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Utilization of Low Dose Depakote for the Treatment of Delirium in Hospitalized Adults: A Retrospective Analysis of Depakote Treatment Protocol

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Abstract

Objective: The primary aim of this study was to evaluate the safety and efficacy of a low-dose Depakote protocol for the treatment of delirium in hospitalized adult patients.

Methods: Participants were selected through a retrospective chart review for 24 months pre- and post- intervention. Demographic variables were compared using univariate statistics. The primary outcome was patient's length of stay (LOS), compared using a Mann-Whitney-U test. The three other outcomes of antipsychotic administration, benzodiazepine administration, and incidence of injury were measured using separate Fisher's exact tests. Mann Whitney-U tests were conducted to compare antipsychotic and benzodiazepine dose administration using haloperidol and lorazepam equivalents. Incidence and severity of adverse effects were analyzed using descriptive statistics for patients administered the Depakote protocol. IBM SPSS version 27 was used to conduct the statistical analysis with αset to .05.

Results: The retrospective analysis evaluated 102 patient records. There were no significant differences in age, sex, or admission diagnosis classification. The hospital length of stay showed no statistically significant difference between-groups (median non-Depakote 7.5, median Depakote 7.0, z= -.188, p= .881). However, there was a difference in antipsychotic medication usage between two groups. Antipsychotic use was measured in haloperidol equivalents, while benzodiazepine use was measured in lorazepam equivalents. Antipsychotic utilization decreased significantly from 92.3% (non-Depakote group) to 42% (Depakote group) (p<.001). Similarly, benzodiazepine utilization also decreased significantly from 57.7% (non-Depakote group) to 6% (Depakote group) (p<.001). Median total antipsychotic dosage also decreased significantly from 14.5mg (non-Depakote group)

to 2.5mg (Depakote group) (z= -4.987, p<.001). The median total benzodiazepine dosage did not change significantly (median non-Depakote 2mg, median Depakote 1mg, z=-1.409, p=.159). The mean time to Depakote initiation was 4.14 days. There was a reduction in the occurrence of delirium-related injury or complication from 7.7% (non-Depakote group) to 2% (Depakote group) though this was not statistically significant (p=.363).

Conclusion: Ultimately, the results of this study establish that Depakote is a safe and effective treatment or adjunct treatment for delirium in delirium hospitalized adults.

Introduction

Delirium remains a pervasive complication in hospitalized adult patients. Delirium is a neuropsychiatric condition that has extensive impacts on patient outcomes, including prolonged length of hospitalization, increased healthcare utilization, increased morbidity and mortality, propensity for patients and healthcare providers injury or further complications, increased length of mechanical ventilation, long term cognitive and functional impairment, increased long-term care placement, and increased healthcare expenditures [1]. Delirium, defined as an acute, fluctuating neurological syndrome of altered attention, awareness, and cognition precipitated by an underlying condition or event [2]. Delirium has numerous synonyms describing the condition including acute confusional state, "sun downing," encephalopathy, and acute organic brain injury [1]. A common complication among hospitalized adults, especially geriatric populations, delirium etiology is often multifactorial [1]. In 2008, healthcare expenditures in the United States related to delirium complications was estimated to be between $38 and $152 billion despite being undiagnosed in 33-66% of cases [1]. Delirium occurs in up to 25% of the total hospitalized population, 50% of surgical patients, 20 % of nursing home patients, and 75-77% of ICU patients. Of note, delirium affects nearly 50% of hospitalized patients with underlying dementia [3].

The underlying pathophysiology of delirium is not entirely understood through mechanisms of its pathogenesis include neuronal aging, oxygen deprivation, neuro-inflammation, oxidative stress, physiologic stress, dysfunctional cellular signaling, and alterations in secondary messenger systems, which result in dysregulation of neurotransmitters [4]. Parasympathetic hypofunction, excess dopaminergic activity, excess gamma-aminobutyric acid (GABA); and dysregulation of serotonin, histamine, and melatonin are implicated in delirium pathogenesis [4]. Despite high rates of delirium among adult patients in critical care environments, treatment guidelines or consensus on the standard treatment of delirium is limited. There are currently no Food and Drug Administration (FDA)-approved medications for the treatment or prophylaxis of delirium [4]; and there has been an international call for clinical studies evaluating delirium prevention and treatment among critically ill adults recently published [5]. Antipsychotic agents such as haloperidol and olanzapine have been the mainstay of treatment for delirium in hospitalized patients at the discretion of the ordering provider. However, there are limitations to the applicability and therapeutic benefit of antipsychotic medications.

A 2015 systematic review in the Journal of Critical Care reviewed seven studies of the effectiveness of dexmedetomidine and antipsychotics for prophylactic and therapeutic treatment of patients with delirium in ICU. Only 1 of the 7 studies concluded a statistically significant reduction in ICU length of stay [6]. Further, none of the studies included in the systematic review proved a statistically significant improvement in major clinical outcomes or mortality [6]. Dexmedetomidine is considered an effective prophylactic medication for the prevention of delirium in critically ill patients but is limited by its restricted use to intensive care units, has considerable side effects, and is only available by intravenous route [4]. Antipsychotics medications have considerable limitations to use, including broad and severe adverse effect profiles, including QTc prolongation leading to fatal arrhythmias, extrapyramidal symptoms, neuroleptic malignant syndrome, blood dyscrasias, seizures, and post-marketing reports

of rhabdomyolysis [4].

Evidence—Literature Review and Synthesis

The current body of literature to evaluate the efficacy and applicability of Depakote for the treatment of delirium establishes statistically and clinically significant improvements in patient outcomes when treated with Depakote, and reports of adverse effects associated with treatment are infrequent. A comprehensive review of the literature, including Medline via PubMed, Embase via Elsevier, CINAHL via EBSCO, and PsycINFO via EBSCO, yielded 308 collective results. The literature review resulted in nine publications consisting of two retrospective cohort studies, two retrospective descriptive analyses, three systematic reviews, one open pilot study, and one case study series. Though no blinded randomized control trials of Depakote for the treatment of delirium have been published to date, the reports of patient outcomes using Depakote protocol is promising. A retrospective cohort study (N= 53) of critically ill patients with agitated delirium were treated with Depakote and compared between day 1 of Depakote initiation and day 3 of valproate therapy observed a significant reduction in agitations, delirium, and concomitant psychoactive drug use within 48-hours of initiating therapy with valproic acid. [7]. Another study that demonstrated the efficacy and safety of valproic acid for the management of agitation and delirium in the ICU evaluated patients who were treated for a minimum of 3 days. The investigators examined the prevalence among 47 patients with delirium during valproic acid therapy for up to 7 days and additionally examined opioid use, sedative use, antipsychotic requirements, and safety outcomes. There were downward trends in both agitation (47.8% vs. 16.7%) and delirium (84.8% vs. 63.3%), respectively, and the administration of dexmedetomidine, benzodiazepines, antipsychotics, and opioids all decreased with no adverse effects [8]. At Stanford University, a retrospective chart analysis (N=15) demonstrated successful treatment of adult patients diagnosed with delirium after a psychiatrist evaluation using DSM-IV-TR criteria. The primary outcome was the resolution of delirium with secondary outcomes of valproic acid-associated adverse effects and resolution of agitation. The patients all had a significant reduction in agitation, impulsivity, restlessness, and aggression and were able to have safety restraints discontinued. Patients required less sedation medication after initiating valproic acid [9].

Another small pilot study (N=9) evaluated the efficacy of valproate as a treatment for delirium and/or aggressive behavior in patients with dementia. The effect of valproic acid on delirium or aggressive behavior was assessed using the Delirium Rating Scale (DRS) and Gottfries-Brane-Steen Scale (GBS). The DRS score decreased in 6 of the 7 participants with delirium within 14 days of treatment ($p<.05$). There was a significant improvement in GBS score indicators, including emotional lability, irritability, and restlessness; all ($p<.01$) [10].

Sher et al. (2015) [9] conducted a systematic review and rationale for applying valproic acid to treat hyperactive and mixed-type delirium based on known and theoretical pathophysiology of delirium and the pharmacological effects of valproic acid. The review concluded that valproic acid has multiple modulatory effects on neurotransmitter function, reduces neuroinflammation and oxidative stress, and alters transcription. Another literature review examined the available literature for the use of valproate, enteral clonidine, and phenobarbital for comfort and improved sedation in adult ICU patients. Though not limited to patients diagnosed with delirium, the evidence demonstrated safe and effective use of valproic acid as an adjunctive for sedation, agitation, and comfort in ICU patients with the benefit of being able to continue the oral formulation once transferred out of the ICU setting. The available literature suggests that valproic acid can be a safe and effective adjunctive therapy for sedation and agitation in adult ICU patients [11].

The current standard of care at our 189-bed community hospital is a low-dose Depakote protocol for the treatment of delirium in all acute care units (medical/surgical, surgical, stepdown, ICU, CCU) established by our psychiatry service in 2016. Patients suspected to have delirium initially receive a psychiatry consultation, ensuring diagnosis is made by the psychiatry service using DSM-V criteria. Once diagnosed with delirium, the patient begins a low-dose Depakote regimen of 125-250mg PO or IV three times daily, continued until resolution of delirium.

Project Aims

The primary aim of this project was to evaluate the efficacy of psychiatry evaluation and initiation of low-dose Depakote protocol

for the treatment of delirium in hospitalized adult patients, which has become a standard practice in our facility. Efficacy was analyzed by comparing the length of stay, antipsychotic medication administration, benzodiazepine administration, and incidence of injury through pre-and post-intervention chart review. The secondary aim was to evaluate the incidence and severity of adverse effects among patients who were treated with the Depakote treatment protocol.

Project Methods

This project was conducted at an acute care facility located in the mid-Atlantic region of the United States. This includes two intensive care units for adult patients. Participants were selected through a retrospective chart review for 24 months of Depakote intervention and 24 months of Depakote intervention . Inclusion criteria included adult patients (> 18 years) with a diagnosis of delirium determined by psychiatry consultation, metabolic

- Age: _____
- Gender (circle one): Male Female
- Length of Stay (Days) _____
- Primary admission diagnosis (Circle one): Surgical Medical
- Psychiatry Consultation: Yes___ No___
- Intervention (circle one): Depakote No-Depakote
- Day of Depakote initiation (i.e. Day 5 or day 7 of admission): _____
- Antipsychotic use before Depakote: Yes____ No____
- Total dosage in mg and drug name: Zyprexa (olanzapine)_____ Haldol (haloperidol)_____ Other:_____
- Antipsychotic use after Depakote: Yes____ No____
- Total dosage in mg and drug name: Zyprexa (olanzapine)_____ Haldol (haloperidol)_____ Other:_____
- Benzodiazepine use before Depakote: Yes____ No____
- Total dosage in mg and drug name: Ativan (lorazepam)_____ Other: _____
- Benzodiazepine use after Depakote: Yes____ No____
- Total dosage in mg and drug name: Ativan (lorazepam)_____ Other: _____
- Any documented adverse effect of Depakote? Yes____ No____
- Adverse effect (hepatotoxicity, hyperammonemia, pancreatitis, blood dyscrasias, DRESS, porphyria, etc.): _____
- Injury or Complication (Fall, urethral trauma, etc.): Yes____ No_____
- Was the injury catastrophic (prolonged stay, required surgical intervention, resulted in death or transfer, i.e., long bone fracture, intracranial hemorrhage, etc.): Yes____ No___
- Patient disposition (circle one): Home Rehab/Skilled nursing facility Deceased Transfer

Figure 1A: Chart Review Form- Post-Intervention

- Age: _____
- Gender (circle one): Male Female
- Length of Stay (Days) _____
- Primary admission diagnosis (Circle one): Surgical Medical Altered Sensorium
- Psychiatry Consultation: Yes___ No___
- Intervention (circle one): No-Depakote
- Antipsychotic use: Yes____ No____
- Total dosage in mg and drug name: Zyprexa (olanzapine)_____ Haldol (haloperidol)_____ Other: _____
- Benzodiazepine use: Yes____ No____
- Total dosage in mg and drug name: Ativan (lorazepam)_____ Other: _____
- Injury or Complication (Fall, urethral trauma, etc.): Yes____ No_____
- Was the injury catastrophic (prolonged stay, required surgical intervention, resulted in death or transfer, i.e., long bone fracture, intracranial hemorrhage, etc.): Yes____ No____
- Patient disposition (circle one): Home Rehab/Skilled nursing facility Deceased Transfer

Figure 2A: Chart Review Form-Pre-Intervention

Table 1

Demographic	Depakote (n=50)	Non-Depakote (n=52)	P-value
Mean Age (Years)	77.28	76.25	.662 (Independent Sample T-test)
Gender (Number)	Female=26, Male=24	Female=33, Male=19	.316 (Fisher's Exact test)
Primary Diagnosis Type (Medical, Surgical, Altered Sensorium)	Medical: 33 Surgical: 15 Altered Sensorium: 2	Medical: 33 Surgical: 15 Altered Sensorium: 4	.731 (Pearson Chi-Square)

Table 2

Adverse effect	**Frequency**
Dizziness	1
Hyperammonemia	2

encephalopathy, altered mental status, or confusion. Exclusion criteria included patients with identified structural diseases of the brain such as intracranial hemorrhage, acute hemorrhagic or thromboembolic cerebrovascular accident, traumatic brain injury, known childhood intellectual disability, pregnant patients, incarcerated patients, and patients who were enrolled in a clinical trial. Among patients who met inclusion criteria, demographic data were collected, including age, gender, LOS, surgical vs. medical admitting diagnosis, presence of psychiatry consultation, day of admission that Depakote was started (no specific date, ex. Depakote started on day 4 of admission), use of antipsychotics before and after Depakote initiation, use of benzodiazepines before and after Depakote initiation, adverse effects, injury, and

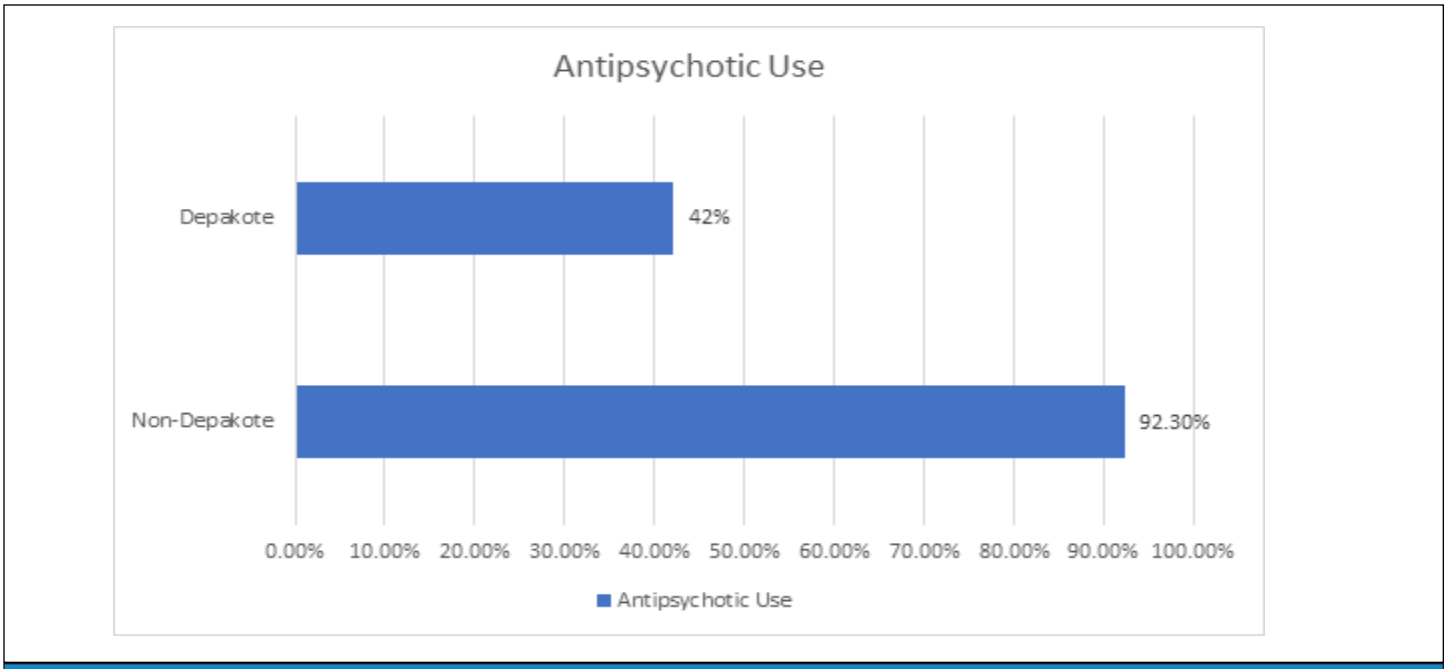

Figure 1: Antipsychotic Use

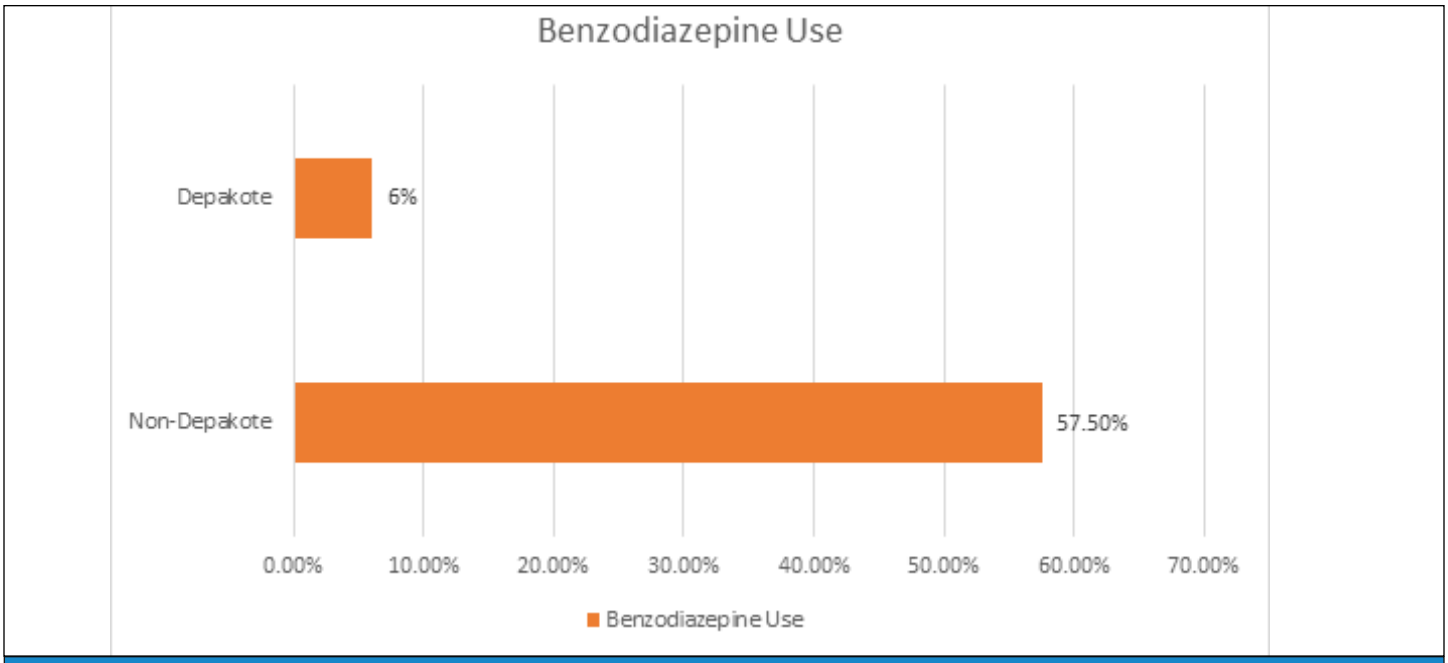

Figure 2: Benzodiazepine Use

patient disposition at the time of discharge. The chart review tools utilized for this process are attached in figure 1a and figure 2a.

Data Collection

Data were collected through a retrospective chart review utilizing the chart review forms in figures 1a and 2a. Data were analyzed using SPSS software. Chart review and data extraction were performed by the primary investigators.

Evaluation Plan

Demographic variables for pre- and post-intervention patients were compared using univariate statistics (chi-square, t-tests,

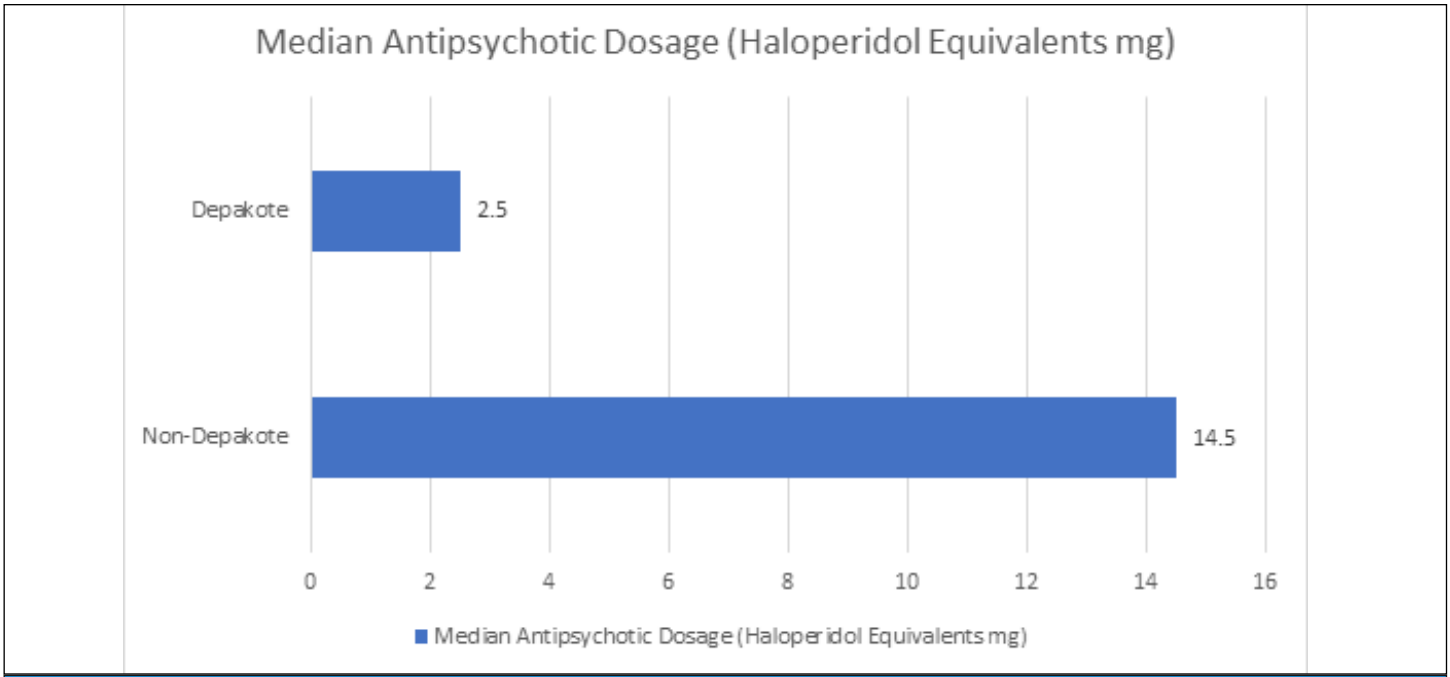

Figure 3: Median Antipsychotic Dosage (Haloperidol Equivalents mg)

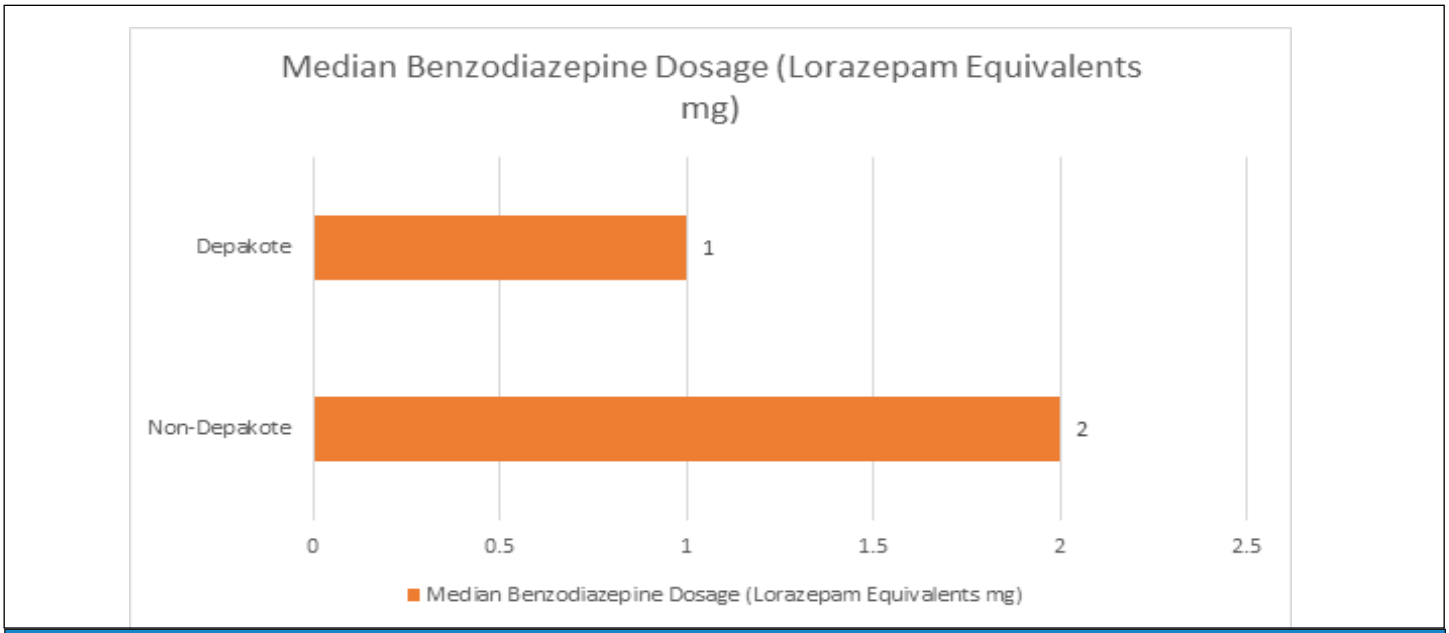

Figure 4: Median Benzodiazepine Dosage (Lorazepam Equivalents mg)

and Fisher's exact test). Four outcomes were used to measure efficacy. The primary outcome was patient length of stay (LOS), compared using a Mann- Whitney-U test as the data was not normally distributed. The three other outcomes of antipsychotic administration, benzodiazepine administration, and incidence of injury were measured using separate Fisher's exact tests. Mann- Whitney-U tests were conducted to compare pre-and post-intervention antipsychotic and benzodiazepine dose administration using haloperidol and lorazepam dose equivalents. Incidence and severity of adverse effects were analyzed using descriptive statistics for patients administered the Depakote protocol. IBM SPSS version 27 was used to conduct the statistical analysis with αset to .05. Outcome measures are supported by the core measures of the Delirium Consensus Recommendation

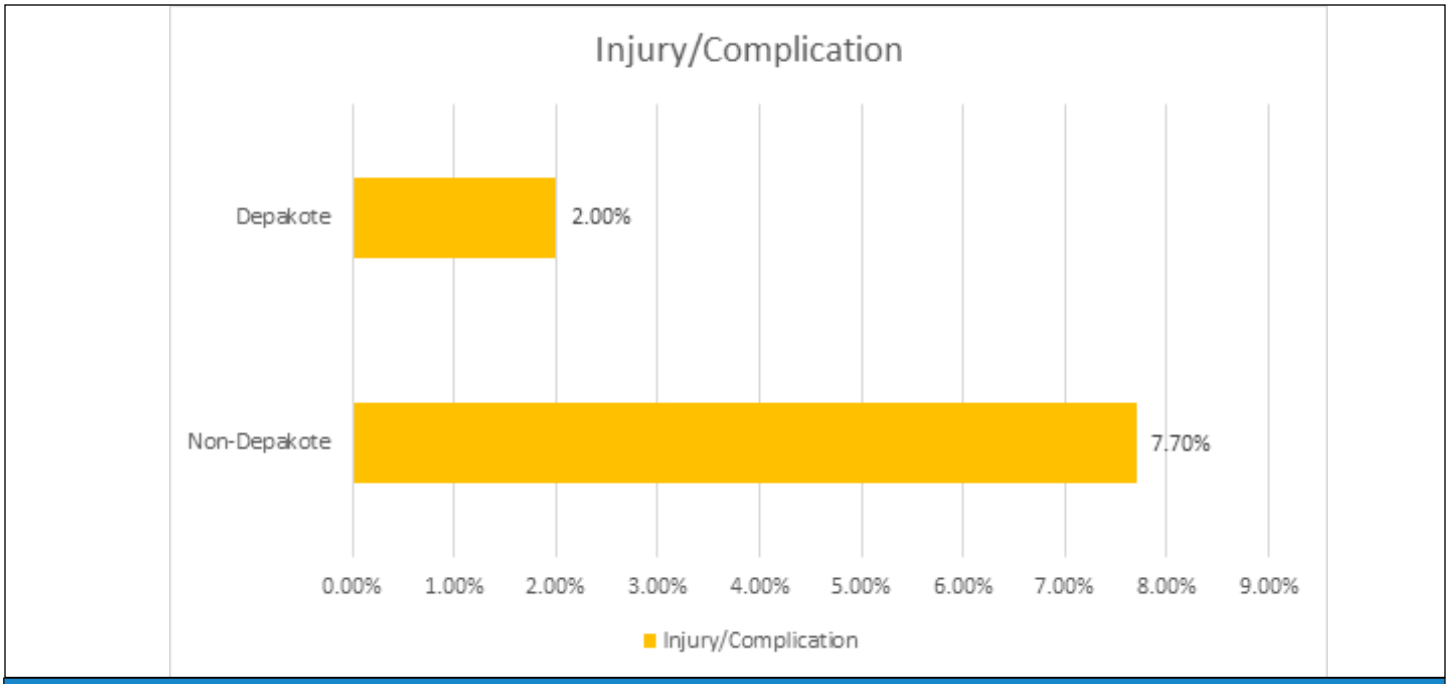

Figure 5: Injury/Complication

Model (Del-COrS), which includes seven outcomes: delirium occurrence, delirium severity, time to delirium resolution, health-related quality of life, emotional distress, cognition, and mortality [5].

Protected Health Information

No identifying protected health information was utilized in the execution of this project. Data were collected through anonymized retrospective electronic medical record chart review using inclusion/exclusion criteria. Using a standardized collection tool, the data was de-identified to include only patient age and gender, Medication Administration Records (MARs) to determine the frequency and quantity of antipsychotic and benzodiazepine use before and after the primary intervention was implemented.

Privacy, Data Storage & Confidentiality

Only project investigators had access to the data which was stored on a password-protected computer. An IRB consent waiver was obtained for the initiation of this retrospective quality improvement project. No prospective intervention or data collection was conducted.

Results

The retrospective analysis evaluated 102 patient records. The pre-intervention (non-Depakote) group included n=52 patients; 33 female, and 19 male. The post-intervention (Depakote) group included n=50 patients, 26 female and 24 males. The mean age of participants among the groups was not significantly different (Depakote=77.28, non-Depakote=76.25, p=.662). The hospital length of stay showed no statistically significant difference in the median length of stay between-groups (median non-Depakote 7.5, median Depakote 7.0, z= -.188, p= .881). However, there was a difference in antipsychotic medication usage between the groups. Antipsychotic use was measured in haloperidol equivalents, while benzodiazepine use was measured in lorazepam equivalents. Antipsychotic utilization decreased significantly from 92.3% (non-Depakote group) to 42% (Depakote group) (p<.001). Similarly, benzodiazepine utilization also decreased significantly from 57.7% (non-Depakote group) to 6% (Depakote group) (p<.001). Median total antipsychotic dosage also decreased significantly from 14.5 mg (non-Depakote group) to 2.5 mg (Depakote group) (z= -4.987, p<.001). Though the incidence of benzodiazepine administration decreased significantly in the Depakote group, the median total

benzodiazepine dosage in lorazepam equivalents did not change significantly (median non-Depakote 2mg, median Depakote 1mg, z=-1.409, p=.159).

The mean time to Depakote initiation in the intervention group was 4.14 days. There was a reduction in the occurrence of delirium-related injury or complication from 7.7% (non-Depakote group) to 2% (Depakote group) though this was not statistically significant (p=.363).

Discussion

Depakote proves to be at least non-inferior to the standard antipsychotic-based treatment of hospital-acquired delirium. Though there was no significant reduction in the primary measure of hospital length of stay, this is not entirely unexpected as hospital length of stay is influenced by numerous factors, and is not the best measure of efficacy. The median length of stay was reduced by 0.5 days from 7.5 days in the non-Depakote group to 7.0 days in the Depakote group. Secondary outcome measures prove that using a low-dose Depakote protocol to treat delirium in hospitalized patients significantly reduces the incidence and total dosage of antipsychotics administered. There was also a significant reduction in the utilization of benzodiazepines. The insignificant change in the total dose of lorazepam administered is not surprising as the standard of care dictates using the lowest possible dosage of these medications to achieve the desired effect. Ultimately, the results of this study establish that Depakote is a safe and effective treatment or adjunct treatment for delirium in hospitalized adults. Implementing similar low dose Depakote protocols in patients with delirium results in reduced demand for antipsychotics and benzodiazepines. Based on these findings, we recommend further research, including prospective blinded RCT with more sensitive and specific alternate measures to track patient progress, such as the DRS.

Reflections

The use of psychiatric referral and Depakote protocol to treat delirium among acutely ill patients as outlined in this project is sustainable. The analysis demonstrates that Depakote has a relatively benign adverse effect profile, can be administered on any hospital unit; is available in oral tabs, sprinkles, and IV formulations limiting barriers to administration; can easily be continued after discharge if indicated; does not cause sedation as many antipsychotics do; and exerts multiple deliriolytic effects, unlike standard antipsychotic treatment.

However, Depakote does have barriers to use and cannot be used in patients who have active pancreatitis or a history of cytopenias. In rare cases, Depakote has been associated with the development of hyperammonemia encephalopathy, especially when combined with antipsychotic drugs such as quetiapine, which may limit its usefulness in patients already taking some antipsychotic agents or with a history of liver diseases that would predispose them to hyperammonemia. During the data collection process, I noticed that patients often have orders for antipsychotic agents such as olanzapine and haloperidol for breakthrough agitation as needed, which adds to the difficulty of discerning the efficacy of Depakote as a mono-therapy rather than an adjuvant therapy. In other instances, patients have alcohol withdrawal delirium and are on Clinical Institute Withdrawal Assessment for Alcohol (CIWA) protocol receiving large doses of benzodiazepines in addition to Depakote. Many patients included in the data collection have prolonged hospitalizations due to complex surgical or medical complications unrelated to their delirium, which may skew the data when comparing the length of stay between the two patient groups.

In conclusion, the limitations to this quality improvement project include limited foundational data, which elicits the need for double-blinded RCT to further evaluate the efficacy and safety profile of Depakote for treatment of delirium in hospitalized patients in a controlled manner yielding high-quality data. Further, outcome measurement variables such as length of stay can be affected by confounding variables such as medical or surgical complications unrelated to the underlying delirium. Thus, additional statistical measures to account for confounding variables may be needed to improve the accuracy and validity of outcome measures. I believe this project has provided the groundwork for implementing a low-dose Depakote protocol for the treatment of delirium in hospitalized adults in other facilities but requires larger-scale RCTs to make this a national standard of care.

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