Epidemiology of Psychiatric Medication Use in Patients Recovering From Critical Illness at a Long-term Acute-Care Facility*

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Study objectives: To describe the pharmacoepidemiology of psychotropic medication prescription in patients recovering from life-threatening medical and surgical illness.

Design: Retrospective analysis of a random sample of medical records.

Setting: Regional referral center.

Patients: Eighty-nine randomly selected patients transferred from an ICU to the study facility.

Interventions: None.

Measurements and results: Patients had been treated at the referring ICU for 33 ± 24 days (mean ± SD) and remained at the study hospital for 64 ± 52 days. Most of the patients had prolonged respiratory failure. Nearly half of the patients (47%) received an antidepressant medication while at the facility, and 48% received at least one dose of a benzodiazepine on the first day after transfer. In the sample of 75 patients not prescribed an antidepressant before transfer, 37% were started on therapy with an agent, usually within 3 weeks and predominantly in the selective serotonin reuptake inhibitor or psychostimulant class. Younger patients and those evaluated by a mental health specialist were more likely to be prescribed an antidepressant, compared to other patients. Forty percent of patients were still receiving at least one dose of a benzodiazepine in a 24-h period after their third week at the facility.

Conclusion: Although the efficacy of antidepressant pharmacotherapy in patients with comparable severity of medical illness has not been established, a substantial proportion of patients recovering from critical illness at a specialized facility are prescribed antidepressant medications. Benzodiazepine exposure is frequent after transfer, and the prevalence in patients who remain at the facility minimally decreases over time.

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Key words: antidepressants; benzodiazepines; critical illness; mechanical ventilation; pharmacoepidemiology

Abbreviation: CI = confidence interval

Advances in life-support technology have created a growing patient population best described as the chronically critically ill. These persons have survived catastrophic acute illness but remain dependent on technologies such as mechanical ventilation, hemodialysis, or nutritional support. Such patients are often transferred to long-term acute-care facilities specifically staffed and equipped for weaning patients from ventilatory support and comprehensive rehabilitation.1

Investigation of depression in the medically ill (although less severely ill than post-ICU patients) has led to several conclusions: The prevalence of major depressive disorder is 10 to 20% (depending on the diagnostic strategy) in medically hospitalized patients and is associated with the severity of medical illness only in elderly patients2,3; depression magnifies bodily symptoms and increases disability4; approximately half of all depressed patients are evaluated solely by nonpsychiatric primary-care physicians5; and selective serotonin reuptake inhibitor antidepressants are effective and safe in patients with medical comorbidities (although they are not more effective than older tricyclic medications).6–8 Whether treatment of depression reduces global

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medical resource utilization, thereby creating a medical cost-offset, remains an unproven hypothesis under current investigation.9,10 Investigations of the psychological outcomes of patients surviving a prolonged ICU stay are disadvantaged by the difficulties in interpreting the somatic signs and symptoms that are common in post-ICU patients, disentangling the adverse effects of medications, and overcoming the communication barriers of patients receiving mechanical ventilation. Conclusions from studies of post-ICU patients have limited by small samples, lengthy follow-up intervals, and the use of depression scales designed as screening instruments or for patient populations with less medical comorbidity.11–13 At the present time, there are insufficient data that clearly support one diagnostic and treatment strategy for depression over another in chronically critically ill patients. Therefore, I reasoned that if a common condition such as major depression presents diagnostic difficulties in very ill medical patients yet can be effectively treated with well-tolerated and safe medications, then a medical facility that treats severely ill patients would have a high prevalence of antidepressant prescription.

This study had two objectives. The first objective was to describe the pharmacoepidemiology of antidepressant medication in a sample of patients recovering from critical illness at a regional long-term acute-care facility. The hypothesis was that medication use would be substantially higher than in previous reports examining medical inpatients and that the majority of the antidepressant prescriptions would be in the selective serotonin reuptake inhibitor class. The second objective was to describe the pattern of weaning from benzodiazepine medications. These medications are widely used in ICUs,14 and both long-term use and abrupt tapering could cause signs and symptoms also present in depressive disorders. I hypothesized that exposure to benzodiazepines early after transfer to the long-term facility would be associated with subsequent antidepressant prescription.

**Materials and Methods**

The design was a retrospective cohort study of randomly selected patient admissions to a long-term acute-care hospital (Vencor Hospital, Minneapolis, MN). The facility has a census of approximately 50 patients and is staffed predominantly by internal medicine physicians with subspecialty training in pulmonary or renal disease.

Random sampling of medical records from 1995 through 1998 was performed by matching consecutive three-digit numbers from a random number table to the last three digits of completed records. Matched charts were reviewed for study eligibility that included patients who had been transferred directly from an ICU to the study hospital after suffering acute illness requiring ICU care for at least 1 week. To minimize abstracting bias, predictor variables were abstracted before the outcome variable of antidepressant prescription.

**Definitions**

Hospital admission mental status was determined by reviewing admission notes from physicians, nurses, and rehabilitation specialists during the first 24 h after transfer. Patients were placed in one of four categories: alert (alert, follows commands easily); confused (awake but confused or not oriented); stupor (decreased level of consciousness but some response to commands or some purposeful movement); coma (unresponsive, minimal or no purposeful movement). If there was a discrepancy between caregivers’ assessments, then the subject was placed in the higher functioning category.

Medical comorbidities or organ failures were defined as follows: respiratory failure (patients transferred while receiving mechanical ventilation); cardiac disease (occurrence of atrial fibrillation or other arrhythmias requiring medication during ICU course, cardiac ejection fraction < 40%, diagnosis of cardiogenic pulmonary edema, myocardial infarction, unstable angina, or coronary artery bypass graft surgery); neurologic disease (occurrence of stroke, neurosurgical procedure on the CNS, traumatic brain or spinal cord injury causing residual deficits, presence of neuromuscular disease that contributes to patient’s illness such as respiratory failure from muscular dystrophy or neuropathy of critical illness, or diagnosis of anoxic or metabolic encephalopathy); diabetes (diagnosis of diabetes on hospital admission or progress notes, or use of insulin or oral glucose-lowering medications); renal failure (serum creatinine > 2 mg/dL at transfer or receiving dialysis therapy); cancer (residual malignancy after treatment or recently diagnosed malignancy not receiving treatment); immunosuppressed (all organ transplant recipients, or patients who received chemotherapy within the previous 2 months or were receiving the equivalent of 60 mg/d of prednisone or more at transfer); and liver disease (serum bilirubin > 3 mg/dL at transfer or a physician’s note documenting symptomatic cirrhosis).

**Medications**

Subjects were categorized as receiving an antidepressant at the time of admission to the study facility if an antidepressant was listed on the medication transfer orders from the transferring hospital or on the initial admitting orders at the study hospital. Prescription of an antidepressant at the study facility was defined as the date of administration documented in the medication administration record. Medications considered as antidepressants for this study included amitriptyline, desipramine, doxepin, imipramine, nortriptyline, phenelzine, trazodone, sertraline, fluoxetine, paroxetine, and methylphenidate.

Cumulative incidence of antidepressant exposure was defined as the number of subjects receiving a new antidepressant medication divided by the number of subjects transferred without an antidepressant prescription. Incidence density was defined as the number of subjects receiving a new antidepressant medication divided by the number of person-months “at-risk” for receiving an antidepressant.

Benzodiazepines included diazepam, lorazepam, midazolam, temazepam, alprazolam, and clonazepam. Benzodiazepine doses were abstracted from the medication administration record, included both scheduled and as-needed doses, and were standardized to “lorazepam equivalents” using a conversion factor of lorazepam, 1 mg, being equal to midazolam, 3 mg; diazepam, 5

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mg; alprazolam, 0.5 mg; and clonazepam, 0.5 mg.15,16 Doses were also recorded for 24-h intervals at 1, 2, 3, 4, 6, and 8 weeks after the first day at the study facility.

A mental health consultation occurred when a psychiatrist or psychologist examined the patient to determine whether a mood disorder was present or to assist in pharmacotherapy or psychotherapy. Consultations obtained for neuropsychological testing were not considered mental health evaluations.

The study was approved by the University of Minnesota Research Subjects’ Protection Program and Vencor Hospital, Minneapolis. Informed consent was waived for this study of discharged patient records.

Statistics

Ninety-five percent confidence intervals (CIs) were calculated to estimate proportions. Comparisons were made between groups using two-tailed unpaired t tests or Fisher’s Exact Test. The null hypothesis was rejected at p < 0.05. Predictors of antidepressant prescription were screened with a series of logistic regression models with a single independent variable (SAS version 6.11; SAS Institute; Cary, NC). Variables with both statistical significance and clinical relevance were then entered into a multivariate model to assess confounding and improvement in model fit. Model discrimination was assessed with the C statistic, which is equivalent to the area under the receiver operating characteristic curve (range, 0 to 1). A model with C = 0.5 predicts a dichotomous outcome no better than chance. With an expected proportion of incident antidepressant prescription of 0.25, a sample size of 73 subjects can estimate the 95% CI to 0.25 ± 0.1.

RESULTS

Two hundred thirty-five records were randomly selected from 989 admissions to the facility from 1995 through 1998. Eighty-nine charts were eligible for abstraction. Ineligible charts (subjects not transferred directly from an ICU to the study facility or with an ICU stay of < 1 week) included patients with acute and chronic neurologic disorders, complicated surgical wounds and decubitus ulcers, orthopedic conditions, and long-term dialysis patients with medical illnesses. The sample was 57% male, with a mean age of 63 ± 13 years (mean ± SD). These patients had survived severe illness, with a mean stay of 33 ± 24 days in the transferring ICU, a mean stay at the study hospital of 64 ± 52 days, and a case fatality rate (at the study facility) of 24% (95% CI, 15 to 33%).

Table 1 shows that cardiopulmonary and neurologic comorbidities were present in a large proportion of patients at the time of transfer. The median number of comorbidities was two. Ninety-four percent of patients required mechanical ventilatory support. An abnormal mental status was common on transfer; only half of the patients were in the alert category on the first day of transfer.

Table 1—Comorbidities, Organ Failures, and Hospital Admission Mental Status for 89 Subjects*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Subjects With Comorbidity, % (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comorbidity</td>
<td></td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>94 (84)</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>51 (45)</td>
</tr>
<tr>
<td>Neurologic disease</td>
<td>42 (37)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>34 (30)</td>
</tr>
<tr>
<td>Renal</td>
<td>11 (10)</td>
</tr>
<tr>
<td>Cancer</td>
<td>10 (9)</td>
</tr>
<tr>
<td>Immunosuppressed</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Admission mental status</td>
<td></td>
</tr>
<tr>
<td>Alert</td>
<td>52 (46)</td>
</tr>
<tr>
<td>Confused</td>
<td>21 (19)</td>
</tr>
<tr>
<td>Stupor</td>
<td>17 (15)</td>
</tr>
<tr>
<td>Coma</td>
<td>10 (9)</td>
</tr>
</tbody>
</table>

*Patients could have more than one comorbidity or organ failure but are categorized into a single mental status class.

Psychoactive Medication Use

Before the ICU admission, 22% of patients had been prescribed a psychoactive medication, predominantly in an antidepressant or antipsychotic class. Sixteen percent of the patients (14 of 89) were receiving an antidepressant at transfer to the study facility. On the first day of the study hospital stay, 61% of patients (54 of 89; 95% CI, 51 to 71%) had an antidepressant or benzodiazepine medication ordered as a scheduled or as-needed dose. Forty-three patients actually received at least one benzodiazepine dose, and 17 patients (40%) received ≥ 3 mg of lorazepam equivalents. A substantial proportion of patients continued to receive at least one dose of a benzodiazepine during a 24-h period surveyed at weekly intervals after hospital admission: first week, 47.6% (40 of 84 patients); second week, 35.8% (29 of 81 patients); third week, 40.2% (29 of 72 patients); fourth week, 36.1% (22 of 61 patients); sixth week, 45.5% (25 of 55 patients); eighth week, 38.3% (18 of 47 patients).

The prevalence of antidepressant prescription was 47% (42 of 89 patients; 95% CI, 37 to 57%). Seventeen patients received two antidepressant agents for a total of 59 prescriptions. Excluding those patients receiving an antidepressant at the time of transfer (n = 14), the cumulative incidence of antidepressant prescription was 37% (28 of 75 patients; 95% CI, 26 to 48%) and the incidence density was 29 prescriptions per 100 person-months. Figure 1 shows that the distribution of antidepressants in patients already receiving these medications at the time of transfer differs from the group started on pharmacotherapy at the study facility. Prescriptions for methylphenidate and selective serotonin re-
uptake inhibitors (especially sertraline) comprised a greater proportion of all new prescriptions, whereas treatment with antidepressants in the tricyclic class was started infrequently. Three patients received methylphenidate as monotherapy; nine other patients received methylphenidate in combination with a selective serotonin reuptake inhibitor antidepressant.

A histogram (Fig 2) shows the time distribution from hospital admission to initiation of antidepressant therapy. The majority of new prescriptions occurred within the first 3 weeks after transfer, although some prescriptions commenced >2 months after transfer. Of the 42 new prescriptions administered to 28 individuals, 18 prescriptions (42%; 95% CI, 27 to 57%) were discontinued. Because of the retrospective nature of the study, one cannot determine whether treatment cessation was due to lack of desired effect, adverse effects, development of a medical contraindication, or other reasons.

Predictors of Antidepressant Therapy

The next analysis was to determine which variables available early in the hospital stay were associated with subsequent antidepressant prescription (28 “events” in 75 patients).
The mean age of those prescribed an antidepressant was 59.5 years, compared to 66.5 years for subjects not receiving a prescription ($t = 2.04$, $p = 0.05$). Dividing the age distribution by quartiles shows a similar trend: 61% of subjects in the youngest quartile (mean age, 49 ± 8.2 years) were prescribed antidepressants; 33% in the next quartile (mean age, 61 ± 2.6 years); 30% in the next oldest quartile (mean age, 70 ± 2.6 years); and 26% in the oldest quartile (mean age, 78 ± 3.2 years). In a logistic regression analysis (youngest quartile compared to the other three quartiles), the youngest patients were more likely to receive an antidepressant relative to older patients (odds ratio, 3.7; 95% CI, 1.2 to 11.2; $p = 0.02$).

Patients in the coma category were also more likely to receive an antidepressant relative to the other mental status categories; however, this association had borderline statistical significance (odds ratio, 4.0; 95% CI, 0.91 to 17.5; $p = 0.07$). The proportions receiving an antidepressant by hospital admission mental status category were as follows: alert (12 of 38 patients; 32%); confused (6 of 17 patients; 35%); stupor (4 of 11 patients; 36%); and coma (6 of 9 patients; 67%).

In a logistic model with age and mental status entered simultaneously, there was no significant confounding of the association of age and antidepressant prescription by mental status (parameter estimate for age changed by < 10%). However, the model fit was not significantly improved by the addition of the mental status variable (difference in $-2 \log$ likelihood $\chi^2$, 2.46; degree of freedom, 1; $p = 0.1$) or other clinically relevant variables, such as patient gender, length of previous ICU stay, and individual comorbidities. The C statistic for the final model with age as the single predictor variable was 0.62, suggesting that age can only weakly predict subsequent antidepressant prescription.

The data did not support the second study hypothesis: there was no association between exposure to a benzodiazepine on the first day and subsequent antidepressant prescription ($p = 0.47$). There was a similar lack of association between sustained benzodiazepine exposure (at 1 month) and new antidepressant prescription at any point during the hospital stay.

Consultation by a mental health specialist was associated with subsequent antidepressant prescription: 70% (7 of 10 patients) of those seen by a mental health specialist received an antidepressant, whereas 31% (19 of 61 patients) of those not receiving a consultation received an antidepressant (relative risk, 2.3; 95% CI, 1.1 to 4.6; $p = 0.02$). Mental health consultation was not used in predictive models because consultations occurred in close proximity to the initiation of antidepressant therapy.

**Discussion**

Patients recovering from critical illness must overcome both physical and psychological challenges if they are to return to an acceptable level of functioning. It is possible that major depression, adjustment, and anxiety disorders impede progress toward important goals such as weaning from mechanical ventilation; however, supportive evidence for this hypothesis is anecdotal. In this study, 37% of patients not previously receiving an antidepressant were started on pharmacotherapy usually within the first 3 weeks after transfer. This proportion is substantially higher than other reports that have examined inpatient antidepressant pharmacoepidemiology. Callies and Popkin reported that the prevalence of antidepressant use on adult nonschizophrenic wards was 1.5%, whereas Koenig et al reported that the incidence of antidepressant prescription in depressed medical inpatients (diagnosed by structured psychiatric interview) was 13%. Initiation of tricyclic antidepressant therapy was uncommon; this transition from older antidepressants to the safer and better-tolerated selective serotonin reuptake inhibitors parallels the change in antidepressant pharmacotherapy in population-based studies.

Methylphenidate was frequently used, although often in combination therapy with a selective serotonin reuptake inhibitor. In patients with stroke or traumatic brain injury, methylphenidate was associated with a modest clinical benefit. Preliminary studies using methylphenidate alone or in combination with antidepressants in samples of complicated medical patients have suffered from uncontrolled study designs or very small sample sizes.

This study cannot determine the reasons for the frequent use of antidepressants in this sample. Possible causes include the following: (1) internal medicine physicians are aware of the decreased adverse effect profile of the newer antidepressants, which may decrease their threshold for initiating pharmacotherapy; (2) there is an appreciation of the deleterious effects of untreated depression in medical patients, and physicians believe that pharmacotherapy is effective; (3) depression in patients recovering from severe illness is common; (4) depression is misdiagnosed when patients’ symptoms are due to delirium, abstinence syndromes, or wholly the result of prolonged medical illness; and (5) a rehabilitation environment encourages identification of psychosocial problems and attracts physicians and other caregivers who are sensitive to the behavioral
aspects of medical care. The study design did not permit examination of the patients to determine a psychiatric diagnosis and the appropriateness of treatment. In addition, the indications for initiating pharmacotherapy were not clearly documented in all records. However, progress notes in proximity to the time of a new prescription indicated that neuropathic pain or sedative-hypnotic indications were rare in this patient sample.

The data did not support the hypothesis that early exposure to benzodiazepines is associated with subsequent antidepressant prescription. Possible explanations include the following: (1) the doses of benzodiazepines that patients were receiving had little effect on mood or level of consciousness, possibly due to the development of tolerance during the previous ICU course; (2) benzodiazepine exposure may have changed by the second or third week when treatment with many antidepressants was initiated; (3) caregivers initiated antidepressant therapy in response to behavioral signs and symptoms unaffected by benzodiazepines; and (4) benzodiazepines ameliorated depressive symptoms, making it less likely that the patient received a subsequent antidepressant.

Younger patients were more likely to receive an antidepressant prescription relative to older patients, and there was no statistical evidence of confounding by mental status. However, the number of patients in the coma category was small, and methylphenidate has been used as a component of a coma-stimulation program at the facility. Therefore, the association between age and antidepressant use may be partially explained by the use of methylphenidate in patients with severe structural or anoxic encephalopathy. In addition, mental status was measured only on hospital admission, and substantial changes may have occurred by the time the decision to start antidepressant therapy was made. The study design did not permit reliable measurement of variables such as the occurrence and severity of depressive symptoms or quantify physicians’ beliefs about the efficacy of antidepressants in medically ill patients. The absence of these likely important variables explains how age is statistically associated with the dependent variable but in a univariate model only weakly predicts subsequent antidepressant prescription.

Nearly half of the patients transferred to the study hospital received a benzodiazepine on the first day, and this proportion (for subjects remaining at the facility) only slightly decreased to 35% by the eighth week. Abrupt decreases in benzodiazepine therapy can induce abstinence syndromes in patients who required deep sedation with benzodiazepines while critically ill.24 However, clinicians must balance the benefits of a prolonged tapering of benzodiazepine therapy with the adverse hypnotic and amnestic effects of the medication that may impede rehabilitation.

The primary finding of this study is that despite serious medical comorbidity and the uncertainties in delineating depressive disorders from other conditions, medical subspecialists initiate antidepressant pharmacotherapy in a markedly higher proportion of patients compared to previous studies.18,19 It is unknown whether this intervention has improved mental health outcomes or accelerated weaning from mechanical ventilation. The efficacy and safety of these medications have not been established in patients with comparable levels of medical illness. Additional research is necessary to determine whether reliable psychiatric diagnoses can be made in cohorts of severely ill patients, and controlled trials should be conducted to evaluate the efficacy and safety of antidepressants in this growing patient population. Further research is needed to discover predictors of depressive disorders in patients recovering from critical illness. It is possible that specific exposures or events that occur in the preceding ICU environment could be modified to reduce the risk of developing depressive symptoms.

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