RISK OF SEROTONIN SYNDROME FOR LINEZOLID AND ANTIDEPRESSANTS

RISK OF SEROTONIN SYNDROME ASSOCIATED WITH ANTIDEPRESSANT USE WHILE ON LINEZOLID TREATMENT

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A Thesis Submitted to the School of Graduate Studies in Partial Fulfilment of the Requirements for the Degree Master of Science

McMaster University MASTER OF SCIENCE (2023) Hamilton, Ontario (Health Research Methodology)

TITLE: Risk of Serotonin Syndrome Associated with Antidepressant Use While on Linezolid Treatment

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NUMBER OF PAGES: xii and 87

Lay Abstract

Linezolid is an antibiotic that can potentially cause serotonin syndrome as an adverse effect when combined with antidepressants. In serotonin syndrome, dysfunction of the nervous system leads to a variety of symptoms that can be life threatening. This study examined people in Ontario aged 66 years or older who were prescribed linezolid from 2014 to 2021 to describe the risk of serotonin syndrome due to linezolid and how antidepressants change this risk. Patients were followed for 30 days from start of linezolid treatment to determine if they had serotonin syndrome based on diagnoses in emergency room or hospital visit records. Of 1,134 patients in the study, 215 (19.0%) patients took antidepressants. The risk of serotonin syndrome was low at less than 0.5%. This risk was not significantly different in patients on antidepressants when compared to those who were not. Therefore, linezolid is likely safe for patients receiving antidepressants.

Abstract

Background: There is a potential drug interaction between linezolid and antidepressants resulting in serotonin syndrome. Thus, clinicians often avoid this drug combination. However, little empirical data exists to support this avoidance. The objective of this study was to describe the risk of serotonin syndrome in patients receiving linezolid and how this risk changed with concomitant antidepressant use.

Methods: A population based retrospective cohort study was conducted using the administrative databases at ICES. The patient population consisted of outpatients aged 66 years or older who were prescribed oral linezolid of any duration from 2014 to 2021 in Ontario, Canada. Patients who were also taking antidepressants during linezolid treatment were compared to patients not on antidepressants during linezolid treatment. The primary outcome was clinically significant serotonin syndrome requiring emergency room visit or hospitalization based on physician diagnosis, Sternbach criteria or Hunter criteria within 30 days of starting linezolid. Secondary outcomes included altered mental status, hospitalization and death due to any cause within 30 days.

Results: Of 1,134 patients who were prescribed linezolid, 215 (19.0%) patients were also taking antidepressants. Less than 6 (<0.5%) patients had serotonin syndrome. The proportion of patients with serotonin syndrome was numerically lower in the antidepressant group. In a propensity score matched cohort, the adjusted risk difference for serotonin syndrome in the antidepressant group minus the no antidepressant group was -1.2% (95% CI -2.9% to 0.5%). The risk of altered mental status, hospitalization and death were similar between the two groups.

Conclusions: The risk of serotonin syndrome was low in patients taking linezolid. Concurrent antidepressants did not significantly increase the risk of serotonin syndrome. These findings suggest that linezolid can be safely used in patients also on antidepressants when indicated.

Acknowledgements

Thanks to Dr. Mark Loeb for his supervision and support throughout the study. As well, Dr. Sudeep Gill at Queen's University offered valuable expertise and advice on how to access and use ICES administrative databases.

This study contracted ICES Data & Analytic Services (DAS) and used de-identified data from the ICES Data Repository, which is managed by ICES with support from its funders and partners: Canada's Strategy for Patient-Oriented Research (SPOR), the Ontario SPOR Support Unit, the Canadian Institutes of Health Research and the Government of Ontario. The opinions, results and conclusions reported are those of the authors. No endorsement by ICES or any of its funders or partners is intended or should be inferred. Parts of this material are based on data and information compiled and provided by Canadian Institute of Health Information (CIHI). However, the analyses, conclusions, opinions, and statements expressed herein are those of the author, and not necessarily those of CIHI. We thank IQVIA Solutions Canada Inc. for use of their Drug Information Database.

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List of Abbreviations and Symbols

ARR: Absolute Risk Reduction

CI: Confidence Interval

CCI: Charlson Comorbidity Index

CIHI: Canadian Institute for Health Information

CNS: Central Nervous System

DAS: Data & Analytic Services

DAD: Discharge Abstract Database

eGFR: estimated Glomerular Filtration Rate

ER: Emergency Room

FDA: Food and Drug Administration

ICD-10-CA: International Classification of Diseases, 10th revision Canadian modification

ICES: Institute for Clinical Evaluative Sciences

IQR: Interquartile Range

MAO: monoamine oxidase

MRSA: methicillin-resistant *Staphylococcus aureus*

NACRS: National Ambulatory Care Reporting System

NDRI: Norepinephrine and dopamine reuptake inhibitor

NNT: Number Needed to Treat

ODB: Ontario Drug Benefit

OHIP: Ontario Health Insurance Plan

OLIS: Ontario Laboratories Information Systems

OMHRS: Ontario Mental Health Reporting System

OR: Odds Ratio

RECORD: Reporting of Studies Conducted Using Observational Routinely-Collected Data

RCT: Randomized Clinical Trial

RPDB: Registered Persons Database

RR: Risk Ratio

SD: Standard Deviation

SNRI: Serotonin–Norepinephrine Reuptake Inhibitor

SSRI: Selective Serotonin Re-uptake Inhibitors

SPOR: Canada's Strategy for Patient-Oriented Research

TCA: Tricyclic Antidepressants

VRE: Vancomycin-Resistant *Enterococcus*

Declaration of Academic Achievement

Anthony Bai conceived and designed the study under the supervision of Dr. Mark Loeb with input from Dr. Sudeep Gill. Anthony Bai performed the data analysis and wrote the first draft of the thesis and manuscript. Dr. Mark Loeb and Dr. Sudeep Gill provided revisions to these drafts.

Chapter 1. Background

1.1 Linezolid

Linezolid is a relatively new antibiotic approved by Canada in 2001 [1]. It is a synthetic oxazolidinone that has excellent activity against resistant gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) as well as mycobacterium [2].

Although linezolid can be taken orally or intravenously, it is most commonly taken orally based on its high bioavailability [1, 2]. The bioavailability of almost 100% means that oral and intravenous linezolid at the same dose would achieve essentially the same drug level in the blood [2]. The excellent bioavailability makes linezolid ideal as step-down oral antibiotic therapy for bacteremia, pneumonia as well as skin and soft tissue infections [2, 3].

The standard dose for linezolid is 600mg by mouth twice daily for complicated skin & soft tissue infections, pneumonia and VRE infections [3]. The duration of linezolid therapy is commonly 14 days or less for the above conditions based on randomized clinical trials (RCTs) [3]. In clinical practice, linezolid is typically prescribed no more than 14 days due to the risk of linezolid-related thrombocytopenia that significantly increases beyond 14 days [2, 4].

In the drug label for linezolid, renal adjustment for linezolid is not recommended, because linezolid is mainly cleared by non-renal mechanisms [3]. In a pharmacokinetic study that included patients with renal dysfunction on and off dialysis, linezolid clearance did not change significantly with renal function [5]. However, 35% of linezolid is renally

cleared and linezolid metabolites do accumulate in renal impairment [5]. Renal impairment is associated with a higher risk of linezolid toxicity, specifically thrombocytopenia [6].

Globally, there is an increasing role for linezolid in the treatment of resistant infections that cannot be substituted with another antibiotic. For example, linezolid was recently re-classified as a group A drug by the World Health Organization for the treatment of multi-drug resistant tuberculosis [7]. In a recent RCT of drug resistant tuberculosis, antibiotic regimens that included linezolid achieved treatment success without relapse in 84 to 93% of patients [8]. Another example is the recent movement towards early switch from intravenous to oral antibiotics, because oral antibiotics are as effective as intravenous antibiotics and safer than intravenous antibiotics in terms of lower risk of intravenous catheter related adverse events and shorter hospitalization for bacteremia, osteomyelitis and endocarditis [9]. Oral linezolid has the most evidence to date as an oral antibiotic switch option for *S. aureus* bacteremia [10], which is one of the most common bloodstream infections with a high mortality rate [11]. Linezolid is also the only oral antibiotic option in Canada for VRE infections [1]. Despite its clinical effectiveness, linezolid use has been limited due to its potential to interact with other medications such as antidepressants.

1.2 Antidepressants

Antidepressants are commonly prescribed medications. In a Canadian Community Health Survey of a nationally representative sample of 36,984 people in 2002,

approximately 6% of Canadians were taking antidepressants [12]. Antidepressants were used for major depression episodes in 33% cases [12]. Other indications for antidepressants included past depression, anxiety, migraine or fibromyalgia, which accounted for 60% of antidepressant use [12].

Major antidepressant classes include Selective Serotonin Reuptake Inhibitors (SSRI), Selective Norepinephrine Reuptake Inhibitors (SNRI), Norepinephrine and Dopamine Reuptake Inhibitor (NDRI), Tricyclic Antidepressants (TCA) and Monoamine Oxidase (MAO) inhibitors [13]. In terms of mechanism of action, these antidepressants all target and activate the serotonin receptor within the Central Nervous System (CNS) [13].

Second generation anti-depressants including SSRI, SNRI and NDRI are first line treatment options for major depression disorder in the Canadian treatment guidelines [14]. Once in remission, antidepressants are usually continued for 6 to 9 months and up to 2 years or more [14]. At the completion of treatment, the recommendation is to slowly taper the antidepressant dose over several weeks before discontinuation [14]. Tapering prevents antidepressant discontinuation syndrome, which occurs in up to 40% of patients when antidepressants are stopped abruptly [14]. Antidepressant discontinuation syndrome is associated with unpleasant somatic symptoms including flu-like symptoms, headache, light-headedness, dizziness, insomnia, nausea, tremors, imbalance, sensory disturbances and hyperarousal [14, 15]. The recommended maintenance treatment followed by taper means that patients are on antidepressant for an extended period of several months to

years. Given the long duration of antidepressant use, there is potential for it to interact with many other medications including linezolid.

1.3 Serotonin syndrome

The combination of an antidepressant and linezolid has the potential to cause serotonin syndrome. As an activator of serotonin receptors in the CNS, an antidepressant usually does not cause serotonin syndrome by itself with the exception of overdoses [14]. The combination of multiple serotonergic medications especially MAO inhibitors have the potential to cause serotonin syndrome. The first described cases of serotonin syndrome were attributed to interactions with MAO inhibitors [16]. Importantly, linezolid exhibits weak activity in the reversible inhibition of MAO enzymes A and B [2, 17, 18]. MAO A and B are responsible for metabolism of serotonin [19], so inhibition of MAO A and B significantly increases serotonin levels. Therefore, co-administration of linezolid with an antidepressant that already activates CNS serotonergic receptors may precipitate serotonin syndrome.

In serotonin syndrome, there is excess activation of serotonin receptors including the 5-HT2A serotonin receptors in the CNS [20]. Neurons with serotonin receptors are located within the brain stem from the midbrain to the medulla, which regulate wakefulness, affective behaviour, and thermoregulation as part of the autonomic nervous system as well as nociception and motor tone [20]. Therefore, excess activation of these serotonin neurons results in a spectrum of clinical findings involving mental status, autonomic nervous system and neuromuscular function. Mental status changes include

anxiety, restlessness, confusion and delirium [18, 20, 21]. Autonomic dysfunction leads to hyperthermia, hypertension, tachycardia, diaphoresis, vomiting and diarrhea [18, 20, 21]. Neuromuscular hyperactivity manifests as tremor, myoclonus, hyperreflexia, clonus and rigidity [18, 20, 21].

The severity of serotonin syndrome can range from mild to severe and life threatening. Severe cases can have severe hypertension and rigidity with complications including seizure, rhabdomyolysis, metabolic acidosis, renal failure, disseminated intravascular coagulopathy and death [20, 22]. In a case series of 56 fatal serotonin syndrome cases reported in the literature, commonly observed clinical features included high grade hyperthermia, seizure and elevated creatinine kinase indicative of rhabdomyolysis [22].

Diagnosis of serotonin syndrome is difficult due to the wide spectrum of clinical findings. The two most used diagnostic criteria for serotonin syndrome are the Sternbach criteria [16] and Hunter criteria [23], which is shown in Table 1. In a study of 2,222 patients with overdose of a serotonergic drug and diagnosis of serotonin syndrome by a clinical toxicologist as the reference standard, the Hunter criteria had 84% sensitivity and 97% specificity whereas the Sternbach criteria had 75% sensitivity and 96% specificity [23].

Table 1. Serotonin syndrome diagnostic criteria

Sternbach criteria [16] Patient must fulfill all of the following: 1) Recent addition or increase in a known serotonergic agent 2) Absence of other possible aetiologies 3) No recent addition or increase of a neuroleptic agent 4) Three or more of the following: mental status changes, agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, incoordination, fever
Hunter criteria [23] Patient must have taken a serotonergic agent plus one of the following: - Spontaneous clonus - Inducible clonus plus agitation or diaphoresis - Ocular clonus plus agitation or diaphoresis - Tremor plus hyperreflexia - Hypertonia plus temperature above 38C plus ocular clonus or inducible clonus

1.4 Risk of serotonin syndrome for linezolid plus antidepressants

The potential for linezolid to cause serotonin syndrome in combination with another serotonergic medication as an adverse event was monitored in RCTs that evaluated the effectiveness of linezolid. In a secondary analysis of 20 RCTs that compared linezolid to another antibiotic in patients who had at least one serotonergic agent, serotonin syndrome was diagnosed in 3/2,208 (0.14%) in the linezolid group and 1/2,057 (0.05%) in the comparator group with an estimated risk ratio (RR) of 2.79 (95% confidence interval (CI) 0.29 to 26.86) [24]. Based on these results, the authors concluded that the risk of serotonin syndrome due to concomitant use of linezolid and serotonergic agents was low and there was insufficient evidence to conclude that the risk of serotonin syndrome was different when linezolid was compared to another antibiotic [24]. However, patients in RCTs may be different from the patient population taking linezolid in clinical settings. For example, in the 20 RCTs on linezolid, the mean age was 49 years and only a minority (40%) were on concomitant serotonergic medications [24]. In addition, less than 10% of trial patients received an antidepressant [24], which is the most prescribed serotonergic medication in clinical practice. Therefore, the risk of serotonin syndrome observed among relatively young patients with few concurrent medications especially antidepressants in RCTs may not translate to clinical settings outside trials.

After linezolid was introduced to the market, case reports subsequently emerged of serotonin syndrome due to linezolid in post marketing surveillance. In a review of post marketing data from the United States Food and Drug Administration (FDA) adverse

event reporting system from 1997 to 2003, there were 29 cases of serotonin syndrome related to linezolid [25]. The most common class of serotoninergic drugs taken concurrently with linezolid was SSRI in 60.5% of concurrent serotonergic medications cases [25]. An updated review of FDA adverse event reporting system up to 2019 that included 669 cases of serotonin syndrome related to linezolid, common drug-drug interactions included citalopram in 112 (16.7%) cases, sertraline in 74 (11.1%) cases, and escitalopram in 65 (9.7%) cases, which were all SSRIs [26]. Other implicated antidepressant classes included SNRIs (e.g. venlafaxine), NDRIs (e.g. bupropion), TCAs (e.g. amitriptyline) and other classes such as trazodone [26]. In response, the FDA issued a warning against linezolid use in patients on antidepressants, making antidepressants a relative contraindication to linezolid treatment [27].

This FDA warning had a great impact on clinicians because antidepressants are commonly prescribed medications. While linezolid is a very useful antibiotic for resistant infections in which there are few antibiotic options, clinicians did not prescribe it in many cases because the patients were also on antidepressants.

However, passive surveillance data of case reports that led to the FDA warning did not give any information on the incidence or risk, because the denominator of the total number of patients being prescribed linezolid and an antidepressant was unknown. In single centred retrospective case series studies of patients receiving linezolid and antidepressants, serotonin syndrome was diagnosed in 2 of 53 (3.8%) patients [28], 1 of 24 (4.2%) patients [29] and 2 of 72 (2.8%) patients [30]. These small case series studies did not have a comparison group of patients who did not take antidepressants, so it was

unknown if antidepressants truly increased the risk of serotonin syndrome in patients receiving linezolid. The only study to make this comparison was a single centre retrospective cohort study of 348 patients on linezolid treatment [31]. Of these 348 patients on linezolid treatment, 87 patients were taking a SSRI or SNRI, and 261 patients were not [31]. Serotonin syndrome occurred in 1 of 87 (1.1%) patients on a SSRI or SNRI versus 1 of 261 (0.4%) patients not on a SSRI or SNRI [31]. The estimated RR was 3.00 (95% CI 0.19 to 47.45 P=0.438) [31]. The small sample size and small number of outcome events in this study led to imprecise estimates with a wide CI and inconclusive results. Precise estimate of increased risk of serotonin syndrome due to antidepressants is important, because clinicians can use it to decide on whether patients on antidepressants can be safely prescribed linezolid especially in cases of resistant infections in which linezolid is the first line therapy and alternative antibiotics would be inferior.

1.5 Research question

To fill in this knowledge gap, we conducted a large population study using the population-based data at ICES (formerly the Institute for Clinical Evaluative Sciences) to answer the following research question: In patients being prescribed linezolid, to what extent does concomitant antidepressant, compared to no concomitant antidepressant, increase the risk of serotonin syndrome?

Chapter 2. Methodological Considerations

2.1 Study design

A retrospective cohort study design was chosen to answer the research question. A cohort study is a type of observational study in which patients are initially categorized based on exposure status and then followed to determine the outcome [32]. In this study cohort of patients receiving linezolid, patients were identified based on exposure status of antidepressant use or not, and then followed to determine the outcome of serotonin syndrome.

A cohort study can be retrospective or prospective. In a retrospective cohort study, the outcome has already occurred, so the follow-up and data are collected retrospectively based on pre-existing data [33]. In contrast, a prospective study is carried out from the present time into the future. The exposure status is determined at the present time before occurrence of the outcome and then patients are followed prospectively in real time to determine if they experience the outcome [33]. For this study, a retrospective study design was chosen over a prospective study design. A prospective study has the advantage of consistency and accuracy in the data collection of the exposure, confounders and outcome [33]. However, it is also associated with significant cost to recruit patients for the study and time to follow them to determine the outcome, which can limit the sample size [33]. A retrospective study design was chosen because it is efficient in obtaining a large sample while saving time and cost. In our case, a large sample size was important to give a precise estimate of the risk of serotonin syndrome in context of antidepressant use when compared to no antidepressant use.

Alternative study designs were considered to answer the same research question including a case-control study and a RCT. A case-control study is another type of observational study in which study participants are identified as cases or controls based on outcome status and then data is collected retrospectively on the exposure status for both the cases and controls [34]. A case-control study has one disadvantage that makes it inappropriate for this research question. A case-control study cannot provide any information about the incidence or prevalence of disease [35]. For this research question, the incidence of serotonin syndrome in all patients taking linezolid and in patients taking linezolid plus an antidepressant would be important for clinicians when making decisions on whether to treat patients with linezolid. A cohort study design addresses this shortcoming by providing information on disease prevalence and incidence [33].

An RCT design was also considered for this research question. An RCT is the most rigorous study design to determine that a cause-effect relation exists between an intervention and outcome [36]. In a well-designed and executed RCT, randomization ensures that the randomized groups are balanced in prognostic factors, both known and unknown, such that any observed difference between the groups could be attributed to the intervention [36]. However, our research question focused on a potentially harmful exposure. An RCT would not be appropriate to test a potential harmful exposure, because it would not be ethical to randomize patients to interventions associated with unnecessary harm [36]. This ethical issue is not applicable to a retrospective cohort study in which patients already had the exposure of antidepressants before the study began.

2.2 Outcome measure

In cohort studies, a commonly used measure of association between an exposure and a dichotomous outcome is RR, which is calculated as proportion of exposed participants who had the outcome divided by proportion of unexposed participants who had the outcome [37]. However, the RR does not tell the magnitude of the absolute risk and does not reflect baseline risk [37]. In cases of very low baseline risk, the RR can mislead and exaggerate the treatment effect [38].

In contrast, absolute risk reduction (ARR) is the difference between the proportion of untreated participants who had the outcome minus the proportion of treated participants who had the outcome [37]. The reciprocal of the ARR is the number needed to treat (NNT) [37]. The NNT is interpretated as the required number of patients to be treated in order to prevent one event [37]. The above calculations assume that the exposure is a beneficial treatment. If the exposure is harmful and the outcome event reflects harm such as in this research question, then the risk difference of the proportion of exposed participants who had the outcome minus the proportion of exposed participants who had the outcome would reflect the absolute increased risk related to the exposure. The reciprocal of this would be number needed to harm, which is interpreted as the number of patients required to be exposed to cause the harmful event in one patient. From a clinician's perspective, the ARR and NNT (or number needed to harm) are more useful than RR when making treatment decisions [37]. For these reasons, we reported the risk differences and number needed to harm as the outcome measure such that it would be useful for clinicians.

2.3 Controlling for confounders

A confounder is a variable that is associated with the exposure and the outcome but does not lie within the causal pathway [33]. If not accounted for, a confounder can strengthen, weaken, or reverse the observed association between an exposure and outcome [39].

Confounding occurs commonly in observational studies such as a cohort study. In these non-randomized studies, participants are allocated to the exposed or non-exposed group likely for non-random reasons. The non-random allocation leads to an imbalance of prognostic factors between the exposed and non-exposed groups, resulting in confounding. For example, the clinical indication for selecting a treatment over another that also affects the outcome would be confounding by indication [39].

There are several methods to control for confounding in a cohort study during the design or analysis stage [39]. In the design stage, restriction or matching can be done to control for confounders [33, 39]. However, matching can only be done for a limited number of confounders and restriction makes the results less generalizable to the population [33]. At the statistical analysis stage, commonly used methods to remove confounding include stratified analyses, regression modeling and propensity scoring [39].

There are many confounders to adjust for in this research question, so restriction and matching are not practical. For statistical methods, we considered using a multivariable logistic regression model or propensity scoring. For this study, multivariable logistic regression model has two disadvantages. First, the correctness of parameter estimation of a multivariable logistic regression model depends on the number

of events [40]. Low event per variable such as less than 10 events per variable within a multivariable logistic regression model may lead to imprecise, biased and unreliable estimates [40]. It should be noted that events per variable is just one of many contributing factors that impacts the correctness of parameter estimation [41]. For this study, serotonin syndrome is a rare adverse event and there may not be enough events to satisfy the event per variable threshold of 10. Second, the outcome measure for a multivariable logistic regression model is odds ratio (OR), which cannot be translated to number needed to harm. In contrast, propensity scoring is not limited by the number of events. In addition, propensity scoring methods can be used to estimate risk differences and thus NNT [42]. Therefore, a propensity scoring method was chosen as the statistical method to control for confounders in this study.

2.4 Propensity scoring

Propensity score is a participant's probability of treatment conditional on the observed baseline covariates [43]. Treated and untreated participants with the same propensity score will have similar distributions of observed baseline covariates [43]. Therefore, adjustment by propensity score will balance the distribution of measured covariates between the two groups [44].

In observational studies, the propensity score is commonly estimated using a multivariable logistic regression model [45]. In this model, the dependent variable is the treatment or exposure status, which is regressed on observed baseline covariates [45]. In terms of what covariates should be selected as independent variables in this model,

experts recommend all potential and true confounders [45]. Potential confounders are covariates that are known to affect the outcome whereas true confounders are covariates that are known to be associated with both exposure and outcome.

Methods to adjust using propensity score include matching on the propensity score, stratification on the propensity score, inverse probability of treatment weighting using the propensity score, and covariate adjustment using the propensity score [45]. Matching by propensity score was chosen for this study based on the following reasons. First, simulation studies have shown that propensity score matching is better than stratification on the propensity score and covariate adjustment using the propensity score at balancing baseline characteristics [46]. Compared to inverse probability of treatment weighting using the propensity score, matching by propensity score is similar in most cases and better in some cases in terms of removing systematic baseline differences [47]. Second, matching by propensity score estimates the average treatment effect for the treated, which is the average effect of treatment on participants who ultimately received treatment [45]. In contrast, inverse probability of treatment weighting using the propensity score estimates the average treatment effect, which is the average effect when an entire population moves from being untreated to treated [45]. For the research question of this study, the average treatment effect for the treated is more relevant than the average treatment effect, because the interest lies in the effect of antidepressants in patients who ultimately received them, not the effect of antidepressants if the entire population received an antidepressant.

Propensity score matching forms matched sets of treated and untreated participants based on a similar value of propensity score [45]. The most used method is one-to-one pair matching [45]. There are several methods to match pairs based on propensity scores. Matching without replacement is simpler than matching with replacement, because variance estimation does not need to account for the same participant being in more than one matched set [48]. Greedy or optimal matching can be used. In greedy matching, treated participant is matched to an untreated participant sequentially, where the nearest untreated participant is matched to a given treated participant even if that untreated participant would be a better match for a subsequent treated participant [45]. In contrast, optimal matching considers the entire data set and form matches to minimize the total within-pair differences of propensity score [45]. In simulation studies, greedy matching performed just as well as optimal matching in producing balance matched samples [45]. The criteria to select the closest neighbor based on propensity score can have no limits or have a specified caliper distance based on logit of the propensity score that set the maximum absolute difference in propensity scores for matched pairs [45]. Across studies, a wide range of caliper widths have been used and there is no universally accepted threshold [45].

After adjustment using propensity score, balance of covariates between the propensity score matched groups should be assessed using standardized differences [44]. A standardized difference of 0.1 is usually used as the threshold in which a standardized difference of 0.1 or above denotes a meaningful imbalance in baseline covariates [44].

After propensity score matching, the treatment effect on the outcome can be directly compared between the two matched groups [45]. However, participants matched by propensity score are more similar on average in terms of baseline covariates when compared to randomly selected participants from each group, so propensity score matched samples are no longer independent observations [47]. Thus, comparison of the propensity score matched groups should account for the matched nature [42]. For a dichotomous outcome, McNemar's test for paired data can be used to test for statistical significance of a difference in proportions [45]. For the absolute risk difference, the 95% CI can account for the paired data using variances as described by Agresti and Min [49].

2.5 Use of administrative databases at ICES

This study used the administrative databases housed at ICES. ICES is an independent, non-profit research institute funded by an annual grant from the Ontario Ministry of Health [50]. As a prescribed entity under Ontario's privacy legislation, ICES is authorized to collect and use health care data for the purposes of health system analysis, evaluation and decision support [51]. Secure access to these data is governed by policies and procedures that are approved by the Information and Privacy Commissioner of Ontario [51]. The use of data for this study is authorized under section 45 of Ontario's Personal Health Information Protection Act [51].

ICES data repository consists of patient-level linked data from publicly funded administrative health service records that are routinely collected by the Ontario

government [50]. These records would include the Ontario population eligible for universal health coverage [50].

There were several ICES databases used to answer the research question for this study. The study population was defined based on data from the Ontario Drug Benefit (ODB) database, which contains prescription claims as covered by the Ministry of Health and Long-Term Care [52]. This drug program covers outpatient drug coverage in the community for the following patient populations [52]:

- People 65 years of age or older
- People on social assistance such as the Ontario Disability Support Program
- People in special care homes and long-term care homes
- People receiving professional home care services
- Registrants for the Trillium Drug Program

The ODB program covers prescription drug products listed in the ODB formulary [52]. Prescription drugs that are not listed in the formulary may be covered by the exceptional access program [52]. The ODB program does not cover over-the-counter medications [52]. The ODB database contains information on the medication name, dosage, start date and duration.

The chosen study population consisted of adults aged 66 years or older who were prescribed linezolid for any duration from October 1, 2014 to January 1, 2021. The age cut-off of 66 years allowed a 1-year look back to ensure that concomitant antidepressants were accurately captured. As an example, suppose a patient is on an antidepressant since the age of 63 years with yearly prescription renewals and is started on linezolid at the age

of 65 years. The concomitant antidepressant that the patient is currently on may be missing from the ODB database as the prescription occurred prior to the age of 65 years. Although other groups of people such as people living in special care home are covered by ODB, these people are excluded from this study because they are not representative of the general population. Oral linezolid was added to the ODB formulary starting in October of 2014 [53]. For this study, linezolid was identified based on the drug identification number from the ODB database.

The exposure status of antidepressant is determined based on the ODB formulary using the drug identification number for each type of antidepressants.

The outcome status of serotonin syndrome is determined based on data from the CIHI Discharge Abstract Database (DAD) and the National Ambulatory Care Reporting System (NACRS). CIHI DAD contains hospitalization data [54] whereas NACRS contains data for emergency room (ER) and ambulatory care visits [55]. The discharge diagnoses from DAD and NACRS are categorized using the International Classification of Diseases, 10th revision Canadian modification (ICD-10-CA) codes [54, 55]. There is no ICD-10-CA code for serotonin syndrome. Therefore, serotonin syndrome was defined as ICD-10-CA diagnosis of toxicity due to any serotonergic medication. In addition, the individual symptoms from the Sternbach criteria and Hunter criteria were matched to ICD-10-CA codes, such that these diagnostic criteria could be used to determine if patients had serotonin syndrome.

CIHI DAD ICD-10-CA diagnoses can also be used to describe comorbidities and calculate the Charlson Comorbidity Index (CCI) [56] using a validated algorithm [57].

Other databases were used to collect data on covariates and secondary outcomes. The Registered Persons Database (RPDB) include age, sex, postal code of residence and date of death for people registered under the Ontario Health Insurance Plan (OHIP) [58]. The CIHI Ontario Mental Health Reporting System (OMHRS) contains information about patients receiving adult mental health services in Ontario including psychiatric diagnostic information and substance use behaviours [59]. The Ontario Laboratories Information System (OLIS) contains lab test results from hospitals, community labs and public health labs [60].

Chapter 3. Study Methods

3.1 Study design and reporting

A retrospective cohort study was conducted using ICES databases. This study was reported as per the Reporting of Studies Conducted Using Observational Routinely-Collected Data (RECORD) reporting guidelines [61].

3.2 Ethics approval

The Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board have approved this research project (project number 6035935). As a prescribed entity under Ontario's Personal Health Information Privacy Act and the Coroners Act, health information custodians are permitted to disclose personally identifiable information to ICES without individual consent [51]. ICES can use this information for approved research projects [51].

3.3 Patient population

Oral linezolid was added to the ODB formulary starting in October of 2014 [53]. Therefore, the study population consisted of adults aged 66 years or older in Ontario who were prescribed oral linezolid for any duration from October 1, 2014 to January 1, 2021. This was a convenient sample size based on study date cut-offs.

3.4 Databases and data collection

The ODB databases were linked at a patient level to the following databases: RPDB, DAD, NACRS, OMHRS, and OLIS. The following patient information was extracted from these databases.

Demographics: age, sex, rural or urban home address

Comorbidities: CCI [56], substance use disorder

Bloodwork: estimated Glomerular Filtration Rate (eGFR) based on baseline serum creatinine [62]

Linezolid: start date, stop date, dose, frequency

Concomitant serotonergic medications **other than antidepressants** covered by ODB that increase risk of serotonin syndrome [20, 25, 26]: lithium, serotonin 3 receptor antagonists (dolasetron, granisetron, ondansetron, and palonosetron), metoclopramide, methylphenidate, dexmethylphenidate, fentanyl, meperidine, methadone, oxycodone, tramadol, triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan), ergot derivatives (dihydroergotamine, ergotamine, and methylergonovine), dextromethorphan, chlorpheniramine, cyclobenzaprine, carbamazepine, valproic acid, tryptophan, dextroamphetamine, rasagiline, and ritonavir.

The variables listed above are all important potential confounders for the outcome of serotonin syndrome. Substance use disorder is a potential confounder, because many medications that can be abused (e.g. fentanyl, oxycodone) and illicit drugs (e.g. methylenedioxymethamphetamine, lysergic acid diethylamide) can cause serotonergic syndrome [20]. Renal function as measured by eGFR is another important potential confounder. Although renal adjustment for linezolid is not recommended in the drug

label [3], 35% of linezolid is renally cleared and linezolid metabolites do accumulate in renal impairment [5]. This accumulation leads to higher risk of linezolid related toxicity such as thrombocytopenia [6]. Therefore, the risk of serotonin syndrome may be higher in patients with renal impairment.

3.5 Exposure

The exposure of interest was concomitant oral antidepressants while on linezolid therapy that were listed in the FDA warnings of interactions with linezolid causing serotonin syndrome [27] as listed below.

1) SSRI: paroxetine, fluvoxamine, fluoxetine, sertraline, citalopram, escitalopram
2) SNRI: venlafaxine, desvenlafaxine, duloxetine
3) TCA: clomipramine, amitriptyline, desipramine, imipramine, nortriptyline, protriptyline, doxepin, trimipramine
4) MAO inhibitors: isocarboxazid, phenelzine, selegiline, tranylcypromine, moclobemide
5) NDRI: bupropion
6) Other psychiatric medications: trazodone, mirtazapine, buspirone, amoxapine, maprotiline, nefazodone

Concomitant antidepressant was defined as one or more antidepressant(s) from the list above of any dose being prescribed for any duration during the time period between linezolid start and stop date. This was a dichotomous variable, where patients were categorized into either the antidepressant group or no antidepressant group.

3.6 Outcomes

The primary outcome was clinically significant serotonin syndrome based on ambulatory care visit, ER visit or hospitalization discharge diagnoses as captured by the ICD-10-CA codes (Table 2). Based on the ICD-10-CA codes, a patient was diagnosed with serotonin syndrome if the patient satisfied any of the following:

1) Physician diagnosis of toxicity due to any serotonergic medication overdose

2) Diagnoses of symptoms that satisfy the Sternbach diagnostic criteria for serotonin syndrome [16]

3) Diagnoses of symptoms that satisfy the Hunter diagnostic criteria for serotonin syndrome [23]

Table 2. ICD-10-CA codes for each symptom of serotonin syndrome

	ICD-10-CA codes[a]
Physician diagnosis	T43.x, T44.x F19.x
Mental status change	F03.x, F05.x, F19.x G45.9 R41.0, R41.8, R40.224
Agitation	R45.0, R45.1 F43.0, F43.8
Myoclonus or spontaneous clonus	G25.3 R25.2
Hyperreflexia	R29.2
Diaphoresis	R61.x
Shivering	R68.83
Tremor	G25.x R25.1
Diarrhea	R19.4, R19.7 K52.9, K58.x A08.x, A09.x
Incoordination	R27.x G11.x, G32.81
Fever	R50.x A68.x
Ocular clonus	H55.x
Hypertonia	G24.x

[a]Codes ending with .x mean that all possible decimal numbers that begin with the same first 3 characters are included

The diagnosis of serotonin syndrome must have occurred within 30 days of starting linezolid. Typically, Linezolid is prescribed for no more than 14 days to limit its bone marrow suppression toxicity [4]. Furthermore, linezolid has a half-life of 5 to 7 hours [17], so it should be cleared within 2 days after discontinuation. Therefore, 30 days as a time frame should capture all serotonin syndrome related to linezolid use.

Secondary outcomes were chosen to represent consequences of severe serotonin syndrome, which included:

1) Altered mental status or encephalopathy requiring ER visit or hospitalization based on ICD-10-CA codes used in a previous study [63]

2) Hospitalization for any reason

3) Death due to any cause

All secondary outcomes must have occurred within 30 days of starting linezolid treatment.

3.7 Statistical analysis

Descriptive analysis was used to describe the two groups (antidepressant group and no antidepressant group). Means and standard deviations (SD) were used for normally distributed continuous variables, whereas median and interquartile range (IQR) were used for non-normally distributed continuous variables. Numbers with percentages were used to describe categorical variables.

For the primary and secondary outcomes, antidepressant group was compared to no antidepressant group using Fisher's exact test. As well, an absolute risk difference

between the two groups was calculated as the risk in the antidepressant group minus the risk in the no antidepressant group. For the absolute risk difference, a 95% CI was estimated using the Newcombe method [64].

To adjust for baseline covariates, matching by propensity score was used. The propensity for antidepressant use was estimated using a logistic regression model. Within this logistic regression model, the following patient baseline covariates were included as the independent variables: age, sex, rural home address, CCI, eGFR, history of substance use disorder, duration of linezolid use and use of other serotonergic medications. Patients in the antidepressant group were matched in a 1:1 ratio to patients in the no antidepressant group without replacement using nearest neighbour greedy matching within a specified caliper width of 0.1 times the SD of the logit of propensity scores. Balance of covariates between the propensity score matched groups were described using standardized differences [44].

The two propensity score matched groups were then compared in terms of primary and secondary outcomes. To account for the matched nature, the two matched groups were compared using the exact McNemar's test and the 95% CI for the absolute risk difference was estimated using a method to account for the matched samples as described by Agresti and Min [49].

All statistical tests were 2-sided with $P < 0.05$ significant level. The statistical software R (version 4.1.2, R Foundation for Statistical Computing) was used for the analysis. The packages DescTools, MatchIt and exact 2x2 were used to estimate absolute

risk difference 95% CI, match by propensity score and perform the exact McNemar's test respectively [65-67].

3.8 ICES data reporting policy

As per ICES data policy, research outputs and reports must not contain information that identifies an individual or could foreseeably be used to re-identify an individual. Data reporting 5 or less individuals within a cell or category are considered potentially identifiable information. Therefore, any cell reporting 5 or less individuals were suppressed in this study to comply with ICES data policy.

Chapter 4. Results

4.1 Cohort description

Of the population aged 66 years or older in Ontario, Canada, 1,134 outpatients were prescribed oral linezolid between October 1, 2014 and January 1, 2021. All patients were linked by the databases and completed follow-up to 30 days, so all patients that satisfied the eligibility criteria were included in the study. The dosage for oral linezolid was 600mg taken twice daily for all prescriptions.

Of all 1,134 patients, 215 (19.0%) patients were on an antidepressant while receiving linezolid treatment. For these 215 patients, the median (IQR) days of overlap between the antidepressant and linezolid prescription was 7 days (IQR 5 to 10 days). The antidepressant was taken during the entire linezolid course for 142 (66.0%) patients. Antidepressant was taken for 3 days or more during linezolid therapy for 197 (91.6%) patients. For antidepressant classes, 103 patients (47.9%) were taking an SSRI, 36 (16.7%) patients were taking an SNRI, 15 (7.0%) patients were taking a TCA, 7 (3.3%) patients were taking a NDRI, and no patients were taking a MAO inhibitor. For each type of antidepressant, the number of patients who took it is described in Table 3.

Table 3. Proportion of patients on different types of antidepressants

	Patients on antidepressants (N=215)
SSRI	
Paroxetine	8 (3.7%)
Sertraline	25 (11.6%)
Citalopram	65 (30.2%)
Escitalopram	0 (0%)
Fluvoxamine	<6
Fluoxetine	<6
SNRI	
Venlafaxine	11 (5.1%)
Desvenlafaxine	0 (0%)
Duloxetine	25 (11.6%)
TCA	
Clomipramine	0 (0%)
Amitriptyline	13 (6.1%)
Desipramine	0 (0%)
Imipramine	<6
Nortriptyline	0 (0%)
Protriptyline	0 (0%)
Doxepin	<6
Trimipramine	0 (0%)
MAO inhibitor	
Isocarboxazid	0 (0%)
Phenelzine	0 (0%)
Selegiline	0 (0%)
Tranylcypromine	0 (0%)
Moclobemide	0 (0%)
NDRI	
Bupropion	7 (3.3%)
Other	
Trazodone	76 (35.4%)
Mirtazapine	22 (10.2%)
Amoxapine	0 (0%)
Maprotiline	0 (0%)
Nefazodone	0 (0%)

4.2 Patient characteristics

The baseline characteristics for the antidepressant group and no antidepressant group are described in Table 4. Of note, linezolid was prescribed for mean (SD) of 11.7 (7.2) days in the antidepressant group and 10.3 (6.2) days in the no antidepressant group. There were 19 (8.8%) patients in the antidepressant group who were on other serotonergic medications compared to 47 (5.1%) patients in the no antidepressant group. For each type of other serotonergic medications, the number of patients who took it is described in Table 5.

Table 4. Baseline characteristics

	Antidepressant (N=215)	No antidepressant (N=919)	Std diff
Age in years			
66 to 69	48 (22.3%)	177 (19.3%)	0.0756
70 to 79	83 (38.6%)	390 (42.4%)	0.0781
80 and above	84 (39.1%)	352 (38.3%)	0.0158
Female	117 (54.4%)	422 (45.9%)	0.1706
Rural home address	23 (10.7%)	105 (11.4%)	0.0216
CCI mean (SD)	2.3 (2.1)	2.0 (2.1)	0.1200
eGFR in mL/min/1.73m^2 mean (SD)	70.7 (28.3)	69.6 (27.2)	0.0393
History of substance use disorder	<6, more in no antidepressant group		0.0221
Days of Linezolid mean (SD)	11.7 (7.2)	10.3 (6.2)	0.2089
Number of antidepressants mean (SD)	1.2 (0.5)	0 (0)	3.8008
On other serotonergic medication(s)	19 (8.8%)	47 (5.1%)	0.1465

CCI = Charlson's comorbidity index; eGFR = estimated glomerular filtration rate; SD = standard deviation; Std diff = standardized difference

Table 5. Proportion of patients on other serotonergic medications

	Antidepressant (N=215)	No antidepressant (N=919)
Lithium	0 (0%)	0 (0%)
Dolasetron	0 (0%)	0 (0%)
Granisetron	0 (0%)	0 (0%)
Ondansetron	<6	13 (1.4%)
Palonosetron	0 (0%)	0 (0%)
Metoclopramide	8 (3.7%)	11 (1.2%)
Alomitriptan	0 (0%)	0 (0%)
Eletriptan	0 (0%)	0 (0%)
Frovatriptan	0 (0%)	0 (0%)
Naratriptan	0 (0%)	0 (0%)
Rizatriptan	0 (0%)	0 (0%)
Sumatriptan	0 (0%)	0 (0%)
Zolmitriptan	0 (0%)	0 (0%)
Dihydroergotamine	0 (0%)	0 (0%)
Ergotamine	0 (0%)	0 (0%)
Methylergonovine	0 (0%)	0 (0%)
Fentanyl	<6	7 (0.8%)
Meperidine	0 (0%)	0 (0%)
Methadone	0 (0%)	0 (0%)
Oxycodone	<6	<6
Tramadol	0 (0%)	0 (0%)
Dextromethorphan	0 (0%)	0 (0%)
Chlorpheniramine	0 (0%)	0 (0%)
Cyclobenzaprine	0 (0%)	0 (0%)
Carbamazepine	<6	0 (0%)
Valproic acid	<6	<6
Tryptophan	<6	11 (1.2%)
Methylphenidate	0 (0%)	0 (0%)
Dexmethylphenidate	0 (0%)	0 (0%)
Dextroamphetamine	0 (0%)	0 (0%)
Rasagiline	<6	0 (0%)
Ritonavir	0 (0%)	0 (0%)

4.3 Outcomes

The primary and secondary outcomes are described in Table 6. In terms of the primary outcome, serotonin syndrome occurred in less than 6 (<0.5%) patients in total. The proportion of serotonin syndrome cases was numerically lower in the antidepressant group. The unadjusted risk difference was -0.3% (95% CI -1.0% to 1.4%).

Table 6. Primary and secondary outcomes

Outcomes within 30 days of starting linezolid	Antidepressant (N=215)	No antidepressant (N=919)	Risk difference (95% CI) P-value
Primary outcome			
Serotonin syndrome	<6 in total, more in the no antidepressant group		-0.3% (-1.0% to 1.4%) P>0.9999
Secondary outcomes			
Altered mental status or confusion	25 (11.6%)	63 (6.9%)	4.8% (0.7% to 10.1%) P=0.0232
Hospitalization	92 (42.8%)	398 (43.3%)	-0.5% (-7.7% to 6.9%) P=0.9391
Death due to any cause	16 (7.4%)	44 (4.8%)	2.7% (-0.6% to 7.1%) P=0.1276

CI = confidence interval

4.4 Propensity score matching

Based on propensity scores, 166 patients in the antidepressant group were matched to 166 patients in the no antidepressant group (Table 7). After propensity score matching, the maximum standardized difference was 0.0845, which suggested good balance of the measured covariates. Within this propensity score matched cohort, the occurrences of primary and secondary outcomes are described in Table 8. The adjusted risk difference for serotonin syndrome was -1.2% (95% CI -2.9% to 0.5%) in the antidepressant group when compared to the no antidepressant group. The upper limit CI of 0.5% corresponded to a number needed to harm of 200.

Secondary outcomes including altered mental status or confusion, hospitalization and death occurred at a similar rate between the two groups matched by propensity scores (Table 8).

Table 7. Baseline characteristics in propensity score matched cohort

	Patients on anti-depressants (N=166)	Patients not on anti-depressants (N=166)	Std diff
Age in years			
66 to 69	39 (23.5%)	37 (22.3%)	0.0287
70 to 79	68 (41.0%)	65 (39.2%)	0.0369
80 and above	59 (35.5%)	64 (38.6%)	0.0624
Female	84 (50.6%)	91 (54.8%)	0.0845
Rural home address	21 (12.7%)	18 (10.8%)	0.0562
CCI mean (SD)	2.2 (1.9)	2.1 (2.1)	0.0358
eGFR in mL/min/1.73m^2 mean (SD)	70.4 (29.0)	70.4 (27.1)	0.0003
History of substance use disorder	0 (0%)	0 (0%)	0
Days of linezolid treatment mean (SD)	10.6 (6.4)	10.7 (6.3)	0.0161
On other serotonergic medication(s)	11 (6.6%)	8 (4.8%)	0.0779

CCI = Charlson comorbidity index; eGFR = estimated glomerular filtration rate; SD = standard deviation; Std diff = standardized difference

Table 8. Primary and secondary outcomes in propensity score matched cohort

Outcomes within 30 days of starting linezolid	Antidepressant (N=166)	No antidepressant (N=166)	Risk difference (95% CI) P-value[a]
Primary outcome			
Serotonin syndrome	<6 in total, more in the no antidepressant group		-1.2% (-2.9% to 0.5%) P=0.5000
Secondary outcomes			
Altered mental status or confusion	20 (12.1%)	19 (11.5%)	0.6% (-6.2% to 7.4%) P>0.9999
Hospitalization	82 (49.4%)	85 (51.2%)	-1.8% (-11.9% to 8.3%) P=0.8151
Death due to any cause	14 (8.4%)	10 (6.0%)	2.4% (-3.4% to 8.2%) P=0.5413

CI = confidence interval

[a]P-value by McNemar's exact test

Chapter 5. Discussion

5.1 Summary of study findings

This large population-based retrospective cohort study included 1,134 older adults who were prescribed linezolid including 215 (19.0%) patients on antidepressants. The risk of serotonin syndrome was rare and below 0.5% in this cohort. After adjusting for covariates using propensity score matching, the risk difference for serotonin syndrome was -1.2% (95% CI -2.9% to 0.5%). Within this CI, the worst-case scenario was an absolute increase in risk of serotonin syndrome by 0.5% in the antidepressant group, which corresponded to a number needed to harm of 200. In addition, there were no significant differences in the secondary outcomes related to consequences due to serotonin syndrome including altered mental status or confusion, hospitalization, and death. Thus, concomitant antidepressant while on linezolid therapy did not significantly increase the risk of serotonin syndrome.

5.2 Study strengths

There are several strengths to this study. First, the large sample size of more than 1,000 patients allowed for precise estimates of the risk for serotonin syndrome. Second, the study consisted of elderly patients with multiple comorbidities on many medications who were at a high risk for medication adverse effects. This is representative of the typical patients who are prescribed linezolid in clinical practice.

Third, the linked databases provided individual patient-linked data on demographics, socioeconomic status, comorbidities, medications and bloodwork results,

which were complete. Matching by propensity score was used to adjust for these important potential confounders. However, as with all observational studies, there could always be the possibility of residual confounding due to unmeasured confounders that were not adjusted for [68].

Fourth, follow-up was complete for all patients. All ER visits and hospitalizations within the province of Ontario should be captured by the CIHI NACRS and DAD databases [54, 55]. Thus, the outcomes could be determined for all patients and there is no attrition bias.

5.3 Study limitations

One limitation of the study was that the exposure was determined based on the ODB database, which captured prescribed medications on the ODB funded formulary. Over-the-counter medications would be omitted. However, most serotonergic medications are prescription medications funded by the ODB. As well, data on prescription did not account for medication adherence, so patients may not have been taking the medication as prescribed. This can cause misclassification bias, as patients who were prescribed antidepressants but not adherent would be misclassified as to be in the antidepressant group. This differential misclassification bias would dilute the difference between the two groups and push the estimates towards the null. However, the study findings would reflect real-world "intent-to-treat" effect of prescribing linezolid to a patient who was also prescribed an antidepressant regardless of adherence. It is plausible that patients withheld antidepressants temporarily while taking linezolid to

decrease the risk of serotonin syndrome. However, prescribers are unlikely to recommend patients to abruptly stop antidepressant while on linezolid due to risk of antidepressant discontinuation syndrome that is associated with unpleasant somatic symptoms [15].

Another limitation was how the primary outcome was defined. There is no ICD-10-CA diagnostic code for serotonin syndrome. Therefore, serotonin syndrome was diagnosed retrospectively based on a constellation of ICD-10-CA codes, which have not been validated previously. These codes do not match perfectly to the Sternbach criteria [16] or Hunter criteria [23]. Patients with serotonin syndrome may have had symptoms that were interpreted as another ICD-10-CA code by the hospital records personnel who entered the data. Alternatively, the symptoms of serotonin syndrome could have been omitted altogether in the hospital records. These serotonin syndrome cases would be misclassified as no serotonin syndrome in our study. However, prior studies have used similar diagnostic codes for the diagnostic criteria [24, 25]. In our study, the use of diagnostic criteria was also complemented by the physician diagnosis based on diagnosis codes. When physician diagnosed toxicity due to a serotonergic medication was reported, individual symptoms were more likely to be omitted in favour of the overarching diagnosis entered in the administrative data. Therefore, the physician diagnoses were meant to complement and not match the Sternbach or Hunter criteria. The incidence of serotonin syndrome in our study was <0.5%, which was similar to the reported incidence of 0.14% in a review of linezolid RCTs [24] and 0.6% in an observational study [31]. This suggests that our definition did not miss a significant number of serotonin syndrome cases. Still, it may not have been sensitive enough to capture all cases. We accounted for

this by including the secondary outcomes that were markers of severe serotonin syndrome including altered mental status or confusion, all-cause hospitalization and mortality. All severe serotonin syndrome cases should have resulted in one of these secondary outcomes. It is reassuring that there was no significant difference between the two groups in terms of these secondary outcomes after matching using propensity scores, which was consistent with what the primary outcome showed.

The third limitation was the small number of events. The low number of events is still clinically useful in context of a large sample size. Fewer than 6 cases of serotonin syndrome among over 1,000 patients and the risk difference 95% CI limit at 0.5% was reassuring in that serotonin syndrome occurred rarely and concomitant antidepressants did not significantly add to this risk. The small number of events did limit the statistical analysis methods that would be appropriate for adjustment of the many covariates in our study. For example, use of a logistic regression model was inappropriate due to the low numbers of events per variable, because less than 10 events per variable may lead to imprecise and biased estimates [40]. In contrast, propensity score matching was able to balance the covariates independent of number of events. In terms of outcome measure, low number of events could make the OR and RR extreme and potentially misleading [38, 69]. We used absolute risk differences to describe the outcomes, which could be calculated when comparing two propensity score matched groups [42]. Absolute risk differences could be translated to number needed to harm, which may be more meaningful and intuitive for clinicians to estimate the additional risk when a patient on an antidepressant was started on linezolid treatment.

Finally, our study did not have any patients on a MAO inhibitor. Among the different antidepressant classes, MAO inhibitors have the highest risk of serotonin syndrome, as the first reported cases of serotonin syndrome were related to MAO inhibitor use [16]. Therefore, our study findings cannot be applied to patients taking MAO inhibitors. This reflects the current practice in which MAO inhibitors are rarely used due to its high risk for toxicity such as serotonin syndrome and hypertensive crisis [70]. For example, within a population study of older adults in Ontario from 1997 to 2007, there were only 348 new users of MAO inhibitors and the rate continued to decrease yearly to 1.4 per 100,000 by 2007 [70]. The declining and rare use of MAO inhibitors make its potential interaction with linezolid irrelevant in clinical practice nowadays.

5.4 Comparison to prior studies

Our study findings are consistent with prior studies. In a secondary analysis of 20 RCTs of patients who were taking at least 1 serotonergic agent, serotonin syndrome occurred in 3 of 2,208 patients (0.14%) in the linezolid group and 1 of 2,057 (0.05%) in the comparator group [24]. The RR was 2.79 (95% CI 0.29 to 26.85) [24]. Similarly, serotonin syndrome occurred rarely, and linezolid did not significantly increase this risk in context of additional serotonergic antidepressants in our study. Our study findings are more applicable to clinical practice than linezolid RCTs, because our study population of older adults with multiple comorbidities and medications is representative of the typical patients being prescribed linezolid in the community. For example, in the secondary

analysis of linezolid RCTs, 70.6% of the patients were younger than 65 years of age [24] whereas all patients in our study were older than 65 years of age. Furthermore, the secondary analysis of RCTs did not describe or account for socioeconomic status, comorbidities, renal function, or days of linezolid therapy [24]. In contrast, our study had accounted for these important potential confounders when the two groups were matched by propensity scores.

Our study is the largest observational study to date on the risk of serotonin syndrome in patients on antidepressants compared to patients not on antidepressants. To our knowledge, there was only one other observational study that asked a similar research question [31]. In this study, 87 patients who were taking an SSRI or SNRI during linezolid treatment were compared to 261 patients who were not taking an SSRI or SNRI during linezolid treatment [31]. The exposure of interest was restricted to SSRI or SNRI. However, TCA, MAO inhibitors, NDRI and other antidepressants could also potentially interact with linezolid and cause serotonin syndrome as per the FDA warning [27]. Our study considered all implicated antidepressants in the exposure group. In terms of results, the study by Karkow et al. found a similarly low incidence of serotonin syndrome in 1.1% patients in the SSRI or SNRI group versus 0.4% patients in the no SSRI or SNRI group with an estimated RR of 3.00 (95% CI 0.19-47.45 P=0.438) [31]. The small sample size and use of RR resulted in a very wide CI of extreme RRs and inconclusive results. In contrast, our study of more than 3 times the sample size resulted in a more precise estimate and a narrow CI around the absolute risk difference and number needed to harm, which is likely more clinically useful [38].

5.5 Implications

Our study characterized the risk of serotonin syndrome during linezolid therapy and how concomitant antidepressants changed this risk. Antidepressants did not significantly increase the risk of serotonin syndrome. Within the 95% CI, the worst-case scenario was an absolute increase in risk by 0.5%, which translated to number needed to harm of 200. Therefore, antidepressants should not be an absolute contraindication for linezolid. Clinicians should be reassured that it is safe to prescribe linezolid to patients taking antidepressants. The removal of concomitant antidepressants as a barrier for linezolid treatment could ensure that more people could get linezolid in a timely manner for their infections. In cases of resistant infection such as multi-drug resistant tuberculosis [8], it would mean that patients on concomitant antidepressants could still be started safely on linezolid, which is the first line and most effective treatment option.

In addition, clinicians can use our study findings to inform patients of the risk of serotonin syndrome during shared decision making. For patients on antidepressants who are about to be started on linezolid, clinicians can reassure them that antidepressants would only increase the risk of serotonin syndrome by less than 1% in the worst-case scenario. This reassurance can help improve patient adherence to both linezolid and antidepressants.

5.6 Directions for future research

Research questions on rare and serious adverse events related to antibiotics cannot be tested by RCTs due to ethical concern of randomizing patients to unnecessary harm.

As a result, evidence for harm related to antibiotic therapy usually comes from retrospective population-based observational studies such as our study. This evidence has limitations due to the nature of retrospective observational studies. Retrospective data on the exposure and outcome are usually not collected systematically for the intended purpose of the research question, resulting in misclassification bias. For our study, use of ICD-10-CA codes may misclassify serotonin syndrome cases as described above. This shortcoming can be addressed by a prospective cohort study. In a prospective cohort study, the systematic and consistent data collection on exposure and outcome improves accuracy and reduces misclassification bias [33]. However, prospective enrolment, follow-up and data collection would significantly increase the cost and time required to complete the study when compared to a retrospective study.

For new medications, prospective cohort studies that monitor for safety and adverse effects exist as phase IV post-marketing surveillance studies [71]. Most phase IV studies focus on drugs for mental health, cardiovascular disease, cancer and rheumatologic diseases [72, 73]. In contrast, there is a dearth of phase IV studies on new antibiotics. There should be more funding so that future research on antibiotic safety can move beyond retrospective observational studies to prospective phase IV post-marketing studies to derive higher quality evidence on antibiotic safety.

In the case of linezolid safety and risk of serotonin syndrome, there should be more replication studies, preferably prospective cohort studies, to answer the same research question of whether concomitant antidepressants increase the risk of serotonin syndrome. Replication of the finding across different populations and settings would

improve the generalizability of the findings. Furthermore, the risk of serotonin syndrome related to concomitant antidepressants can be summarized across studies in a meta-analysis, which may produce a more precise estimate. It is hoped that accumulation of evidence that support the safety of linezolid in patients taking antidepressants will lead to the removal of the FDA warning on the drug interaction between linezolid and antidepressants [27].

While waiting for higher quality evidence, our study adds to the existing evidence for safety of linezolid even in context of concomitant antidepressants. Based on the current existing evidence, clinicians should not hesitate to prescribe linezolid to patients on antidepressants, especially if there are limited antibiotic options or alternative antibiotic options would be inferior.

Chapter 5. References

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Chapter 7. Appendix

Published Journal Article

This study was published in JAMA Network Open (citation: Bai AD, McKenna S, Wise H, Loeb M, Gill SS. Association of Linezolid With Risk of Serotonin Syndrome in Patients Receiving Antidepressants. *JAMA Netw Open.* 2022;5:e2247426.). The published manuscript is copied below.

Title: Linezolid and risk of serotonin syndrome in patients receiving antidepressants

Subtitle: Linezolid and serotonin syndrome

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Abstract word count: 323 words

Manuscript word count: 2954 words

Tables and figures: 4 tables and 0 figure

Key Points

Question: Do antidepressants increase risk for serotonin syndrome in patients on linezolid treatment compared to no antidepressant?

Findings: In this population-based retrospective cohort study of 1,134 patients who were prescribed linezolid, 215 (19.0%) patients were taking antidepressants. Serotonin syndrome occurred in less than 0.5% of patients and the risk was numerically lower in the antidepressant group. The adjusted risk difference was -1.2%, which was not significantly different between the antidepressant and no antidepressant group.

Meaning: Antidepressants did not significantly increase the risk of serotonin syndrome while on linezolid treatment. Linezolid is likely safe for patients receiving antidepressants.

Abstract

Importance: There is potential for linezolid to interact with some antidepressants leading to serotonin syndrome. However, there is little empirical data supporting warnings to avoid linezolid in patients taking antidepressants.

Objective: To describe the incidence of serotonin syndrome in patients receiving oral linezolid and how concomitant antidepressant treatment changes this risk.

Design: Population-based retrospective cohort study using linked administrative databases at Institute for Clinical Evaluative Sciences (ICES) from 2014 to 2021 with follow-up to 30 days.

Setting: Population of Ontario, Canada.

Participants: Outpatients aged 66 years or older who were prescribed oral linezolid for any duration.

Exposure: Antidepressants while on linezolid therapy versus no antidepressant while on linezolid therapy.

Main Outcome: Clinically significant serotonin syndrome based on physician diagnosis, Sternbach's criteria or Hunter's criteria within 30 days of starting oral linezolid. Secondary outcomes were altered mental status, hospitalization or death within 30 days of starting linezolid.

Results: The study included 1,134 patients who were prescribed linezolid. There were 595 (52.5%) males and 539 (47.5%) females. The age range was 66 to 69 years for 225 (19.8%) patients, 70 to 79 years for 473 (41.7%) patients, and 80 years or older for 436 (38.4%) patients. Of 1,134 patients, 215 (19.0%) patients were also on antidepressants. Serotonin syndrome occurred in less than 6 (<0.5%) patients. The proportion of patients

who had serotonin syndrome was numerically lower in the antidepressant group. In a propensity score matched cohort, the adjusted risk difference for serotonin syndrome between the antidepressant group and no antidepressant group was -1.2% (95% CI -2.9% to 0.5%). There were similar rates of altered mental status, hospitalization and death between the propensity matched groups.

Conclusions and Relevance: In this cohort study of older patients who were prescribed linezolid, serotonin syndrome occurred rarely. Concurrent antidepressants did not significantly increase the risk of serotonin syndrome. These findings suggested that linezolid is likely safe for patients receiving antidepressants. Nevertheless, prescribers should remain vigilant for this potential drug interaction.

Keywords: Linezolid; Serotonin syndrome; Antidepressants; Adverse events

Introduction

Linezolid is a synthetic oxazolidinone antibiotic with activity against resistant Gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus*.[1,2] The bioavailability of linezolid approaches 100%,[1] making it ideal as first line or step-down oral antibiotic therapy for bacteremia, pneumonia as well as skin and soft tissue infections.[3]

Linezolid use has been limited due to concerns of drug interactions. Linezolid can reversibly inhibit monoamine oxidase (MAO).[2] Co-administration with antidepressants such as non-selective MAO inhibitors, selective serotonin re-uptake inhibitors (SSRI), serotonin–norepinephrine reuptake inhibitors (SNRI) and bupropion may precipitate serotonin syndrome.[2] Serotonin syndrome can present with a range of manifestations including hyperthermia, hypertension, tachycardia, agitation, tremor, myoclonus, hyperreflexia, muscle rigidity, flushed skin, and diaphoresis.[4,5] Severe cases may have hyperthermia and shock that are life-threatening.[4,5]

In 2020, the United States Food and Drug Administration (FDA) issued a warning against linezolid use in patients on antidepressants.[6] Antidepressants are commonly prescribed, so many patients who needed linezolid for an infection could not receive it due to this relative contraindication.

However, data on the risk of serotonin syndrome associated with linezolid are scarce. Most of the data were case reports or case series from passive surveillance,[7,8] which do not give any information on the incidence or how antidepressants change this risk. A review of linezolid trials showed no conclusive evidence that linezolid increased risk of

serotonin syndrome in patients already on serotonergic medications.[9] However, real-world data on patients outside trials are lacking. The largest observational study to date had a sample size of 348 that included only 87 patients receiving antidepressants.[10] In this study, concurrent antidepressant treatment conferred a relative risk (RR) of 3.00 (95% confidence interval (CI) 0.19 to 47.45) for serotonin syndrome.[10] The small sample size likely led to imprecise estimates with a wide CI and inconclusive results.

To address this knowledge gap, we conducted a retrospective cohort study using the population-based data housed at ICES in Ontario, Canada[11] to estimate the incidence of serotonin syndrome and how this risk changes due to concomitant antidepressant use in patients on linezolid treatment.

Methods

We conducted a retrospective population-based cohort study using the ICES databases. ICES is an independent, non-profit research institute funded by the Ontario Ministry of Health. As a prescribed entity under Ontario's privacy legislation, ICES is authorized to collect and use health care data for the purposes of health system analysis, evaluation and decision support. Secure access to these data is governed by policies and procedures that are approved by the Information and Privacy Commissioner of Ontario.[11] This study was approved by the Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board (project number 6035935).

This study was reported as per the STROBE and RECORD reporting guidelines (Supplement eTable 1).[12]

Population

The ICES databases included the Ontario Drug Benefit (ODB) database, which captured outpatient prescription medications dispensed to people 65 years of age and older in Ontario, Canada. Oral linezolid was originally listed on formulary with restrictions and then added to the ODB starting in October of 2014.[13] Therefore, this study included adults aged 66 years or older in Ontario who were dispensed oral linezolid for any duration between October of 2014 and January of 2021. This was a convenient sample size based on the study date cut-off.

Data Collection

The ODB data was linked to the following databases at a person-level. Census data included demographics and vital statistics. The Canadian Institute for Health Information (CIHI) discharge abstract database, National Ambulatory Care Reporting System (NACRS) and the Ontario Health Insurance Plan (OHIP) database had information on diagnoses and healthcare utilization including ambulatory care visits, emergency room (ER) visits and hospitalizations. Finally, Ontario Laboratories Information Systems (OLIS) included bloodwork results. All patients had complete linked data.

The following information were collected for each patient:

1) Demographics: age, sex, rural or urban home address

2) Comorbidity: Charlson comorbidity index (CCI)[14]

3) Psychiatric diagnoses: substance use disorder

4) Bloodwork: estimated glomerular filtration rate (eGFR) based on baseline serum creatinine[15]

5) Linezolid: dose, frequency, start date and stop date

The investigators had access to the deidentified database that was prepared by the ICES team based on the eligibility criteria on a secure online server for analysis. Data cleaning was done by data checking and removing data outside the relevant timeframe for the study.

Exposure

Exposure of interest was concomitant oral antidepressants while on linezolid that were known to predispose patients to serotonin syndrome as per the FDA warnings[6]:

1) SSRI: paroxetine, fluvoxamine, fluoxetine, sertraline, citalopram, escitalopram

2) SNRI: venlafaxine, desvenlafaxine, duloxetine

3) Tricyclic antidepressants (TCA): clomipramine, amitriptyline, desipramine, imipramine, nortriptyline, protriptyline, doxepin, trimipramine

4) MAO inhibitors: isocarboxazid, phenelzine, selegiline, tranylcypromine, moclobemide

5) Norepinephrine and dopamine reuptake inhibitors (NDRI): bupropion

5) Other: trazodone, mirtazapine, buspirone, amoxapine, maprotiline, nefazodone

We also collected data on other concomitant prescribed serotonergic medications that may increase risk of serotonin syndrome[4,7,8] and was covered by ODB: lithium, 5-HT3 receptor antagonists (dolasetron, granisetron, ondansetron, palonosetron), metoclopramide, methylphenidate, dexmethylphenidate, fentanyl, meperidine, methadone, oxycodone, tramadol, triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan), ergot derivatives (dihydroergotamine, ergotamine, methylergonovine), dextromethorphan, chlorpheniramine, cyclobenzaprine, carbamazepine, valproic acid, tryptophan, dextroamphetamine, rasagiline, and ritonavir.

Outcomes

The primary outcome was clinically significant serotonin syndrome requiring ambulatory care visit, ER visit or hospitalization. The discharge diagnoses from ambulatory care visits, ER visits and hospitalization were captured by the International Classification of Diseases, 10th revision (ICD-10) codes. As per the ICD-10 codes, serotonin syndrome was defined as any of the following: diagnosis of drug induced serotonin syndrome or

toxicity related to serotonergic drugs by the physician, diagnosis based on the Sternbach's criteria,[16] or diagnosis based on the Hunter's criteria (Supplement eTable 2).[17] Serotonin syndrome must have occurred within 30 days of starting linezolid. This was considered a reasonable time frame, because linezolid is typically prescribed for no more than 14 days and it should be cleared from the system in 2 days after discontinuation given its half-life of 5 to 7 hours.[1,18]

Secondary outcomes were chosen to describe potential consequences of clinically significant serotonin syndrome that may not be captured by the criteria for serotonin syndrome as described above. All secondary outcomes were defined to be within 30 days of starting linezolid:

1) ER visit or hospitalization for acute altered mental status change or confusion

2) Hospitalization for any cause

3) Death due to any cause

Statistical Analysis

Descriptive analysis included mean with standard deviation (SD) or median with interquartile range (IQR) for continuous variables. Counts with percentage were used to describe categorical variables. ICES data policy requires that research outputs and reports must not contain information that identifies an individual or could foreseeably be used to re-identify an individual. Therefore, all cells containing or revealing 5 individuals or less were suppressed to comply with this policy.

Primary and secondary outcomes were compared between the antidepressant and no antidepressant group using Fisher's exact test and absolute risk differences with 95% CI as per the Newcombe method.[19] Risk difference was calculated as risk in antidepressant group minus the risk in the no antidepressant group. There was no loss to follow-up as data for all outcomes were captured by the administrative databases.

To address potential bias, propensity score for antidepressant use was estimated using a logistic regression of the following patient baseline characteristics chosen *a priori*: age, sex, rural home address, CCI, eGFR, history of substance use disorder, days of linezolid use and other serotonergic medications. Age in years was categorized into 66 to 69, 70 to 79, and 80 or above. Patients on antidepressants were matched in a 1:1 ratio to patients not on antidepressants using nearest neighbor matching with a specified caliper width of 0.1 times the standard deviation of the logit of propensity scores. The two propensity matched groups were then compared in terms of the primary and secondary outcomes using a complete case analysis. To account for the matched nature of samples,[20] statistical significance and 95% CI for risk difference were estimated using the exact McNemar's test and variance of the risk difference as described by Agresti and Min.[21] respectively.

All reported CIs were two-sided 95% intervals and all tests were two-sided with a $P<0.05$ significance level. All analyses were done using statistical software R (version 3.3.0 and 4.1.2). The statistical packages DescTools,[22] MatchIt,[23] and exact2x2[24] were used for risk difference CI estimation, propensity score matching, and exact McNemar's test respectively.

Results

Patient Characteristics

The study included 1,134 patients who were prescribed linezolid. There were 595 (52.5%) males and 539 (47.5%) females. The age range was 66 to 69 years for 225 (19.8%) patients, 70 to 79 years for 473 (41.7%) patients, and 80 years or older for 436 (38.4%) patients. All eligible patients were included in the study, linked by the databases and completed follow-up to 30 days. All linezolid prescriptions were for 600 milligram tablets to be taken twice daily. Of the 1,134 patients, 215 (19.0%) patients were on antidepressants. In terms of antidepressant classes, 103 (47.9%) patients were on a SSRI, 36 (16.7%) patients were on a SNRI, 15 (7.0%) patients were on a TCA, 7 (3.3%) patients were on NDRI, and no patient was on a MAO inhibitor. Supplement eTable 3 describes the proportion of patients by antidepressant type. For the 215 patients on antidepressants, the median (IQR) days of overlap for linezolid and antidepressant was 7 (5 to 10) days. In 142 (66%) patients, antidepressant was taken during the entire linezolid course. In 197 (91.6%), antidepressant use overlapped with linezolid therapy for 3 days or more.

Baseline characteristics for patients on and not on antidepressants are described in Table 1. Of note, 19 (8.8%) and 47 (5.1%) patients were also taking other serotonergic medications in the antidepressant and no antidepressant group respectively. The proportion of patients in each group by type of other serotonergic medications are described in Supplement eTable 4.

Serotonin Syndrome

Serotonin syndrome occurred in less than 6 (<0.5%) patients in total. The exact numbers were not reported as per ICES data policy on potentially identifiable patient information. Based on less than 6 events, the possible risk difference for serotonin syndrome ranged from -0.5% to 2.3%. The observed proportion of patients with serotonin syndrome was numerically lower in the antidepressant group. Secondary outcomes are described in Table 2.

Propensity Score Matching

Using propensity scores, 166 patients in the antidepressant group were matched to 166 patients in the no antidepressant group. The maximum standardized difference of matched variables was 0.0845 (Table 3), which suggested good balance on the measured baseline characteristics.

In this propensity matched cohort, the risk for serotonin syndrome was lower in the antidepressant group with an adjusted risk difference of -1.2% (95% CI -2.9% to 0.5% P=0.50). There was a similar rate of altered mental status or confusion, hospitalization, and death within 30 days between the two propensity score matched groups (Table 4).

Discussion

In this large population-based retrospective cohort study of 1,134 outpatients who received oral linezolid, serotonin syndrome was rare and occurred in less than 0.5% of patients. After matching by propensity score, the risk difference for serotonin syndrome was -1.2% with 95% CI of -2.9% to 0.5% when compared between the antidepressant and no antidepressant group. Similarly, there was no significant difference in secondary outcomes related to consequences from serotonin syndrome including altered mental status or confusion, hospitalization, and death. Thus, antidepressants did not significantly increase the risk of serotonin syndrome while on linezolid treatment.

In a secondary analysis of 20 randomized controlled trials that compared linezolid to a comparator agent in patients who had at least one serotonergic agent, serotonin syndrome occurred in 3/2,208 (0.14%) in the linezolid group and 1/2,057 (0.05%) in the comparator group with a RR of 2.79 (95% CI 0.29 to 26.85).[9] The authors concluded that the potential risk for serotonin syndrome in patients already on a serotonergic agent was low,[9] which is consistent with our study finding. Our study adds to this study by comparing serotonin syndrome risk associated with linezolid with focus on antidepressants while adjusting for demographics, comorbidities, renal function, substance use disorder, and medications. Moreover, our study described real-world data on an aging population with multiple comorbidities, which reflects the population being treated with linezolid in clinical practice that is different from trials. For example, over 70% of the population were younger than 65 years in the trial population,[9] whereas all patients in our study were older than 65 years of age. To our knowledge, our study is the

largest observational study to date on the risk of serotonin syndrome associated with linezolid use outside the context of clinical trials. The next largest study was a single-centre observational study of 348 inpatients on linezolid.[10] In this study, serotonin syndrome was diagnosed in 1.1% patients on a SSRI or SNRI versus 0.4% patients without a SSRI or SNRI with RR of 3.00 (95% CI 0.19 to 47.45).[10] With more than 3 times the sample size, our study allowed for a more precise estimate and presented absolute risk differences, which may be easier to interpret and less misleading than relative risk given very low event rate.[25]

Strengths and Limitations

Our study has several strengths. First, it is a large cohort study with over a thousand patients, which allows for more precise estimates. Second, the study population consisted of all elderly patients with multiple comorbidities and medications, which is the most vulnerable population at the highest risk for medication adverse events that is representative of the typical patients being prescribed with linezolid in clinical practice. Third, multiple linked administrative databases allowed for detailed and comprehensive information on demographics, socioeconomic status, comorbidities and bloodwork results, which were then adjusted using propensity scores when comparing the primary and secondary outcomes between the two groups.

Several limitations merit mentioning. First, serotonin syndrome was diagnosed retrospectively based on a constellation of diagnoses codes, which did not match perfectly with the diagnostic criteria. However, this is the most common method used in previous studies.[8,9] We used multiple definitions for serotonin syndrome (physician diagnosis, Sternbach's criteria and Hunter's criteria) to be inclusive. Physician diagnosis complemented the diagnostic criteria, because the diagnosis codes for individual symptoms were likely omitted when there was an overarching physician diagnosis that was entered into the hospital records. Still, it may not be sensitive enough to capture all cases. This is addressed by the secondary outcomes that included altered mental status or confusion, hospitalization, and death. Any clinically significant serotonin syndrome likely resulted in one of these secondary outcomes. It is reassuring that antidepressants did not significantly increase risk of serotonin syndrome or the secondary outcomes after

adjustment by propensity score matching. The observed risk for serotonin syndrome at less than 0.5% in our study is similar to the estimated incidence of 0.14% in clinical trials[9] and 0.6% in another observational study,[10] which suggests that we did not miss a significant number of cases.

Second, the small number of events limited the possible analyses and precision of the estimates. For example, it was not possible to perform a multivariable logistic regression model due to low number of events. As well, odds ratio or RR may be extreme and misleading due to low event rate. We were able to adjust for patient baseline characteristics using propensity scores, which is an appropriate method to adjust for cofounders independent of event rate.[26] Propensity score matching also allows for calculation of risk differences,[20] which is related to number needed to harm and thus easier to interpret for clinicians. The low number of events is still useful in the context of a large sample size. Less than 6 cases of serotonin syndrome out of over a thousand patients with a risk difference CI limit of an excess risk of 0.5% was reassuring in that serotonin syndrome was rare and antidepressant did not significantly add to this risk.

Third, only prescribed and funded medications were captured by ODB. Over-the-counter medications not funded by ODB would be missed, but most clinically important serotonergic medications were prescription medications. The database also did not account for medication adherence. However, this would reflect real-world "intent-to-treat" effect of prescribing linezolid to a patient who was also prescribed antidepressants. It would be unlikely for prescribers to recommend abruptly stopping an antidepressant temporarily while on linezolid due to risk of antidepressant discontinuation syndrome.

Conclusions

Our study findings have important implications. In our study, concomitant antidepressants did not significantly increase risk of serotonin syndrome in patients on linezolid. Within the 95% CI, the worst-case scenario would be a 0.5% increase in the risk of serotonin syndrome due to antidepressants, which would be a number needed to harm of 200. As such, it is likely safe to prescribe linezolid in patients on antidepressants and antidepressants should not be an absolute contraindication for linezolid. It should be noted that no patient was on a MAO inhibitor antidepressant in our study, which has a very high risk of serotonin syndrome. This reflects the current practice where MAO inhibitor antidepressants are rarely used. Therefore, this study may not be generalized to patients on MAO inhibitor antidepressants.

The evidence for rare and serious adverse events related to antibiotics often comes from retrospective population observational studies such as our study. This evidence has limitations due to the nature of retrospective observational studies. As well, such studies are not efficient because they often focus on a particular adverse event. Future research should move beyond observational studies to phase 4 studies, which would prospectively monitor for all types of adverse events. While waiting for higher quality evidence, our study adds to the existing evidence for safety of linezolid even in context of concomitant antidepressants. Based on the existing evidence, clinicians should be reassured that it appears safe to prescribe oral linezolid to patients on antidepressants, especially if there are limited antibiotic options or alternative antibiotic options would be inferior.

Acknowledgements

Funding/Support: This project was funded by the Queen's University Research Initiation Grant.

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study.

Non-author Contributions: This study contracted ICES Data & Analytic Services (DAS) and used de-identified data from the ICES Data Repository, which is managed by ICES with support from its funders and partners: Canada's Strategy for Patient-Oriented Research (SPOR), the Ontario SPOR Support Unit, the Canadian Institutes of Health Research and the Government of Ontario. The opinions, results and conclusions reported are those of the authors. No endorsement by ICES or any of its funders or partners is intended or should be inferred. Parts of this material are based on data and information compiled and provided by CIHI. However, the analyses, conclusions, opinions, and statements expressed herein are those of the author, and not necessarily those of CIHI. We thank IQVIA Solutions Canada Inc. for use of their Drug Information Database.

Access to Data and Data Analysis: Anthony Bai had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Anthony Bai conducted and is responsible for the data analysis.

Data Sharing Statement: The dataset and analysis codes for this study is held securely in coded form at the Institute for Clinical Evaluative Sciences (ICES). While data sharing agreements prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre- specified criteria for confidential access, available at www.ices.on.ca/DAS. The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

Conflict of Interests Disclosures: Mark Loeb reports having served on advisory boards for Sanofi, Pfizer, Medicago, Merck, Seqirus, Paladin Labs; Pan Data Safety and Monitoring Committees for Medicago, CanSino biologics, NIH, and the WHO EML Antibiotic Working Group. Anthony Bai, Susan McKenna, Heather Wise and Sudeep Gill do not have any conflict of interest.

Ethical approval statement: The study was approved by the Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board (HSREB) (project number 6035935).

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Table 1. Baseline characteristics

	Antidepressant (N=215) No. (%)	No antidepressant (N=919) No. (%)	Std diff
Age in years			
66 to 69	48 (22.3)	177 (19.3)	0.0756
70 to 79	83 (38.6)	390 (42.4)	0.0781
80 and above	84 (39.1)	352 (38.3)	0.0158
Female	117 (54.4)	422 (45.9)	0.1706
Male	98 (45.6)	497 (43.8)	0.1706
Rural home address	23 (10.7)	105 (11.4) N=918	0.0216
Charlson comorbidity index mean (SD)	2.3 (2.1) N=175	2.0 (2.1) N=760	0.1200
eGFR in mL/min/1.73m^2 mean (SD)	70.7 (28.3) N=208	69.6 (27.2) N=897	0.0393
History of substance use disorder	<6	<6	0.0221
Days of Linezolid mean (SD)	11.7 (7.2)	10.3 (6.2)	0.2089
Number of antidepressants mean (SD)	1.2 (0.5)	0 (0)	3.8008
On other serotonergic medication(s)	19 (8.8)	47 (5.1)	0.1465

eGFR = estimated glomerular filtration rate; SD = standard deviation; Std diff = standardized difference

For variables where there is missing data, N in the cells refer to number of patients with available data

Table 2. Secondary outcomes within 30 days of starting linezolid

	Antidepressant (N=215) No. (%)	No antidepressant (N=919) No. (%)	Risk difference in % (95% CI)[a]	P-value
Altered mental status or confusion	25 (11.6)	63 (6.9)	4.8 (0.7 to 10.1)	0.02
Hospitalization	92 (42.8)	398 (43.3)	-0.5 (-7.7 to 6.9)	0.93
Death due to any cause	16 (7.4)	44 (4.8)	2.7 (-0.6 to 7.1)	0.13

CI = confidence interval;

[a]Risk difference calculated as risk in antidepressant group minus risk in no antidepressant group

Table 3. Baseline characteristics in propensity score matched cohort

	Antidepressant (N=166) No. (%)	No antidepressant (N=166) No. (%)	Std diff
Age in years			
66 to 69	39 (23.5)	37 (22.3)	0.0287
70 to 79	68 (41.0)	65 (39.2)	0.0369
80 and above	59 (35.5)	64 (38.6)	0.0624
Female	84 (50.6)	91 (54.8)	0.0845
Male	82 (49.4)	75 (45.2)	0.0845
Rural home address	21 (12.7)	18 (10.8)	0.0562
Charlson comorbidity index mean (SD)	2.2 (1.9)	2.1 (2.1)	0.0358
eGFR in mL/min/1.73m^2 mean (SD)	70.4 (29.0)	70.4 (27.1)	0.0003
History of substance use disorder	0 (0)	0 (0)	0
Days of Linezolid mean (SD)	10.6 (6.4)	10.7 (6.3)	0.0161
On other serotonergic medication(s)	11 (6.6)	8 (4.8)	0.0779

eGFR = estimated glomerular filtration rate; SD = standard deviation; Std diff = standardized difference

Listwise deletion was used, so there were no missing data in the propensity score matched cohort

Table 4. Secondary outcomes within 30 days of starting linezolid in propensity score matched cohort

	Antidepressant (N=166) No. (%)	No antidepressant (N=166) No. (%)	Risk difference in % (95% CI)[a]	P-value[b]
Altered mental status or confusion	20 (12.1)	19 (11.5)	0.6 (-6.2 to 7.4)	>0.99
Hospitalization	82 (49.4)	85 (51.2)	-1.8 (-11.9 to 8.3)	0.82
Death due to any cause	14 (8.4)	10 (6.0)	2.4 (-3.4 to 8.2)	0.54

CI = confidence interval
[a]Risk difference calculated as risk in antidepressant group minus risk in no antidepressant group
[b]P-value by McNemar exact test