Agitation During Prolonged Mechanical Ventilation at a Long-Term Acute Care Hospital: Risk Factors, Treatments, and Outcomes
Heidi O'Connor, Nada S. Al-Qadheeb, Alexander C. White, Vishal Thaker and John W. Devlin
J Intensive Care Med published online 29 April 2013
DOI: 10.1177/0885066613486738

The online version of this article can be found at:
http://jic.sagepub.com/content/early/2013/04/29/0885066613486738

Published by:

SAGE
http://www.sagepublications.com

Additional services and information for Journal of Intensive Care Medicine can be found at:

Email Alerts: http://jic.sagepub.com/cgi/alerts

Subscriptions: http://jic.sagepub.com/subscriptions

Reprints: http://www.sagepub.com/journalsReprints.nav

Permissions: http://www.sagepub.com/journalsPermissions.nav

>> OnlineFirst Version of Record - Apr 29, 2013

What is This?
Agitation During Prolonged Mechanical Ventilation at a Long-Term Acute Care Hospital: Risk Factors, Treatments, and Outcomes

Heidi O’Connor, MD1,2, Nada S. Al-Qadheeb, PharmD, FCCP3, Alexander C. White, MD1,2, Vishal Thaker3, and John W. Devlin, PharmD, FCCM, FCCP2,3

Abstract

Introduction: The prevalence, risk factors, treatment practices, and outcomes of agitation in patients undergoing prolonged mechanical ventilation (PMV) in the long-term acute care hospital (LTACH) setting are not well understood. We compared agitation risk factors, management strategies, and outcomes between patients who developed agitation and those who did not, in LTACH patients undergoing PMV. Methods: Patients admitted to an LTACH for PMV over a 1-year period were categorized into agitated and nonagitated groups. The presence of agitation risk factors, management strategies, and relevant outcomes were extracted and compared between the 2 groups. Results: A total of 80 patients were included, 41% (33) with agitation and 59% (47) without. Compared to the nonagitated group, the agitated group had a lower Sequential Organ Failure Assessment score (P < .0006), a greater transfer rate from an academic center (P = .05), a greater delirium frequency at both baseline (P = .04) and during admission (P < .001), and a greater rate of benzodiazepine discontinuation (P = .02). Although the use of scheduled antipsychotic (P = .0005) or restraint (P = .002) therapy was more common in the agitated group, use of benzodiazepines (P = .16), opioids (P = .11), or psychiatric evaluation (P = .90) was not. Weaning success, duration of LTACH stay, and daily costs were similar. Conclusion: Agitation among the LTACH patients undergoing PMV is associated with greater delirium and use of antipsychotics and restraints but does not influence weaning success or LTACH stay. Strategies focused on agitation prevention and treatment in this population need to be developed and formally evaluated.

Keywords
agitation, delirium, antipsychotic, benzodiazepine, opioid, restraints, LTACH, prolonged mechanical ventilation, outcome, cost

Agitation occurs frequently in patients with respiratory failure in the intensive care unit (ICU).1,2 This may lead to adverse outcomes including cardiopulmonary instability, ventilator dysynchrony, inadvertent removal of invasive devices, and other complications.2-7 When patients first exhibit signs of agitation, every effort should be taken to promptly identify and treat the underlying causes that may often include pain, anxiety, delirium, and hypoxemia.1,8 Although efforts should be taken to reduce patient anxiety and agitation by maintaining patient comfort and providing frequent reorientation and assurance, sedative and antipsychotic agents are often administered and physical restraints are frequently applied.1,8-10 Over the past decade, the availability of validated tools for the identification of pain, agitation, and delirium in the ICU, coupled with a protocolized approach to comfort and safety in this setting, has improved patient outcome.11-16

Once chronic critically ill patients with respiratory failure are stabilized, they may undergo placement of a tracheostomy tube and transfer to a long-term acute care hospital (LTACH) for continued medical care and ongoing attempts at weaning from mechanical ventilation.17 Agitation may persist or develop in these patients after transfer.17-21 However, the prevalence and clinical importance of agitation, a possible marker

1 Rose Kalman Research Center, New England Sinai Hospital, Stoughton, MA, USA
2 Division of Pulmonary, Critical Care and Sleep Medicine, Tufts Medical Center, Boston, MA, USA
3 Northeastern University School of Pharmacy, Boston, MA, USA

Received June 19, 2012, and in revised form November 26, 2012. Accepted for publication January 8, 2013.

Corresponding Author:
John W. Devlin, Northeastern University, 360 Huntington Ave R218 TF, Boston, MA 02115, USA.
Email: j.devlin@neu.edu
of delirium, in patients undergoing prolonged mechanical ventilation (PMV) in the LTACH setting are not well understood. To better characterize the importance of agitation in the LTACH setting, we compared the presence of agitation risk factors, including delirium, agitation management strategies, and outcomes including weaning success, LTACH disposition, mortality, and cost of care between patients undergoing PMV who developed agitation and those who did not.

Methods

This retrospective study evaluated consecutive patients admitted to an LTACH, New England Sinai Hospital–Stoughton campus (NESH-S), over a 1-year period (July 2008 to June 2009) for PMV. Patients were excluded from the analysis if they had a documented history of schizophrenia, bipolar disorder, or severe dementia. New England Sinai Hospital–Stoughton is a 140-bed hospital located in southeast Massachusetts. The study was approved by the institutional review board at NESH. For the purpose of the analysis, agitation was deemed to have occurred on a particular day when any of the following words were documented in the patient record: agitation, agitated, belligerent, belligerence, restless, restlessness, hyperactive, hostile, disturbed, distress, distressed, tossing, and shaking. Based on this review, the following data were collected from the medical record of each patient: evaluation by a psychiatrist, use of an antipsychotic (either scheduled or “as needed”), benzodiazepine (either scheduled or as needed), or scheduled opioid, administration of wrist restraints, and use of 1:1 patient supervision (ie, a sitter). Pertinent outcome data including patient falls, successful weaning from PMV, successful decannulation, unplanned transfers back to an acute care hospital, duration of LTACH stay, LTACH disposition, LTACH mortality, and cost of care were also collected. A fall was deemed to occur when a description of such was recorded in the record.

All study data, including patient eligibility for inclusion in the analysis, were identified through a manual review of the patient’s electronic medical record (Meditech; Westwood, Massachusetts) on all days the patient was admitted to the LTACH. A patient’s paper record was reviewed in situations where the data were missing in the electronic medical record. Data extraction was completed by 2 different trained data extractors who independently gathered the study information from each patient record. All situations where the extracted data differed between extractors were resolved through consensus.

All demographic variables, and each of the above agitation-related factors, treatments, and outcomes, were compared between patients who developed agitation and those who did not. The Student t test was used to compare parametric data and the Mann-Whitney test for nonparametric data. A P value of less than .05 was considered statistically significant for all analyses. Statistical analysis was done using SPSS version 18.0 (IBM, Chicago, Illinois).

Results

Among the 180 patients admitted to the LTACH over the 1-year evaluation period, 87 were receiving mechanical ventilation on admission. Of these patients, 4 had a history of severe dementia and 3 a history of schizophrenia or bipolar disorder; thus, 80 patients were included in our analysis. Among these 80 patients, 33 (41%) experienced agitation and 47 (59%) did not.

Most (68%) of the patients who developed agitation experienced only one episode of agitation. The median (interquartile range [IQR]) duration of each agitation episode was 1 (1-2) day and occurred 5 (3-7) days after LTACH admission. Patients
who experienced agitation had a lower baseline severity of illness \( (P \leq .0006) \) and were more likely to be transferred from an academic medical center rather than a community hospital \( (P = .06; \) Table 1). Patients developing agitation were more likely to have delirium at LTACH admission \( (P = .04) \), at any time during their LTACH admission \( (P < .001) \), and for 4 or more consecutive days \( (P = .001; \) Table 2). The patients who experienced agitation were twice as likely to have a week-long course of scheduled benzodiazepine therapy discontinued \( (P = .02) \). A history of depression, presence of infection, or use of high-dose corticosteroids or metoclopramide was similar between the 2 groups.

Patients who developed agitation were more likely to be administered \( \geq 24 \) hours of scheduled antipsychotic therapy \( (P = .0003) \) and/or as-needed antipsychotic therapy \( (P = .03) \) and have wrist restraints applied \( (P = .00008) \) during their LTACH stay (Table 3). Use of psychiatric consultation, scheduled benzodiazepine or opioid therapy, or 1:1 supervision by a sitter was similar. Among the 33 patients who developed agitation, the 4 most frequently used management strategies during the first episode of agitation were scheduled antipsychotic therapy \( (52\%) \), wrist restraints \( (52\%) \), as-needed benzodiazepine therapy \( (39\%) \), and scheduled benzodiazepine therapy \( (30\%; \) Figure 1). During these agitated episodes, 30\% of the patients received both antipsychotics and restraints, 21% received both an antipsychotic and a benzodiazepine, and 15% received an antipsychotic, a benzodiazepine, and restraints. Quetiapine accounted for 77\% of the antipsychotic use in both the groups and was administered at a (median [IQR]) daily dose of 50 (30–72) mg.

The proportion of patients who were weaned from PMV \( (P = .60) \), and successfully decannulated \( (P = .70) \), did not differ between the agitated and nonagitated groups (Table 4). The unplanned transfer rate back to an acute care institution \( (P = .82) \), duration of LTACH stay \( (P = .66) \), daily cost of care \( (P = .07) \), and mortality \( (0.6) \) did not differ significantly between the 2 groups.

### Discussion

This is the first study to measure the prevalence, risk factors, treatment practices, and outcomes of agitation in patients undergoing PMV at a LTACH. Patients who develop agitation are less severely ill, are more likely to arrive from the ICU at an academic medical center, have delirium, and be at risk of benzodiazepine withdrawal. Patients who develop agitation often receive multiple pharmacological therapies and both medication and nonmedication interventions. Although agitation is usually of great concern to LTACH caregivers, its presence does not appear to influence ventilator weaning, tracheostomy decannulation, duration of stay, or costs of care based on an analysis over 1 year at 1 LTACH.

The underlying causes for agitation in the LTACH setting among patients requiring PMV are numerous and include pain, anxiety, delirium, sleep disturbances, hypoxemia, ventilator dysynchrony, depression, drug withdrawal, and infection.\(^{1,7,8,17,18,20,21,25–27}\) Given the complexity of establishing the etiology for agitation in some patients, particularly when it is

---

**Table 1.** Comparison of Baseline Demographic Variables Between Agitated and Nonagitated Groups.\(^{a}\)

<table>
<thead>
<tr>
<th></th>
<th>Agitated, ( N = 33 )</th>
<th>Nonagitated, ( N = 47 )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>71 ± 12</td>
<td>68 ± 12</td>
<td>.23</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>48</td>
<td>51</td>
<td>.80</td>
</tr>
<tr>
<td>Admission SOFA score</td>
<td>0.9 ± 1.1</td>
<td>1.3 ± 1.6</td>
<td>(&lt; .0006)</td>
</tr>
<tr>
<td>Transfer from an academic hospital (%)</td>
<td>73</td>
<td>34</td>
<td>.05</td>
</tr>
<tr>
<td>History of depression (%)</td>
<td>21</td>
<td>24</td>
<td>.88</td>
</tr>
</tbody>
</table>

Abbreviations: SOFA, sequential organ failure assessment; SD, standard deviation.

\(^{a}\) Results presented as mean ± SD.

**Table 2.** Comparison of Presence of Potential Risk Factors for Agitation Between Agitated and Nonagitated Groups.

<table>
<thead>
<tr>
<th></th>
<th>Agitated, ( N = 33 )</th>
<th>Nonagitated, ( N = 47 )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delirium at admission (%)</td>
<td>24</td>
<td>6</td>
<td>.04</td>
</tr>
<tr>
<td>Delirium at any time during LTACH (%)</td>
<td>85</td>
<td>36</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Delirium present ( \geq 4 ) consecutive days (%)</td>
<td>33</td>
<td>4</td>
<td>.001</td>
</tr>
<tr>
<td>Infection on LTACH admission (%)</td>
<td>18</td>
<td>21</td>
<td>1.00</td>
</tr>
<tr>
<td>Infection at any time during LTACH (%)</td>
<td>27</td>
<td>26</td>
<td>.92</td>
</tr>
<tr>
<td>Discontinuation of scheduled benzodiazepine use ( \geq 7 ) days of use (%)</td>
<td>55</td>
<td>28</td>
<td>.02</td>
</tr>
<tr>
<td>Use of high-dose corticosteroid therapy (%)(^a)</td>
<td>12</td>
<td>21</td>
<td>.45</td>
</tr>
<tr>
<td>Use of metoclopramide (%)(^a)</td>
<td>18</td>
<td>23</td>
<td>.78</td>
</tr>
<tr>
<td>Use of diphenhydramine (%)(^a)</td>
<td>9</td>
<td>17</td>
<td>.34</td>
</tr>
</tbody>
</table>

Abbreviation: LTACH, long-term acute care hospital.

\(^{a}\) During period of LTACH admission.

**Table 3.** Comparison of Use of Potential Agitation Treatment Strategies Between Agitated and Nonagitated Groups.\(^{a}\)

<table>
<thead>
<tr>
<th></th>
<th>Agitated, ( N = 33 )</th>
<th>Nonagitated, ( N = 47 )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultation by a psychiatrist (%)</td>
<td>39</td>
<td>38</td>
<td>.90</td>
</tr>
<tr>
<td>Scheduled antipsychotic therapy (%)</td>
<td>61</td>
<td>21</td>
<td>(&lt; .0005)</td>
</tr>
<tr>
<td><em>As-needed</em> antipsychotic therapy (%)</td>
<td>36</td>
<td>15</td>
<td>.03</td>
</tr>
<tr>
<td>Scheduled benzodiazepine therapy (%)</td>
<td>38</td>
<td>55</td>
<td>.16</td>
</tr>
<tr>
<td>Scheduled opioid therapy (%)</td>
<td>18</td>
<td>34</td>
<td>.11</td>
</tr>
<tr>
<td>1:1 patient supervision (%)(^b)</td>
<td>27</td>
<td>23</td>
<td>.70</td>
</tr>
<tr>
<td>Restraint use (%)</td>
<td>58</td>
<td>21</td>
<td>.002</td>
</tr>
</tbody>
</table>

Abbreviation: LTACH, long-term acute care hospital.

\(^{a}\) Use for \( \geq 24 \) hours at any time during LTACH admission.

\(^{b}\) Also known as bedside sitter use.
suspected to be caused by an underlying psychiatric or neurologic condition, it is surprising that the patients with agitation in our study were just as likely to be evaluated by a psychiatrist as those who did not have agitation. This is particularly interesting, given that the agitated patients had 4 times the incidence of delirium at admission and more than twice the incidence of delirium over the course of their LTACH stay. Depression and anxiety are seen in patients with chronic critical illness, and psychiatric evaluations may assist in the management of weaning from PMV.21

Although hypoactive (ie, not accompanied by agitation) delirium may occur in patients admitted to the ICU, more recent evidence suggests that delirium occurring in the ICU is mixed (ie, both hypoactive and hyperactive) and that symptoms of agitation will appear in more than 90% of patients over the course of the delirium episode.11,12,31,34 The fact that the proportion of patients who had delirium for at least 4 days was more than 8 times greater in the agitated group suggests a link between delirium and agitation. The frequent use of quetiapine for the treatment of agitated delirium is noteworthy, given that there is only one small randomized trial to support its use in ICU patients with delirium, but among the different symptoms of delirium that may be present, agitation has been shown to be the symptom of delirium that resolves the slowest with quetiapine use.35,36 The use of scheduled antipsychotic therapy in patients with agitation, even when delirium was present, is concerning, given the lack of large controlled studies demonstrating antipsychotic efficacy or safety for the prevention or treatment of agitation or delirium in either the ICU or LTACH setting.37 The safety concerns of antipsychotic therapy are well known and are increased in the elderly patients and those patients with critical illness.38

Pain and discomfort are the most common causes of agitation in critically ill populations.1,2,8 Hence, it is noteworthy that the use of scheduled opioid therapy was nearly 50% lower among the agitated group.1,8 It may be possible that the greater use of analgesic therapy in the nonagitated group may have prevented agitation in this group. Given the role of pain as a cause for agitation in the critically ill and the sedative properties of opioids, the fact opioids were only used on 20% of the agitated days is surprising. The fact that antipsychotics were administered 3 times more frequently than opioids and twice as often as benzodiazepines is surprising, given a recent controlled

Figure 1. Frequency of use of different agitation management strategies at the time of first agitated episode among patients who developed agitation.

Table 4. Comparison of Clinical and Economic Outcomes Between Agitated and Nonagitated Groups.a

<table>
<thead>
<tr>
<th></th>
<th>Agitated, N = 33</th>
<th>Nonagitated, N = 47</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient falls (%)</td>
<td>3</td>
<td>11</td>
<td>.39</td>
</tr>
<tr>
<td>Successful wean from PMV (%)</td>
<td>48</td>
<td>55</td>
<td>.60</td>
</tr>
<tr>
<td>Successful decannulation (%)</td>
<td>42</td>
<td>38</td>
<td>.70</td>
</tr>
<tr>
<td>Unplanned transfer back to acute care hospital (%)</td>
<td>55</td>
<td>51</td>
<td>.82</td>
</tr>
<tr>
<td>LTACH stay (days)</td>
<td>36 (21-62)</td>
<td>33 (15-62)</td>
<td>.66</td>
</tr>
<tr>
<td>Patient disposition (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute care hospital</td>
<td>55</td>
<td>70</td>
<td>.65</td>
</tr>
<tr>
<td>SNF/extended care</td>
<td>18</td>
<td>27</td>
<td>1.0</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>6</td>
<td>2</td>
<td>0.60</td>
</tr>
<tr>
<td>Daily cost of care (US $1000)</td>
<td>2.7 (2.4-3.0)</td>
<td>3.0 (2.7-3.3)</td>
<td>.07</td>
</tr>
</tbody>
</table>

Abbreviations: LTACH, long-term acute care hospital; PMV, prolonged mechanical ventilation; SNF, skilled nursing facility; IQR, interquartile range. a Data presented as median (IQR) unless otherwise indicated.
studies demonstrating the advantages of an analgosedation approach to sedation in the ICU.39

It remains unclear why the presence of agitation, particularly when it was frequently accompanied by delirium, did not hinder mechanical ventilation liberation or prolong the time to LTACH discharge. Uncontrolled agitation would be expected to truncate weaning attempts and delirium is associated with a longer duration of mechanical ventilation and hospital stay.21,40 Although weaning success, sitter use, and duration of LTACH stay were nearly identical between the agitated and nonagitated groups, it remains unclear why there was a trend for the average daily costs of care to be lower in the agitated group than nonagitated group.

Although our data did not demonstrate an increase in mortality in the agitated group, agitation has shown to be an independent marker of mortality in the critically ill.34 Delirium was more frequent and more persistent in the agitated group. Multiple studies have now demonstrated that duration of delirium is an independent predictor of hospital mortality.31,43

Our analysis has a number of potential limitations. The retrospective design limits the accuracy of the chart review. Although we used multiple key words to identify agitation in our study cohort, it may be possible that patients had agitation that was not documented in the patient record using one of these terms or was not documented in the patient record at all. It is also possible that patients had periods of agitation that was not detected by their nurse, given the higher patient–nurse ratio that exists in the LTACH setting compared to that in an ICU. Although we used a validated, chart-based method to identify delirium that has been valid for use in mechanically ventilated ICU patients, this strategy is not a replacement for a bedside evaluation of delirium with a validated screening tool and may have missed delirium in some patients if the symptoms associated with delirium were not documented in the patient record.

A number of potential risk factors (eg, sleep abnormalities) and treatments for agitation (eg, patient reassurance, chances to the patient environment) were deemed to be very unlikely to be documented in the patient record and thus were not collected as part of our analysis. Due to the size of our cohort, we did not attempt to conduct a multivariate analysis of the agitation risk factors that were identified in the analysis, given the high likelihood that model overfitting would occur. Although data were extracted by 2 trained reviewers and all reviewer differences were resolved by consensus, we did not formally measure the agreement between the 2 abstractors. Finally, the results of our analysis reflect the practices at only 1 LTACH and may not represent the practices at other LTACHs, where formal protocols for the treatment of agitation are in place or the threshold for caregiver use of agitation treatment strategies such as antipsychotic or restraint therapy may be different.

The result of our study highlights a number of potential strategies that might be used in the LTACH setting to recognize, prevent, and treat agitation in patients undergoing PMV. Patients’ level of both sedation and agitation should be regularly evaluated using a validated ICU sedation instrument.1,8,13 When agitation is detected, clinicians should carefully evaluate patients for an underlying cause that includes pain, delirium, anxiety, a new infection, or medication initiation or withdrawal. Pain should be regularly evaluated using a nonverbal assessment tool when necessary, and when present treated.14 Patients should be evaluated at least once a day for the presence of delirium using a validated ICU delirium screening tool.11,12 In patients who have delirium and are agitated, a trial of antipsychotic therapy may be warranted if other causes for agitation are not apparent.1,8 However, given the current lack of evidence to support this strategy in the LTACH setting and safety concerns with prolonged use, the lowest effective dose should always be used and the need for continued therapy regularly reevaluated.37,38 Psychiatric consultation should be sought in cases where an etiology for agitation is not apparent.

This study highlights an opportunity to improve both the prevention and the treatment of agitation in the LTACH setting. Evidence-based strategies focused on the prevention, diagnosis, and treatment of both agitation and delirium will likely improve outcomes in patients undergoing PMV.

Acknowledgments

The authors acknowledge the efforts of Aura Neidhardt and Mark Albizati toward the completion of this study.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References


