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Delirium Associations with Antibiotics: A Pharmacovigilance Study of the FDA Adverse Event Reporting System (FAERS)

Chengwen Teng¹ · Christopher R. Frei^{2,3,4,5}

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Abstract

Background Ertapenem, cefepime, imipenem, ofloxacin, ceftazidime, clarithromycin, cefaclor, levofloxacin, linezolid, moxifloxacin, azithromycin, piperacillin–tazobactam, trimethoprim–sulfamethoxazole, metronidazole, ciprofloxacin, and cefuroxime are known to be associated with delirium. Other antibiotics may also lead to delirium, but no study has systematically compared delirium associations for many available antibiotics.

Objective The objective of this study was to evaluate the association between delirium and antibiotics using the FDA Adverse Event Reporting System (FAERS).

Methods FAERS reports from January 1, 2004 to December 31, 2018 were included in the study. Reporting odds ratios (RORs) and corresponding 95% confidence intervals (95% CI) for the association between antibiotics and delirium were calculated. An association was considered to be statistically significant when the lower limit of the 95% CI was greater than 1.0.

Results A total of 10,015,622 reports (including 16,982 delirium reports) were considered, after inclusion criteria were applied. Statistically significant delirium RORs (95% CI) for antibiotics were: ertapenem 21.07 (16.38–27.10), cefepime 9.8 (6.37–15.09), imipenem 9.68 (6.75–13.89), ofloxacin 7.73 (4.00–14.92), ceftazidime 6.09 (2.73–13.62), clarithromycin 5.34 (4.37–6.53), cefaclor 5.32 (1.71–16.58), ampicillin–sulbactam 4.49 (2.13–9.45), levofloxacin 4.47 (3.88–5.16), linezolid 4.33 (3.28–5.72), moxifloxacin 3.51 (2.81–4.38), azithromycin 2.76 (2.09–3.64), piperacillin–tazobactam 2.41 (1.47–3.93), trimethoprim–sulfamethoxazole 2.36 (1.61–3.47), metronidazole 1.85 (1.31–2.60), ciprofloxacin 1.83 (1.44–2.33), and cefuroxime 1.81 (1.03–3.20).

Conclusion This study found statistically significant increased risk of reporting delirium with ertapenem, cefepime, imipenem, ofloxacin, ceftazidime, clarithromycin, cefaclor, ampicillin–sulbactam, levofloxacin, linezolid, moxifloxacin, azithromycin, piperacillin–tazobactam, trimethoprim–sulfamethoxazole, metronidazole, ciprofloxacin, and cefuroxime.

Key Points

This study identifies previously unknown delirium reporting association with ampicillin–sulbactam.

Ertapenem had the highest delirium reporting association among antibiotics evaluated in the study.

Older patients had a higher delirium Reporting Odds Ratio than younger patients among most of the antibiotic classes analyzed.

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1 Introduction

Delirium is diagnosed in the presence of a disturbance in attention and awareness that develops over a short period of time, represents a change from baseline, tends to fluctuate, has an additional cognitive disturbance (e.g., memory deficit, disorientation, language, visuospatial ability, or perception), all of which are not better explained by other diagnoses (e.g., coma) [1]. Delirium is associated with higher mortality rates, affects up to 50% of hospitalized elderly patients, and costs more than \$164 billion per year in the United States [2]. Delirium may be nothing more than a marker of severity of illness likened to a cough for pneumonia. Treatment of pneumonia resolves the cough like treatment of sepsis may resolve delirium. This point was proven in multiple trials of critically ill patients including BRAIN-ICU, which showed ICU delirium is associated with long-term cognitive impairment, and MIND-USA, which showed delirium treatment in those with hypoactive delirium does not improve outcome [3, 4].

Many antibiotics are known to be associated with delirium. Overall quality of evidence for many reports is very low. Multiple case reports have reported on ertapenem-induced delirium [5–7]. A case of hypoactive delirium and another case of encephalopathy as adverse effects of imipenem were reported [8, 9]. A case report demonstrated a case of delirium with hallucinations likely caused by a combination of diphenhydramine and linezolid [10]. Delirium was also reported to be induced by clarithromycin monotherapy or a combination of clarithromycin and fluoxetine [11–13]. Delirium was associated with azithromycin in two geriatric patients treated for lower respiratory tract infection [14]. There are at least 6 published case reports of delirium associated with the use of azithromycin, including one pediatric patient, and 12 published case reports of delirium associated with the use of clarithromycin [15]. Four fluoroquinolone antibiotics, which were ofloxacin, levofloxacin, moxifloxacin, and ciprofloxacin, were all reported to be associated with delirium [16–19]. Cefepime use was associated with increased likelihood and duration of acute encephalopathy (presence of delirium or depressed level of consciousness in the absence of deep sedation) in critically ill patients in a retrospective case–control study [20]. A nested cohort study concluded that first, second, and third-generation cephalosporins doubled the odds of delirium [21]. A case report reported higher-level gait disorder and nocturnal delirium likely induced by trimethoprim–sulfamethoxazole [22]. In another case report, metronidazole and levofloxacin induced delirium in a chronic kidney disease patient [23]. Delirium was also reported to be induced by piperacillin–tazobactam in a peritoneal dialysis patient [24].

Few studies have looked at antibiotics and compared their associations with delirium. The objective of this study was to evaluate the association between delirium and antibiotics using FDA Adverse Event Reporting System (FAERS).

2 Methods

2.1 Data Source

FAERS is a publicly available database composed of adverse event reports that were submitted to United States Food and Drug Administration (FDA) [25]. FAERS data contain drug information (drug name, active ingredient, route of administration, the drug's reported role in the event) and reaction information. Healthcare professionals, consumers or manufacturers may submit reports. The types of data found in FAERS include reason for administration, specific reaction, seriousness, outcome, gender, event data, patient age, who sent the report, reporter type, country, whether or not it was reported to the manufacturer and whether or not it was published. Quarterly Data Files were used to obtain FAERS data. The Institutional Review Board (IRB) of The University of South Carolina determined that this study is not human subjects research (IRB number: Pro00101342).

2.2 Study Design

FAERS data from January 1, 2004 to December 31, 2018 were included in the study. Some adverse event reports were submitted multiple times with updated information. Therefore, duplicate reports were removed by case number, with the most recent submission included in the study.

2.3 Drug Exposure Definition

Each antibiotic was identified in FAERS by generic and brand names listed in the Drugs@FDA Database [26]. Antibiotics with less than three delirium Adverse Drug Reaction (ADR) reports were excluded from this data analysis [27]. All reports were included, regardless of route of administration and the drug's reported role in the event. Antibiotics included in the study were ertapenem, imipenem, meropenem, linezolid, clarithromycin, azithromycin, erythromycin, ofloxacin, levofloxacin, moxifloxacin, ciprofloxacin, cefepime, ceftazidime, cefaclor, cefuroxime, cephalexin, ceftriaxone, trimethoprim–sulfamethoxazole, metronidazole, ampicillin–sulbactam, piperacillin–tazobactam, amoxicillin–clavulanate, amoxicillin, nitrofurantoin, daptomycin, vancomycin, minocycline, and clindamycin. Antibiotic classes included in the study were carbapenems, macrolides, fluoroquinolones, cephalosporins, and penicillin combinations.

2.4 Adverse Drug Reaction Definition

FAERS defines ADRs using Preferred Terms (PT) from the Medical Dictionary for Regulatory Activities (MedDRA) [28]. Preferred Term “Delirium” was used to identify delirium cases.

2.5 Statistical Analysis

A disproportionality analysis was conducted by computing Reporting Odds Ratios (ROR) and corresponding 95% confidence intervals (95%CI) for the association between delirium and each antibiotic class or individual antibiotic [29]. ROR was calculated as the ratio of the odds of reporting delirium versus all other ADRs for a given drug, compared with this reporting odds for all other drugs present in FAERS [29]. An association was considered to be statistically significant if the lower limit of 95% CI was above 1.0 [29]. A subgroup analysis was performed on patients who were 65 years or older and patients less than 65 years old. Data analysis was performed using Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA) and SAS 9.4 (SAS Institute, Cary, NC).

3 Results

A total of 10,015,622 reports (including 16,982 delirium reports) were considered, after inclusion criteria were applied (Fig. 1). The number of cases for each drug and drug class is listed in Fig. 2. Statistically significant delirium RORs (95% CI) for antibiotic classes were: carbapenems 10.49 (8.59–12.80), macrolides 3.65 (3.11–4.28), fluoroquinolones 3.40 (3.05–3.78), cephalosporins 2.54 (1.99–3.23), and penicillin combinations 1.62 (1.20–2.18).

Statistically significant delirium RORs (95% CI) for antibiotics were: ertapenem 21.07 (16.38–27.10), cefepime 9.8 (6.37–15.09), imipenem 9.68 (6.75–13.89), ofloxacin 7.73 (4.00–14.92), ceftazidime 6.09 (2.73–13.62), clarithromycin

5.34 (4.37–6.53), cefaclor 5.32 (1.71–16.58), ampicillin–sulbactam 4.49 (2.13–9.45), levofloxacin 4.47 (3.88–5.16), linezolid 4.33 (3.28–5.72), moxifloxacin 3.51 (2.81–4.38), azithromycin 2.76 (2.09–3.64), piperacillin–tazobactam 2.41 (1.47–3.93), trimethoprim–sulfamethoxazole 2.36 (1.61–3.47), metronidazole 1.85 (1.31–2.60), ciprofloxacin 1.83 (1.44–2.33), and cefuroxime 1.81 (1.03–3.20) (Fig. 2).

Among patients who took carbapenems, linezolid, macrolides, fluoroquinolones, cephalosporins, trimethoprim–sulfamethoxazole, metronidazole, penicillin combinations, and clindamycin, patients who were 65 years or older had a higher delirium ROR than those less than 65 years old (Fig. 3). Among patients who took amoxicillin and vancomycin, patients who were 65 years or older had a lower delirium ROR than those less than 65 years old (RORs were not statistically significant considering that the lower limit of 95% CI was below 1.0).

4 Discussion

Our results indicated significant delirium reporting associations (from strongest to weakest) with the following antibiotic classes: carbapenems, macrolides, fluoroquinolones, cephalosporins, and penicillin combinations (Fig. 2).

Our results demonstrated significant delirium reporting associations (from strongest to weakest) with the following antibiotics: ertapenem, cefepime, imipenem, ofloxacin, ceftazidime, clarithromycin, cefaclor, ampicillin–sulbactam, levofloxacin, linezolid, moxifloxacin, azithromycin, piperacillin–tazobactam, trimethoprim–sulfamethoxazole, metronidazole, ciprofloxacin, and cefuroxime (Fig. 2). Our results were in agreement with previously known delirium associations with ertapenem, cefepime, imipenem, ofloxacin, ceftazidime, clarithromycin, cefaclor, levofloxacin, linezolid, moxifloxacin, azithromycin, piperacillin–tazobactam, trimethoprim–sulfamethoxazole, metronidazole, ciprofloxacin, and cefuroxime [5–24]. Ampicillin–sulbactam was found to be associated with delirium in FAERS, which was not reported in the literature.

Cefepime is known to be able to induce neurotoxicity due to its ability to cross the blood–brain barrier and to exhibit concentration-dependent competitive gamma-aminobutyric acid (GABA) antagonism [30–32]. The signs and symptoms of cefepime-induced neurotoxicity included altered mental status, reduced consciousness, confusion, myoclonus, aphasia, agitation, and seizures [32]. Many of the signs and symptoms of cefepime-induced neurotoxicity correlated well with signs and symptoms of delirium [1]. Therefore, it is not surprising to find the significant association between cefepime and delirium in FAERS.

Carbapenem antibiotics may have a higher neurotoxic potential than that of penicillins and cephalosporins [33].

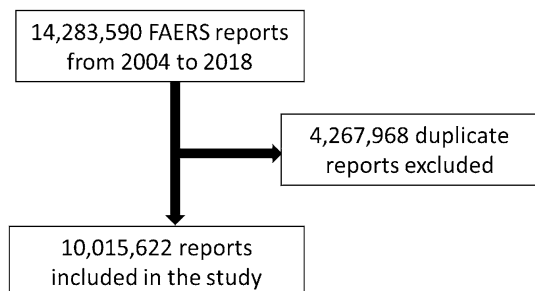
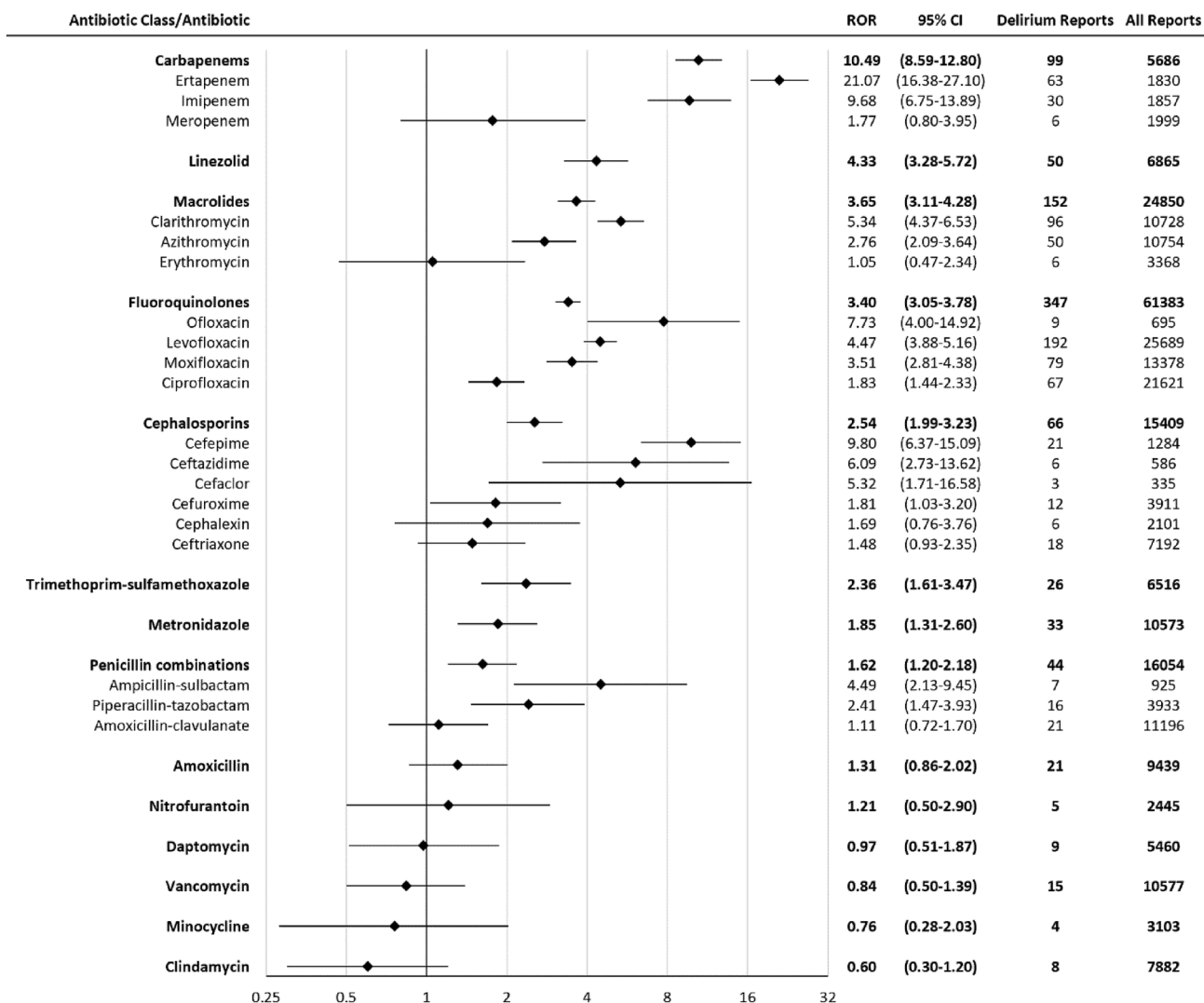


Fig. 1 Flow diagram for inclusion and exclusion of the FAERS reports



CI = confidence interval

Fig. 2 Reporting odds ratios (ROR) for delirium with antibiotics

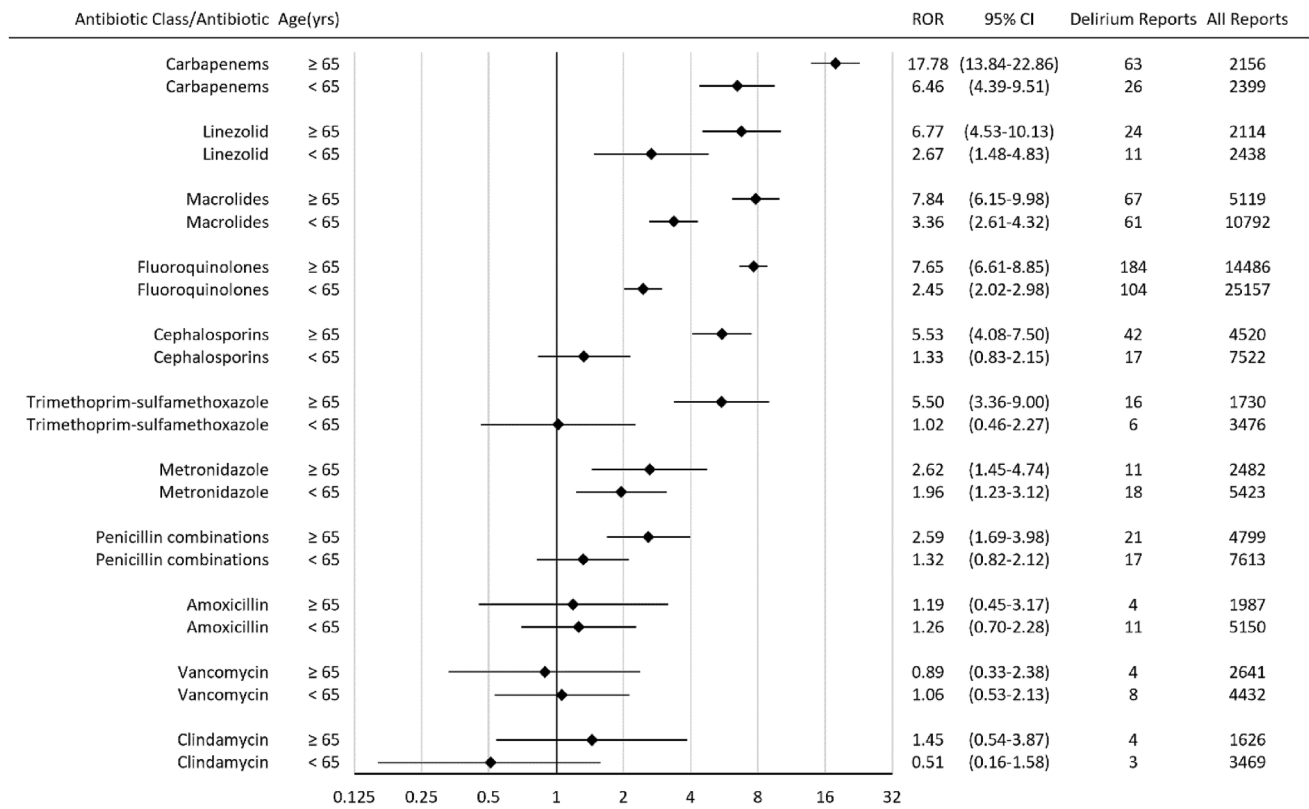
Indeed, in our study, carbapenem antibiotic class had the highest delirium ROR among all antibiotic classes included in the study (Fig. 1). This may not be a class-wide effect and certain carbapenems may be more offensive (e.g., imipenem) than others (e.g., meropenem). Prior studies have suggested that cefepime may have a tenfold greater risk for neurotoxicity than meropenem [34, 35]. Neurotoxicity of carbapenems was also thought to be caused by an interaction with GABA receptors [33]. The association between imipenem and delirium found in FAERS may be due to this mechanism.

Although ampicillin-sulbactam-induced delirium was not reported in the literature, ampicillin-sulbactam is a beta-lactam, which has the potential to induce neurotoxicity via interactions with GABA receptors [31]. The association between ampicillin-sulbactam and delirium found in

FAERS may be explained by this mechanism. It is interesting that ampicillin-sulbactam was associated with delirium given its minimal penetration across the blood-brain-barrier. Prior reports have stated its penetrance is 1% of the plasma concentration and only increases in the setting of inflamed meninges [36].

Although a case of meropenem-associated delirium was reported in the literature, our study did not find statistically significant ROR for meropenem and delirium. The low number of meropenem delirium reports in FAERS may be the reason of statistical insignificance (Fig. 2).

In the subgroup analysis, the delirium ROR rank order in both subgroups (< 65 years old and ≥ 65 years old) were similar to that in all patients. Our results showed that older patients had a higher delirium ROR than younger patients



CI = confidence interval

Fig. 3 Reporting odds ratios (RORs) for delirium with antibiotics stratified by age

among most of the antibiotic classes analyzed (Fig. 3). Carbapenems, macrolides, fluoroquinolones, cephalosporins, and trimethoprim–sulfamethoxazole had significantly greater associations with delirium in older patients than those in younger patients. It is known that delirium risk is higher in older patients [1]. To note, ciprofloxacin and trimethoprim–sulfamethoxazole were also included in the American Geriatrics Society Beers Criteria for potentially inappropriate medication use in older adults [37]. Ciprofloxacin was in the Beers Criteria for tendon rupture and hyperkalemia, but not for delirium.

4.1 Limitations

A causal relationship between a drug and an ADR cannot be determined by FAERS. Significant bias may occur because of the spontaneous and voluntary reporting of ADRs. Media attention and recent publication of an ADR in the literature might affect the reporting behaviors. The association between a drug and an ADR is confounded by comorbidities and concomitant drugs. According to FDA, information submitted has not been verified by a medical professional. FAERS data may be submitted by

healthcare professionals, consumers and manufacturers. Source of submission must be considered. Some information is missing or incomplete in FAERS. There have been cases in which age was not reported or drug names were misspelled. FDA does not receive reports for every adverse event or medication error that occurs with a product. In addition, ROR only investigates an increased risk of ADR reporting and not risk of ADR occurrence in absolute terms [38]. Some of the confidence intervals are quite wide such as cefaclor 5.32 (1.71–16.58) because of the low number of cefaclor ROR reports for delirium. An additional limitation of this study is the reliance on “delirium” as the search term in the FAERS database. Terms such as delirium, encephalopathy, acute confusional state, acute brain dysfunction and acute brain failure are often used synonymously and inappropriately in the literature [39]. Without the ability to determine how delirium was diagnosed, it is possible that numerous cases were misclassified and could have altered the findings. Despite the limitations, FAERS has a large sample size and is suitable for discovering a signal of new and rare drug-ADR associations.

5 Conclusion

This study found statistically significant increased risk of reporting delirium with ertapenem, cefepime, imipenem, ofloxacin, ceftazidime, clarithromycin, cefaclor, ampicillin–sulbactam, levofloxacin, linezolid, moxifloxacin, azithromycin, piperacillin–tazobactam, trimethoprim–sulfamethoxazole, metronidazole, ciprofloxacin, and cefuroxime. Results obtained from FAERS should be interpreted with caution in the context of data limitations. Antibiotic stewardship is needed to prevent delirium and to improve health outcomes.

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Declarations

Funding No funding was sought for this research study. Dr. Frei was supported, in part, by a NIH Clinical and Translational Science Award (National Center for Advancing Translational Sciences, UL1 TR001120 and UL1 TR002645) while the study was being conducted. The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Conflict of interest Dr. Frei's institution has received grants for research from AstraZeneca Pharmaceuticals in the last 36 months.

Ethics approval The Institutional Review Board (IRB) of The University of South Carolina determined that this study is not human subjects research (IRB number: Pro00101342).

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Code availability Codes used during the current study are available from the corresponding author on reasonable request.

Author contributions Study concept and design: all authors. Statistical analysis: CT. Interpretation of data: all authors. Drafting of the manuscript: CT. Critical revision of the manuscript for important intellectual content: all authors. Study supervision: CT.

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