-occipital metastatic adenocarcinoma; lesion was resected on day 1 of vancomycin treatment; patient was noted to have occasional facial twitching and agitation and was restless postsurgery
69	Lower respiratory tract infection	12	12	Levodopa (−8–EOT), metoclopramide (−4–7), diphenhydramine (−8–EOT)	HS	Rigidity (4–6), agitation (5–12)	Patient with Parkinson's disease, dementia, hallucinations, coronary artery disease, and abdominal aortic aneurysm; admitted for left hip intertrochanteric fracture postfall; patient developed recurrent pneumonias on postoperative day 3 of hospitalization; upper- and lower-extremity rigidity and agitation were noted in multiple nursing notes
72	SSTI due to MSSA	19	2	Metoclopramide (−1–EOT)	HS/HE	Tremor (10–11), hyperreflexia (11)	Patient with extensive past medical history (ESRD, ischemic cardiomyopathy, PVD); presented with osteomyelitis of toe, which was amputated on day 11 of vancomycin therapy; tremors and hyperreflexia due to severe PVD and transient ischemic attacks due to cerebral hypoperfusion; syncope episodes coincided with upper-extremity tremors and hyperreflexia; patient expired 2 days after vancomycin treatment was stopped
83	SSTI due to *Enterococcus*	14	32	Metoclopramide, diphenhydramine, ondansetron, SSRI	HS	Myoclonus (2–3), twitching (1–3)	Male with complicated postoperative course (subtotal colectomy with loop ileostomy, terminal ileum resection, ileostomycin, proctostomy tube); patient was noted to have spontaneous movements attributed to morphine-induced myoclonus or metabolic issues
76	Respiratory tract infection due to MRSA	4	1	Risperidone (2–EOT), diphenhydramine (3–4)	HS	Generalized muscular rigidity (3)	Patient with dementia hospitalized for pneumonia; generalized muscular rigidity of unknown etiology was noted on day 3 of vancomycin therapy
58	Intra-abdominal	9	Started upon admission	Ondansetron (1–9)	HS	Rigidity (1)	Patient status post-inguinal hernia repair with 3-day history of SSTI; preperitoneal abscess and infected bilateral hernia mesh; as per PE, his abdomen was semirigid
49	Respiratory tract infection due to *Enterococcus*	6	49	Carbamazepine (chronic medication), venlafaxine (chronic medication)	HS	Clonus (1)	Patient with chronic progressive multiple sclerosis; patient had profound bilateral clonus in feet, consistent with his condition

54	Unknown, possible aspiration pneumonia	9	8	Risperidone (−5, 3), metoclopramide (5)	HS	Twitching (9)	Patient with alcohol abuse, hepatitis, cirrhosis, and ascites; admitted to ICU with respiratory distress, hypotension, alcoholic encephalitis, and hyponatremia; nurses noted twitching of eyelids for <5 s; symptoms were not present upon recheck in 15 min
52	Respiratory tract infection	14	5	Trazodone (−5, 1), diphenhydramine (−5, 1), sertraline (−5, 1)	HS	Myoclonic twitch (2–13), agitation (1–7, 9–14)	Female with multiple medical problems admitted for treatment of pneumonia; frequent twitching of right lower extremity and abdomen was noted upon PE; twitching was attributed to anoxic brain injury and florid pulmonary edema
45	Unknown	5	2	Ondansetron (1–EOT)	HS	Twitching (2)	Patient with history of substance abuse, multiple psychiatric diagnoses, and seizure disorders; admitted for overdose of chloral hydrate plus alcohol; upon admission, patient was noted to have renal insufficiency and metabolic and respiratory acidosis; while patient was intubated, one episode of twitching was noted
85	Urinary tract	8	3	Carbamazepine (−15–EOT), risperidone (−15–EOT)	HS	Rigidity (1–8), agitation (1–8)	Patient with multiple comorbidities with end-stage Parkinson's disease and COPD; resting tremor and rigidity in upper extremities, consistent with Parkinson's disease; agitation associated with recent neuropetic malignant syndrome due to schizophrenia medication
57	Intra-abdominal	43	Started upon admission	Buspirone (−36–30), trazodone (−36–30), citalopram (−36–30), ondansetron (1–EOT)	HS	Rigidity (31), agitation (31–33)	Patient with Huntington's chorea, bladder and prostate cancer, and seizure disorder; admitted with *Clostridium difficile* infection; patient was rigid and hypertonic, attributed to Huntington's disease and medications
62	i.v. CRBSI (CNS)	3	2	Risperidone (chronic medicine)	HS	Rigidity (2), agitation (3)	Patient with dementia admitted from nursing home with i.v. CRBSI; myoclonus believed to be secondary to Alzheimer's dementia; lead pipe rigidity in all extremities; as per nursing note, he was anxious
39	Respiratory tract infection	44	1	Fentanyl (1–12)	HS	Rigidity (6), agitation (5), restlessness (5)	Female with recent resection of clival meningioma; hepatitis, epilepsy, occipital astrocytoma; positive nucal rigidity and photophobia (1 day post-brain tumor resection) were noted upon PE and thought to indicate infection
81	SSTI due to MSSA	4	1	Sertraline (1–EOT), trazodone (1–EOT)	HS	Muscle twitch (1)	Patient with chronic venous insufficiency, hyperlipidemia, and idiopathic progressive polyneuropathy admitted with abscess status postfall (on the ground for 7 h); elevated CPK levels and possible rhabdomyolysis; occasional muscle twitches in upper chest attributed to fall
85	Lower respiratory tract infection	20	2	Fentanyl (14–EOT), levodopa (−21–EOT)	HS	Rigidity (11)	Patient with longstanding severe Parkinson's disease, hyperlipidemia, idiopathic progressive polyneurosis
60	i.v. CRBSI (CNS)	26	25	Fentanyl (−25–16)	HS	Myoclonus (19–20)	Patient with severe COPD and stage IV squamous cell carcinoma of lung with multiple ICU admissions; patient experienced myoclonus, likely due to opioids (morphine); symptoms dissipated when morphine was changed to hydromorphone
83	SSTI (septic knee)	3	3	None	HS	Rigidity (1), agitation (1)	Patient with disseminated streptococcal disease (*Streptococcus pneumoniae*); neck was noted to be rigid upon examination; meningitis was ruled out

[a] Abbreviations: CNS, central nervous system; COPD, chronic obstructive pulmonary disease; CPK, creatine phosphokinase; ESRD, end-stage renal disease; HS, Hunter surrogate; HE, Hunter exact; i.v. CRBSI, intravenous catheter-related bloodstream infection; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; PE, physical evaluation; PVD, peripheral vascular disease; SSTI, skin/soft tissue infection; CAD, coronary artery disease; ICD, implantable cardioverter defibrillator; GI, gastrointestinal.

from the surrogate HSTC search, only 4 patients on linezolid (0.15%) and 11 patients on vancomycin (0.44%) met the criteria. Collectively, the findings failed to establish an increased risk of ST with linezolid relative to vancomycin among this highly vulnerable patient population.

Several caveats should be considered when interpreting the findings of this paper. This was an observational study, and the natural word search algorithm was applied to existing data. Our findings are subject to all the caveats that are associated with this approach. Most notably, the major concern is the potential for prescribing bias due to a lack of randomization of treatment. In the case of our study, the concern is that prescribers would avoid using linezolid in patients perceived to be at risk for ST. While this is a reasonable concern, we do not believe that it is a major issue for our study. We purposely examined a time period when the potential risk of ST was not as well appreciated by clinicians. We also matched patients to ensure that they were as comparable as possible at baseline. When selecting matching variables, we selected covariates that not only would ensure that populations were similar at baseline but also minimized the potential for measure-of-association distortions due to prescribing bias. Although the baseline platelet count is unlikely to be associated with risk of ST, we matched patients with this covariate since selection of linezolid or vancomycin for a given patient may be related to this covariate. Even with our intensive pairwise matching, concurrent receipt of SAs was still more pronounced in the vancomycin group. However, this higher usage among vancomycin patients was driven by antiemetics and antihistamines, medications not well recognized to cause ST in isolation (1). Please note that much of the antihistamine and antiemetic use in the vancomycin treatment group was directly prescribed as prophylaxis against vancomycin-induced toxicity. The two groups received antidepressants and SSRIs in similar proportions, suggesting that prescribing bias was not a major factor contributing to the observed results.

It is also important to note that only 251 case pairs were evaluated. Since the incidence of ST with linezolid may be $<0.4\%$ (1/251), it is possible that our sample size did not allow us to fully delineate the associated risk of this adverse event. We do not believe that this negates the importance of our findings, since this is the first study to provide comparative information on the risk of ST with linezolid in the real-world setting. Rather, our findings highlight the need for further large-scale, comparative, real-world studies to further quantify the associated risk of this adverse event, particularly among patients receiving a concurrent SA. It is also important to realize that the sensitivity and specificity of HSTC are $<100\%$. Surrogate terms were included in the natural word search algorithm to improve sensitivity, but it is possible, although unlikely, that a few cases were missed. If cases were missed, we anticipate that the misclassification error would likely be independent and nondifferential and thus would not bias the relative measures of associations.

Since the VA study largely involved only elderly men, the choice of study population may again limit the clinician's ability to generalize these results to other populations, namely, women. While we do not anticipate a markedly different threshold for ST between men and women, studies of women should be conducted to confirm this assertion. It is important to note that while there are always external validity concerns when studying VA patients, the VA population was an ideal study population for the research question because the relatively homogeneous patient population maximized internal validity. A more heterogeneous population might improve generalizability, but it would do so at the expense of internal validity by yielding too few patients across important confounders, ultimately resulting in unstable and biased measures of association.

In conclusion, after applying a sensitive and thorough word search algorithm to the electronic medical record data of hospitalized VA patients, we were not able to detect any increased risk of ST with linezolid relative to vancomycin. No patients were found to have ST by the exact or surrogate word search algorithm, and low rates of potential ST were found when applying the HSTC for ST. Of the patients meeting the HSTC, most had past or present comorbidities that may have contributed to or overlapped the reported adverse events. Our findings suggest that the theoretical potential for ST should not completely deter the use of linezolid in patients receiving another medication with serotonergic activity. Rather, clinicians need to be attentive in monitoring all patients receiving SAs, including linezolid, for ST, and the use of linezolid in a patient on an SA is a risk-versus-benefit situation. As it is possible that our sample size did not allow us to fully delineate the associated risk of this adverse event, our findings highlight the need for further large-scale, comparative, real-world studies to further quantify the associated risk of this adverse event, particularly among patients receiving a concurrent SA.

ACKNOWLEDGMENTS

This material is based upon work partially supported by the Office of Research and Development, Department of Veterans Affairs. The work presented in the manuscript was supported by an investigator-initiated grant from Pfizer internal funding. T.P.L. was the principal investigator for this grant.

Pfizer provided support only to complete the project and was not involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation and review of the manuscript.

We acknowledge the contributions of the following individuals, who participated in data collection and database entry: Amanda Dihmess, Benjamin Woo, and Rasha Masoud. This article has greatly benefited from the thoughtful editing of Allison Krug.

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