Anticholinergic Medication Use and Transition to Delirium in Critically Ill Patients: A Prospective Cohort Study

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Objective: Although cholinergic deficiency is presumed to increase delirium risk and use of medication with anticholinergic properties in the ICU is frequent, the relationship between anticholinergic medication use and delirium in this setting remains unclear. We investigated whether exposure to medication with anticholinergic properties increases the probability of transitioning to delirium in critically ill adults and whether this relationship is affected by age or the presence of acute systemic inflammation.

Design: Prospective cohort study.

Setting: A 32-bed medical-surgical ICU at an academic medical center.

Patients: Critically ill adults admitted to the ICU for more than 24 hours without an acute neurological disorder or another condition that would hamper delirium assessment.

Interventions: None.

Measurements and Main Results: Daily anticholinergic burden was calculated for each patient based on the sum of the Anticholinergic Drug Scale score for each medication administered. Daily mental status was classified as “coma,” “delirium,” or an “awake without delirium” state. The primary outcome, the daily transition from an “awake without delirium” state to “delirium,” was analyzed using a first-order Markov model that adjusted for eight covariables. A total of 1,112 patients were evaluated over 9,867 ICU days. The daily median summed Anticholinergic Drug Scale score was 2 (interquartile range, 1–3). The transition from being in an “awake without delirium” state to “delirium” occurred on 562 of ICU days (6%). After correcting for confounding, a one-unit increase in the Anticholinergic Drug Scale score resulted in a nonsignificant increase in the probability of delirium occurring the next day (odds ratio, 1.05; 95% CI, 0.99–1.10). Neither age nor the presence of acute systemic inflammation modified this relationship.

Conclusions: Exposure to medication with anticholinergic properties, as defined by the Anticholinergic Drug Scale, does not increase the probability of delirium onset in patients who are awake and not delirious in the ICU. (Crit Care Med 2015; 43:1846–1852)

Key Words: anticholinergic medication; delirium; ICU; risk factor

Delirium is frequent among the critically ill and is associated with poor outcome (1–3). Avoidance of risk factors for delirium remains the most important strategy to reduce the burden of delirium in ICU patients (4, 5). Disturbances in attention, a key clinical finding among any patient diagnosed with delirium, are regulated, in part, by the cholinergic neurotransmitter system (6–8). A number of reports have therefore proposed cholinergic deficiency as being an important mechanistic cause for delirium occurrence (7, 9–12). Given the premise that the use of a medication with anticholinergic properties will result in some degree of cholinergic deficiency and that the administration of medications with anticholinergic properties in the ICU is common, anticholinergic medication use may represent an important modifiable risk factor for delirium in the critically ill (13–15).

Prior ICU studies attempting to evaluate the association between anticholinergic medication exposure and delirium occurrence have suffered from important methodological limitations and have yielded inconclusive results (13–15). The likelihood of residual confounding is high due to the evaluation...
of small patient samples and the crude analysis methods that have been used (13–15). Because of the time-varying nature of severity of illness, exposure to medication with anticholinergic properties, and delirium occurrence in the critically ill, it is essential to use time-dependent regression analyses when characterizing this relationship (16). Furthermore, in previous studies, neither the influence of age nor acute systemic inflammation was evaluated. This is important as increased age and an acute inflammatory state each may lead to greater cholinergic neurotransmitter system dysfunction, thus exaggerating the effect that anticholinergic medication exposure may have on delirium occurrence (10).

The aim of this study was to investigate whether exposure to medications with anticholinergic properties increases the daily risk of delirium occurrence in critically ill adults and whether this relationship is affected by age or the presence of acute systemic inflammation.

**MATERIALS AND METHODS**

**Study Design**

This study was conducted as part of a prospective cohort study of consecutively admitted adult patients who stayed for at least 24 hours in the 32-bed medical-surgical ICU of the University Medical Center Utrecht (UMCU) between January 2011 and June 2013. Patients who had been transferred from an ICU at another hospital or with an acute neurological illness or condition with the potential to hamper delirium assessment were excluded. The Medical Research Ethics Committee of the UMCU approved this study and waived the need for informed consent given the anonymity of data collection and the noninterventional nature of the study (protocol 12–421 and 10–056).

**Mental Status Assessment**

Level of sedation was evaluated by the bedside nurse every 3 hours using the Richmond Agitation-Sedation Scale (17). The presence of delirium during the preceding 24 hours was determined daily using a previously validated five-step algorithm (interobserver agreement, 0.94–0.97; sensitivity, 0.75; and specificity, 0.85) (18). This multistep algorithm incorporates a review by a research nurse of all Confusion Assessment Method for the ICU (CAM-ICU) (19) assessments conducted by the bedside nurses, whether delirium treatment was initiated and a meticulous chart review for the presence of documented terms clinically associated with delirium (18). When delirium could not be ruled in or out using this procedure, the research nurse conducted an additional CAM-ICU assessment. The daily mental status for each patient was then classified as “coma,” “delirium,” or an “awake without delirium” state.

**Evaluation of the Anticholinergic Burden of Medication Use**

The daily anticholinergic burden was calculated using the sum of the Anticholinergic Drug Scale (ADS) levels for each medication administered on a particular ICU day (20). The ADS of the previous day was linked to the outcome (i.e., “awake without delirium,” “coma,” “delirium,” or “discharge or death”) on the next day, so the calculated ADS preceded the assessment of the outcome entirely. The ADS characterizes the anticholinergic activity for 340 different medications, many of which are frequently used in the ICU. The level of anticholinergic activity for each medication is rated across four levels, with a score of 0 indicating no known anticholinergic activity, a score of 1 indicating a potential anticholinergic effect based on the result of receptor binding studies, a score of 2 indicating that anticholinergic adverse events have been observed with the use of medication, and a score of 3 indicating that anticholinergic clinical effects nearly always occur (20). To account for the fact that a patient who received multiple intermittent doses of a medication with potential anticholinergic properties over a 24-hour period could end up with an ADS score higher than a patient who received the same medication, but as a continuous infusion, an ADS score was assigned only once per day for each medication, regardless of the number of doses administered. If a patient was receiving a medication not included in the ADS nomenclature, a score of 0 was assigned.

To explore whether any relationship between anticholinergic medication use and delirium occurrence is dose related, the dose-adjustment strategy as proposed by Carnahan et al (20) was incorporated in a sensitivity analysis. In this analysis, the administered daily dose was determined for all ADS levels 2 and 3 medications. This daily dose was compared with the maximal daily dose of the medication as advised by the Royal Dutch Pharmacists Association. If the daily dose was less than or equal to one third of the defined maximum daily dose, the dosing weight was defined as 1. If the daily dose was between one third and two thirds of the defined maximum daily dose, the dosing weight was defined as 2. If the daily dose was greater than two thirds of the maximum dose, but did not exceed the maximum daily dose, the dosing weight was defined to be 3. If the daily dose exceeded the maximum daily dose, the dosing weight was deemed to be 4. The ADS-defined level for the medication was then multiplied by the dosing weight and summed for each patient each day to determine a dose-adjusted ADS score. For example, a level 2 medication with an administered dose between one third and two thirds of the maximum daily dose would have a dose-adjusted ADS score of 4. The application of a dose-adjustment strategy requires that the maximal daily dose should be defined. However, for the most frequently used level 1 medications (e.g., morphine and midazolam), this has never been defined and thus a dose-adjustment strategy was deemed unfeasible for level 1 medications.

Benzodiazepines are a potential risk factor for delirium in the ICU (14, 15, 21) through both anticholinergic and nonanticholinergic mechanisms. Although the relationship between benzodiazepine's weakly anticholinergic properties and delirium was accounted for in our analysis given that the ADS categorizes benzodiazepines as a level 1 medication, we conducted two sensitivity analyses to explore the importance of potential non-anticholinergic delirigenic mechanism(s): 1) Benzodiazepines were excluded from the daily ADS and
Benzodiazepine use (in milligrams of midazolam equivalents) was incorporated as a separate covariable in the model.

Additional sensitivity analysis was conducted using only the levels 2 and 3, and using only the level 3 medications, to explore whether consideration of these medications alone would affect the association between the ADS score and transitioning from an “awake without delirium” state to “delirium.”

Although the ADS is currently the recommended scale when characterizing the anticholinergic effects of medications (22, 23), we repeated all steps of our parent analysis in a post hoc fashion using the Anticholinergic Risk Scale (ARS) (24).

Covariables and Stratification

Based on a prior literature review (21), variables with the potential to confound the occurrence of delirium were chosen for inclusion in the multivariable analyses. Those present at the time of ICU admission, and deemed to remain unchanged over the course of the ICU stay, included age, gender, Charlson Comorbidity Index (25), type of ICU admission (i.e., medical, elective surgical, or acute surgical), and Acute Physiology and Chronic Health Evaluation IV score (as a measure of severity of illness during the first 24 hr of ICU admission) (26). Other covariables, measured daily over the course of ICU stay, were the use of mechanical ventilation, the duration of the ICU stay in days until the particular transition occurred, and the daily cumulative Sequential Organ Failure Assessment (SOFA) score (27). The SOFA score was calculated without the neurological component to prevent adjusting for a component of the outcome. Trend imputation was used for any missing value of a covariable, given the availability of longitudinal data both preceding and following each observation day (28). Data were stratified by age (i.e., younger than 65 vs 65 yr or older) and the daily presence of acute systemic inflammation defined as the presence of the systemic inflammatory response syndrome (29).

Statistical Analyses

To explore the isolated effect of the ADS score, age, and the presence of an acute systemic inflammation on the probability of transitioning from an “awake without delirium” state to “delirium,” first-order Markov multinomial logistic regression models were used. These models included the patient’s mental status in the prior 24 hours as a covariable. Additional adjustments were made for the covariables described above. In this study, the first-order Markov models included 12 transitions (3 by 4) to account for competing events, as follows: from “coma,” “delirium,” or an “awake without delirium” state on a particular ICU day, to the next day either “coma,” “delirium,” an “awake without delirium” state, or “discharged from the ICU or deceased.” The primary outcome was the transition from an “awake without delirium” state to “delirium” the next day. The transition from an “awake without delirium” to an “awake without delirium” state the next day was used as the reference transition. The transition from “coma” to “delirium” was also explored, with the transition from “coma” to “awake without delirium” as reference.

Subsequently, data were stratified and the same first-order Markov regression model as described above was used to assess the daily temporal association between the ADS score in patients with an “awake without delirium” state and the transition to a “delirium.” Odds ratios (ORs) were presented with 95% CIs. Subset analysis excluding the 1% of patients with the longest length of ICU stay was conducted to see whether these patients disproportionally influenced the association between the ADS and delirium.

All data analyses were performed using IBM SPSS Statistics 20.0 for Windows (Armonk, NY) and R version 3.0.2 for Windows (R Foundation for Statistical Computing, Vienna, Austria). The null hypotheses were tested against two-sided alternatives, and a significance level of 0.05 was used for all statistical inferences.

RESULTS

During the study period, among 2,669 patients screened, 1,112 patients (42%) were included in the analyses. Reasons for patient exclusion are described in Figure 1. Characteristics of the study population are outlined in Table 1. The 1,112 patients stayed in the ICU for a median of 5 days (interquartile range [IQR], 2–10 d), and the data represented 9,867 ICU observation days. Acute systemic inflammation was present on 6,233 of the observation days (63%). Among the 535 patients (48%) where delirium occurred, it was present for 3 days (IQR, 1–6 d). A transition from an “awake without delirium” state to “delirium” occurred on 562 of the ICU days (6%) at a median of 9 days (IQR, 4–20 d) after ICU admission. The frequency of occurrence of all daily transition is described in Appendix 1 (Supplemental Digital Content 1, http://links.lww.com/CCM/B315).

Appendix 2 (Supplemental Digital Content 2, http://links.lww.com/CCM/B316) provides an overview of the medication administered in the study cohort for ADS levels 1, 2, and 3 and

Figure 1. Study flowchart. *Inability of screening due to, for example, mental retardation or language barrier.
the frequency of administration across all ICU days. The daily exposure to anticholinergic medication, as characterized by the
summed ADS score, ranged between 0 and 10 with a median of 2 (IQR, 1–3). Among the cumulative daily ADS scores across all patients and ICU days, level 1 medications contributed for
90% of the total score, level 2 medications for 1%, and level 3 for 9%. Morphine, furosemide, midazolam, and prednisone were the most frequently used ADS-scored medications with an ADS score greater than 0.

No significant increase in the odds for the daily transition from an “awake without delirium” state to “delirium” was found with every one-unit ADS increase in the anticholinergic burden (adjusted OR, 1.05; 95% CI, 0.99–1.10) (Table 2). For every increase in age of 1 year, the probability of having “delir-ium” the day after being in an “awake without delirium” state increased significantly (adjusted OR, 1.02; 95% CI, 1.01–1.02). The probability of transitioning from an “awake without delirium” state to “delirium” also increased significantly on days that patients had acute systemic inflammation compared with days where acute systemic inflammation was not present (adjusted OR, 1.37; 95% CI, 1.13–1.65). The stratified analyses revealed that neither age nor acute systemic inflammation affected the reported relationship between daily ADS score and the daily odds of transitioning to “delirium” (Table 3). The crude results of the primary outcome from an “awake without delirium” state to “delirium” as well as the additional results for the transitions from “coma” to “delirium” can be found in Appendix 3 (Supplemental Digital Content 3, http://links.lww.com/CCM/B317). In a subset analysis that excluded the 1% of

<table>
<thead>
<tr>
<th>TABLE 1. Characteristics of the Study Population (n = 1,112)</th>
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<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>Age, yr, mean (sd)</td>
</tr>
<tr>
<td>Male, n (%)</td>
</tr>
<tr>
<td>Charlson comorbidity index, median (IQR)</td>
</tr>
<tr>
<td>Type of admission, n (%)</td>
</tr>
<tr>
<td>Medical</td>
</tr>
<tr>
<td>Elective surgical</td>
</tr>
<tr>
<td>Acute surgical</td>
</tr>
<tr>
<td>Acute Physiology and Chronic Health Evaluation IV score IV, mean (sd)</td>
</tr>
<tr>
<td>Sequential Organ Failure Assessment per day, median (IQR)a</td>
</tr>
<tr>
<td>Delirium, n (%)</td>
</tr>
<tr>
<td>Number of delirium days during ICU stay, median (IQR)</td>
</tr>
<tr>
<td>Length of ICU stay in days, median (IQR)</td>
</tr>
<tr>
<td>Ever use of mechanical ventilation, n (%)</td>
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1IQR = interquartile range.
2Sequential Organ Failure Assessment score without the neurological component.

TABLE 2. Odds Ratios for Daily Transitioning to Delirium (n = 9,867)

<table>
<thead>
<tr>
<th>Determinant</th>
<th>Adjusted Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergic Drug Scale, per unit increase</td>
<td>1.05 (0.99–1.10)</td>
</tr>
<tr>
<td>Age, per year increase</td>
<td>1.02 (1.01–1.02)</td>
</tr>
<tr>
<td>Presence of acute systemic inflammation</td>
<td>1.37 (1.13–1.65)</td>
</tr>
</tbody>
</table>

aAdjusted for age, gender, Charlson Comorbidity Index, type of admission, Acute Physiology and Chronic Health Evaluation IV score, use of mechanical ventilation, length of ICU stay until transition, and Sequential Organ Failure Assessment score without the neurological component. The primary outcome was the transition from an “awake without delirium” state to “delirium.” The transition from an “awake without delirium” to an “awake without delirium” state the next day was used as the reference transition.

bOdds ratio for days with acute systemic inflammation compared with days without acute systemic inflammation.

In our cohort, the administered benzodiazepines defined in the ADS were alprazolam, clonazepam, lorazepate, diazepam, midazolam, lorazepam, oxazepam, and temazepam; all of which were registered as level 1 anticholinergic medications. The OR for the daily transition from an “awake without delirium” state to “delirium” did not significantly change when either benzodiazepines were excluded from the ADS (adjusted OR, 1.06; 95% CI, 0.99–1.13, per one-unit increase in ADS) or the daily amount of benzodiazepine administered in midazolam equivalents was incorporated as a separate covariable (adjusted OR, 1.04; 95% CI, 0.99–1.09).

When using only levels 2 and 3, and only level 3 medications to describe the association between the ADS score and the daily transition from an “awake without delirium” state to “delirium,” the results did not differ significantly (adjusted OR, 0.82; 95% CI, 0.65–1.03) per two-unit increase for levels 2 and 3 medications (adjusted OR, 0.89; 95% CI, 0.79–1.00) per three-unit increase for level 3 medications.

Use of the ARS, rather than the ADS, to calculate anticholinergic burden resulted in a significant increase in the probability to transition from an “awake without delirium” state to a “delirium” (adjusted OR, 1.12; 95% CI, 1.03–1.22). However, this association was present in only those patients who were older and on the days they were acutely inflamed (Appendix 4, Supplemental Digital Content 4, http://links.lww.com/CCM/B318).

DISCUSSION

This investigation is the first to describe the association between exposure to medication with anticholinergic properties and
the daily risk of delirium in a large cohort of critically ill adults. Exposure to medication with anticholinergic properties, as defined by the ADS, was not associated with an increased probability for transitioning from an “awake without delirium” state to “delirium” the following day.

Microglia are the macrophages of the brain and when activated will result in neuronal dysfunction, an important precursor for delirium (10, 12). Although microglia are inhibited by the cholinergic system, they are also sensitive to activating factors like the acute neuroinflammation commonly seen during critical illness (10, 11, 30). During the aging process, the cholinergic system will start to atrophy and thus microglial priming will increase. The critically ill, especially those that are older, have therefore been hypothesized to be particularly sensitive to the anticholinergic properties of medications, specifically in the setting of acute systemic inflammation (10). Our results confirm the importance of acute systemic inflammation and increasing age as individual risk factors for delirium. However, they do not support the hypothesis that use of a medication that increases cholinergic inhibition (i.e., anticholinergic medication) in the critically ill are a clinically important factor for the development of delirium (5, 7, 10). Alternative anticholinergic burden scales to the ADS, such as the ARS (24), the list by Summers et al (31), and the Anticholinergic Cognitive Burden Scale exist (32). However, unlike the ADS, none is validated against serum anticholinergic activity rather than a validated ADS was used to define anticholinergic exposure and that factors with the potential to confound delirium occurrence were not accounted for (13). Although two other published studies in ICU populations reached the same conclusion as our analysis, neither were designed to answer this question in a robust manner given the number of patients evaluated were small, a validated method to characterize anticholinergic drug exposure was not used, and important baseline and time-dependent risk factors for delirium were analyzed in an independent way (14, 15).

Our analysis has several potential limitations. Measures of anticholinergic burden, including the ADS, may lack the sensitivity to detect small differences in anticholinergic burden between days, hence, potentially resulting in a type II error. Although the ADS score was corrected for the medication dose on the day before the delirium transition rate for these medications. Although levels 2 and 3 medications together accounted for only 10% of the total ADS score, sensitivity analyses using only the levels 2 and 3, and only the level 3 medications, did not differ from results of analyses that considered all anticholinergic medications. Exposure to medication with anticholinergic effects in our cohort is likely similar to that of other institutions. However, we cannot exclude that confounding by (contra)indications

### TABLE 3. Stratified Effect for Every One-Unit Increase in the Anticholinergic Drug Scale and the Odds of Transitioning to Delirium

<table>
<thead>
<tr>
<th>No. of Observation Days</th>
<th>No. of Transitions From an “Awake Without Delirium” State to “Delirium”</th>
<th>Age Group, Yr</th>
<th>Acute Systemic Inflammation Present</th>
<th>Adjusted Odds Ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,832</td>
<td>70</td>
<td>&lt; 65</td>
<td>No</td>
<td>1.04 (0.90–1.20)</td>
</tr>
<tr>
<td>1,802</td>
<td>127</td>
<td>≥ 65</td>
<td>No</td>
<td>0.98 (0.85–1.11)</td>
</tr>
<tr>
<td>3,644</td>
<td>178</td>
<td>&lt; 65</td>
<td>Yes</td>
<td>1.09 (0.99–1.19)</td>
</tr>
<tr>
<td>2,589</td>
<td>187</td>
<td>≥ 65</td>
<td>Yes</td>
<td>1.10 (0.99–1.23)</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, Charlson Comorbidity Index, type of admission, Acute Physiology and Chronic Health Evaluation IV score, use of mechanical ventilation, length of ICU stay until transition, and Sequential Organ Failure Assessment score without the neurological component. The primary outcome was the transition from an “awake without delirium” state to “delirium.” The transition from an “awake without delirium” to an “awake without delirium” state the next day was used as the reference transition.
might have occurred (i.e., a clinician might have avoided prescribing a medication with anticholinergic effects for a patient they deemed to be at higher risk for delirium). This was addressed by covariable adjustment and the use of multiple different measures for the same construct (e.g., severity of illness). However, residual confounding may still have occurred. Although potential risk factors for delirium, other than anticholinergic drug exposure, were based on a recent systematic review and incorporated in the analysis whenever possible, the number of patients with a history of delirium preceding ICU admission was unknown. This may also have led to residual confounding. This is unfortunately a common issue in all observational studies. Under the first-order Markov assumption, all day-to-day transitions are considered independent. Yet, this is not true, as patients are represented in the dataset multiple times. The assumption may in particular be violated in patients with a long ICU length of stay. However, our findings did not change when we excluded the 1% of study participants with the longest ICU length of stay. This indicates that these patients did not influence the calculated associations disproportionately. Last, although anticholinergic medication use prior to ICU admission was not considered, the fact that a transition from an “awake without delirium” state to “delirium” occurred a median of 9 days (IQR, 4–20 d) after ICU admission makes preadmission ICU medication use likely to be of little importance.

CONCLUSIONS
This study did not find that exposure to higher ADS scores, as a measure of anticholinergic burden, increases the probability of transitioning to delirium in ICU patients. However, given the complexity of characterizing anticholinergic burden, further research in this area is required.

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REFERENCES

Clinical Investigations


