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Supratherapeutic Psychotropic Drug Levels in the Emergency Department and Their Association with Delirium Duration: A Preliminary Study

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Abstract

Background—Polypharmacy is associated with delirium, but the mechanisms for this are unclear.

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Author Contributions

JHH, JFS, EWE, RDM, TPR, SD, and JS conceived the trial and participated in the study design. JHH and EEV recruited patients and collected the data. RC and JHH analyzed the data. All authors participated in the interpretation of results. JHH and AC drafted the manuscript, and all authors contributed to the critical review and revision of the manuscript. JHH takes responsibility for the manuscript as a whole.

Conflicts of Interest

RDM, TPR, SD, and JS received salaries and holding shares from Precera Biologic, Inc. The other authors have no conflicts of interests to disclose.

Objective—To determine the frequency of supratherapeutic psychotropic serum drug levels (SPDLs) in older hospitalized patients and if it is associated with emergency department (ED) delirium duration.

Design—Secondary analysis of a prospective cohort study

Setting—Tertiary care, academic medical center

Participants—ED patients ≥ 65 years old who were admitted to the hospital

Measurements—Delirium was assessed in the ED and the first seven days of hospitalization using the modified Brief Confusion Assessment Method (bCAM.) Drug concentrations were determined in serum samples collected at enrollment via a novel liquid chromatograph-mass spectrometry-based platform capable of identifying and quantitating 78 clinically approved medications, including opioids, benzodiazepines, antidepressants, antipsychotics, and amphetamines. Patients with serum psychotropic drug concentrations above established reference ranges were considered supratherapeutic and have a SPDL. We performed proportional odds logistic regression to determine if SPDLs were associated with ED delirium duration adjusted for confounders. Medical record review was performed to determine if the doses of medications associated with SPDLs were adjusted at hospital discharge.

Results—A total of 158 patients were enrolled; of these, 66 were delirious in the ED. SPDLs were present in 11 (17%) of delirious and 4 (4%) non-delirious ED patients. SPDLs were significantly associated with longer ED delirium duration (adjusted proportional odds ratio= 6.0, 95%CI: (2.1 to 17.3) after adjusting for confounders. Of the 15 medications associated with SPDLs, 9 (60%) were prescribed at the same or higher doses at the time of hospital discharge.

Conclusions—SPDLs significantly increased the odds of prolonged ED delirium episodes. Approximately half of the medications associated with SPDLs were continued after hospital discharge at the same or higher doses.

Keywords

delirium; adverse drug reactions; liquid chromatography-mass spectrometry; older adults

Introduction

Delirium is a form of acute brain failure that affects 17% and 25% of older emergency department (ED) and hospitalized patients, respectively.[1,2] For every day a patient is delirious, there is an increased mortality risk,[3] and poorer long-term cognition and function.[4] Delirium is also associated with significant distress for both patients and family members.[5]

There is substantial interest in developing effective interventions to reduce the duration and severity of delirium and its resultant outcomes. The initial step is to identify modifiable risk factors. Polypharmacy (defined as >5 medications) occurs in 60% of older hospitalized patients and is associated with delirium.[6] While medications such as benzodiazepines and opioids have been implicated with delirium development, the mechanism for these associations are unclear.[7] We hypothesized that supratherapeutic psychotropic drug levels

(SPDLs), as determined by a liquid chromatography, tandem mass spectrometry-based (LC/MS/MS) assay, would be associated with ED delirium duration.

Methods

Study Design, Setting, and Selection of Participants

We performed a secondary analysis of a prospective cohort study (DELINEATE) that enrolled hospitalized older patients admitted from a tertiary care, academic emergency department (ED).[4] Details of and rationale for the methods have been previously described.[4] We included patients if they were 65 years or older, in the ED for less than four hours at the time of enrollment, and unlikely to be discharged home. We excluded patients if they were non-English speaking, previously enrolled, deaf, comatose, non-verbal or unable to follow simple commands before their current illness or were considered unsuitable for enrollment by the treating physician or nurse. For the original cohort, we approached all delirious and one out of six (~16.7%) randomly selected non-delirious older ED patients to account for the expected 6:1 ratio of non-delirious to delirious patients in the ED.[2,8,9] For this secondary analysis, we included patients who agreed to provide blood specimens at enrollment.

Sample Collection, Storage, and Serum Drug Concentration Measurement

Blood was collected at enrollment. Within one hour, samples were centrifuged at 3,000g. Supernatants were removed and stored in aliquots at −80 degrees Celsius until batched analyses. After DELINEATE study enrollment was completed, serum drug concentrations were measured using a LC/MS/MS-based assay (Precera Bioscience, Inc., Franklin, TN) that quantified 78 medications simultaneously in a single serum sample. Samples were thawed, mixed, and transferred to 96-well plates for processing. Internal standard working solution was added, and protein precipitation was performed using Phenomenex Impact Protein Precipitation Plates. Eluate was transferred to a new plate and dried under nitrogen prior to reconstitution for LC/MS/MS analysis. Reconstituted samples were processed using a Shimadzu Nexera X2 liquid chromatography system (Columbia, MD) fitted with a Phenomenex 2.1 × 50 mm, 1.7 μm C18 column (Torrence, CA). Sample analysis was performed on a Sciex 5500 Q-Trap Mass Spectrometer (Framingham, MA) with TurboV ion source. Data collection was performed with Sciex Analyst software, version 1.6.2, and data analysis was performed using Indigo BioAutomation Ascent software (Indianapolis, IN).

We defined SPDLs as any psychotropic (opioids, benzodiazepines, antidepressants, antipsychotics, and amphetamines) serum drug concentrations above the upper limits of respective reference ranges for that molecule. Reference ranges were derived from literature and are presented in Supplemental Table 1.[10,11]

Outcome Variable

The primary outcome variable was the total number of days a delirious ED patient remained delirious throughout the hospitalization (ED delirium duration); the ED delirium episode was considered resolved if the patient was non-delirious for two consecutive days. Because SPDLs measured at enrollment are less likely to affect incident delirium especially later in the hospital course, patients who were not delirious in the ED were assigned an ED delirium

duration of 0 days even if they later developed delirium during hospitalization. We assessed delirium in the ED at the time of enrollment (0 hours) and at 3 hours after enrollment and once daily during their hospitalization for up to 7 consecutive days after the ED visit or until hospital discharge, whichever came first. A patient was considered delirious in the ED if either the initial (0-hour) or 3-hour delirium assessment was positive. We used the modified Brief Confusion Assessment Method (bCAM) to ascertain delirium in non-mechanically ventilated patients; it is 82% to 86% sensitive and 93% to 96% specific for delirium as diagnosed by a psychiatrist with a kappa of 0.87 indicating excellent reliability.[12] We used the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) to assess delirium in mechanically ventilated patients.[13] The CAM-ICU is 93% to 100% sensitive and 98% to 100% specific for delirium in these patients, with a kappa of 0.96.[14]

Additional Data Collection

At enrollment, pre-illness functional status was prospectively determined using the Older American Resources and Services activities of daily living (OARS ADL) questionnaire which ranges from 0 (completely dependent) to 28 (completely dependent). Pre-illness (baseline) cognition was characterized using the short form Informant Questionnaire on Cognitive Decline in the Elderly score (IQCODE) which ranges from 1 (improved cognition) to 5 (worse cognition).[15] This informant-based cognitive screen was used because global tests of cognition would not accurately reflect pre-illness cognition during a delirium episode. The IQCODE was only completed by informants who knew the patient for at least 10 years. A patient was considered to have dementia if they had: (i) a pre-illness short form Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) greater than 3.38,[16] (ii) documented dementia in the medical record, or (iii) prescribed cholinesterase inhibitors prior to admission. As part of the bCAM or CAM-ICU, the Richmond Agitation Sedation Scale (RASS) was collected. The RASS is a level of arousal scale that ranges from −5 (coma) to +4 (combative), with a score of 0 indicating normal.

Dementia status and cholinesterase inhibitor use prior to enrollment were obtained from the medical record. In addition, the total number of home medications prescribed, comorbidity burden, history of moderate to severe liver disease, history of moderate to severe kidney disease, severity of illness, and the presence of acute kidney injury at enrollment or a central nervous system (CNS) diagnosis during the index hospitalization were also collected from the medical record. The Charlson Comorbidity Index was used to quantify the patient's comorbid burden.[17] The Acute Physiology Score (APS) of the Acute Physiology and Chronic Health Evaluation II (APACHE II) assessment was used to quantify severity of illness; age was also incorporated into the APS for this analysis.[18] Acute kidney injury at enrollment was collected from the treating emergency or hospital physicians' impressions located in their initial history and physical examinations. The Charlson Comorbidity Index was used to quantify the patient's comorbid burden. A past history of depression and psychosis was also abstracted from the medical record. For patients with SPDLs, the discharge medication list was reviewed to determine if the offending medication was continued or discontinued or if the dose was adjusted. We used double-data entry for all medical record data collection; medical record reviews, except for CNS diagnosis, were performed by medical students and physicians. Two independent physician reviewers

determined the presence of a CNS diagnosis (e.g., meningitis, seizure, cerebrovascular accident, intraparenchymal hemorrhage). A third physician reviewer adjudicated any disagreements.

Data Analysis

We performed proportional odds logistic regression to determine if SPDLs were associated with ED delirium duration adjusted for the following covariates chosen a priori: total number of home medications prescribed, dementia status, pre-illness functional status (OARS ADL), comorbidity burden (Charlson), past history of moderate to severe liver disease, past history of moderate to severe kidney disease, severity of illness (APS), acute kidney injury at enrollment, and presence of a CNS diagnosis. The adjusted proportional odds ratio (POR) with its 95% confidence interval (95%CI) was reported. The proportionality odds assumption between SPDL and ED delirium duration was evaluated graphically and was met.[19]

To test the robustness of our findings, we performed several sensitivity analyses. To assess the effect of including non-delirious patients in the analysis, the proportional odds logistic regression model was performed in a subset of patients who were delirious in the ED. To assess the effect of incident delirium on our outcome, we re-ran the proportional odds logistic regression with delirium duration for both prevalent and incident delirium. Because psychotropic medications may have sedating effects, we added a RASS of −1 (slightly drowsy) and RASS of −2 or −3 (moderately or severely drowsy) to the proportional odds regression model. To account for potential confounding by indication, a past history of depression or psychosis was added to the model. Because 14 (8.9%) of patients were discharged from the hospital prior to delirium resolution, we performed Cox proportional hazards regression. Days to delirium resolution was the outcome variable and delirious patients were censored at the time of discharge. All statistical analyses were performed with SAS version 9.4 (SAS Institute, Carey, NC).

Results

The DELINEATE study screened a total of 3,383 older ED patients and enrolled 228 older ED patients who were hospitalized.[4] Of those enrolled, serum drug concentration measurements were performed on 158 patients; 92 were non-delirious and 66 were delirious in the ED. A total of 15 (9.5%) SPDLs were detected at enrollment. Table 1 shows the patient characteristics stratified by SPDL status. There were no differences in the total number of medications or proportion with a past history of depression or psychosis between patients with and without SPDLs. Patients with SPDLs were more likely to be female, have a history of dementia, be more functionally impaired at baseline, have a past history of moderate to severe liver disease or moderate to severe kidney disease, and have acute kidney injury at enrollment. Patients with SPDLs were younger, less likely to be non-white race, and less likely to have a CNS diagnosis.

Table 2 lists the 15 SPDLs at enrollment. Of the 66 patients who were delirious in the ED, 11 (16.7%) had SPDLs and of the 92 who were non-delirious in the ED, 4 (4.3%) had SPDLs. Only one patient received a medication (lorazepam) associated with an SPDL prior

to the blood draw in the ED. Using proportional odds logistic regression, SPDLs were associated with prolonged delirium duration (adjusted POR = 6.0, 95%CI: 2.1 to 17.3) after adjusting for covariates. The results of the sensitivity analyses can be seen in Supplemental Table 2. The effect sizes for SPDLs remained similar for all sensitivity analyses models. Of the 15 SPDLs across all participants, 9 (60.0%) were prescribed at hospital discharge at the same or even higher doses (Table 2).

Discussion

To our knowledge, this study is the first to utilize a multiplex LC/MS/MS-based assay to prospectively evaluate SPDLs and delirium in older ED patients admitted to the hospital. We observed that SPDLs occur in 17% of delirious older patients and is significantly associated with a longer duration of delirium. These findings support a mechanistic hypothesis that supratherapeutic drug levels may lead to increased duration of delirium. Future studies should evaluate if a deprescribing intervention (i.e., removing or reducing the dose of the offending medications) in older delirious patients will decrease the duration of delirium and improve long-term outcomes following hospital discharge.

In outpatient settings, drug concentration measurements have been traditionally used for therapeutic drug monitoring (TDM) to optimize medication dosing to maximize effectiveness and minimize adverse effects. TDM has demonstrated its utility for monitoring medications with narrow therapeutic indices, such as lithium and tricyclic antidepressants, to minimize adverse effects.[20,21] More recent investigations have extended the clinical application of TDM to additional psychotropic medications.[22–25] Towards this end, an international TDM Task Force (Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie, AGNP) released consensus guidelines to refine TDM usage wherein they advocated for measurement-based approaches to monitor the exposure of psychotropic drugs and reduce adverse events.[26] Our data suggest that TDM may have clinical utility in the ED and inpatient settings to help identify drug-induced delirium and inform medication adjustments prior to hospital discharge to improve outcomes.

Psychotropic drugs have variable volume of distributions and mechanisms in which they are transported through the blood brain barrier. Despite such differences, serum concentrations of most psychotropic medications have been shown to be highly correlated with brain concentrations and correlate better than prescribed dosages.[27–29] For this reason, AGNP states that “for neuropsychiatric medications, drug concentrations in blood can therefore be considered a valid marker of concentrations in the brain.”[26] Other methods to measure psychotropic drug concentrations in the brain exist such as obtaining cerebrospinal fluid or using magnetic resonance spectroscopy.[30] These techniques, however, are typically not feasible to obtain during routine clinical care.

Our study has several limitations. First, the sample size was relatively small. Consequently, the 95%CI was wide despite collapsing all SPDLs into a single category. The relatively small number of SPDLs may increase the possibility that the regression model was overfit. Larger studies are needed to confirm our findings, increase the precision of our estimates, and determine if specific classes of SPDLs are more strongly associated with delirium.

Second, the modified bCAM is 82% to 86% sensitive and 93% to 96% specific for delirium. This may have introduced misclassification bias which could have magnified or attenuated the observed effect size. Third, we did not record the time of ingestion of each medication, and the assay utilized did not specifically analyze active metabolites, which may contribute to the clinical presentation. Fourth, we were not able to ascertain if the SPDLs were secondary to chronic toxicity versus acute toxicity, which may impact delirium's clinical course and outcomes differently. Fifth, this was an observational study, and hence the possibility of bias due to unmeasured confounders cannot be excluded. Even though the proportion of patients with a past history of depression or psychosis was similar in the SPDL and non-SPDL groups, confounding by indication may still exist. Due to the relatively small sample size, propensity score matching was not feasible. In our sensitivity analyses, however, adjusting for a past history of depression or psychosis did not change SPDL's effect size.

In conclusion, we found that SPDLs were associated with an increased duration of delirium in hospitalized older patients admitted from the ED. The LC/MS/MS approach described herein may provide useful, timely clinical information to the inpatient team regarding circulating medications that require dose adjustments prior to hospital discharge. Future studies should include a randomized controlled trial with a larger sample size and an evaluation of long-term outcomes of supratherapeutic drug levels based on deprescribing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Sponsor's Role

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Table 1.

Patient characteristics and demographics.

	Non-SPDL n=143	SPDL n=15
Median age (IQR)	74 (69, 80)	70 (67, 85)
Female gender	74 (51.8%)	14 (93.3%)
Non-white race	17 (11.9%)	1 (6.7%)
Total # of home medications	9 (6, 14)	10 (6, 17)
Dementia	60 (42.0%)	10 (66.7%)
Median (IQR) OARS ADL	25 (17, 27)	21 (10, 23)
History of moderate to severe liver disease	6 (4.2%)	3 (20.0%)
History of moderate to severe kidney disease	22 (15.4%)	3 (20.0%)
History of depression or psychosis	19 (13.3%)	2 (13.3%)
Median (IQR) Charlson	3 (2, 5)	3 (2, 5)
Median (IQR) APS with age	9 (7, 11)	9 (8, 11)
Acute kidney injury at enrollment	31 (21.7%)	5 (33.3%)
CNS diagnosis	23 (16.1%)	0 (0.0%)
Level of arousal at enrollment		
RASS = −1	34 (23.8%)	6 (40.0%)
RASS = −2 or −3	11 (7.7%)	2 (13.3%)
Median (IQR) ED delirium duration days	0 (0, 2)	3 (0, 6)

Abbreviations: SPDL, supratherapeutic psychotropic drug levels; IQR, Interquartile range; OARS ADL, Older American Resources Activities of Daily Living scale; APS, Acute Physiology Score; CNS, central nervous system; RASS, Richmond Agitation Sedation Scale; ED, emergency department. SPDLs were defined as serum opioid, benzodiazepine, antidepressant, antipsychotic or amphetamine concentrations above the therapeutic reference range. Serum drug concentrations were measured using a liquid chromatography-mass spectrometry assay that measured 78 medications simultaneously.

Table 2.

Patients with supratherapeutic psychotropic drug levels measured at enrollment. ED, emergency department. Of the 15 supratherapeutic psychotropic drug levels detected at enrollment, 9 (60%) were prescribed at hospital discharge at the same or even higher doses.

Patient	Medication	Delirious in ED?	Drug Concentration (ng/mL)	Upper limit of normal (ng/mL)	Given in ED before blood draw	Dose of medication after hospital discharge
1	Duloxetine	No	247	120	No	Same
2	Citaprolam	No	213	110	No	Decreased
3	Lorazepam	Yes	26.2	15	No	Higher
4	Citaprolam	Yes	132	110	No	Higher
5	Nortryptyline	Yes	414	170	No	Same
6	Alprazolam	Yes	117	50	No	Decreased
7	Lorazepam	No	15.2	15	Yes	Stopped
8	Duloxetine	Yes	423	120	No	Same
9	Alprazolam	Yes	60.3	50	No	Stopped
10	Amphetamine	Yes	145	100	No	Same
11	Citaprolam	Yes	114	110	No	Stopped
12	Sertraline	Yes	207	150	No	Same
13	Citaprolam	No	215	110	No	Same
14	Duloxetine	Yes	595	120	No	Same
15	Duloxetine	Yes	246	120	No	Decreased