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Guanfacine for the management of the behavioral manifestations of delirium in older hospitalized adults

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Abstract

Introduction: Delirium affects nearly half of hospitalized older adults and is associated with prolonged hospitalization, dementia, and death. The behavioral manifestations of delirium are generally managed with antipsychotics, but there is growing interest in alternative medical therapy, including guanfacine.

Methods: This retrospective cohort study included patients ≥65 years of age admitted to Maine Medical Center between January 2021 and April 2023 and treated with guanfacine for delirium management on a non-ICU unit. Effectiveness outcomes included antipsychotic use and dose as well as a change in positive delirium screen after guanfacine initiation. Safety outcomes included incidence of hypotension, bradycardia, or transfer to ICU.

Results: A total of 56 patients who received at least 1 dose of guanfacine were evaluated, and 38 patients (68%) with complete data for days −1 to +2 were included in the effectiveness analysis. Before guanfacine initiation, 22/38 patients (58%) were receiving an antipsychotic medication, compared with 18/38 (47%) after guanfacine initiation ($p = 0.86$). Patients received a median (interquartile range) 6.4 (3.3 to 16) olanzapine equivalents (OE) before guanfacine was initiated and 4.2 (1.7 to 10.0) OE after guanfacine (absolute difference 2.2 OE; relative difference, 34 %; $p = 0.8$). All 56 patients were included in the safety analysis; 21 (38%) experienced hypotension, and of these, 7 (33%) patients required intervention. Twenty-three (41%) experienced bradycardia while on guanfacine, resulting in 1 patient being transferred to the ICU.

Discussion: Upon initiation of guanfacine, patients with delirium had a reduction in daily antipsychotic exposure and a decrease in positive delirium screens. However, guanfacine was associated with hypotension and bradycardia.

Keywords: delirium, guanfacine, antipsychotic agents

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Introduction

Delirium affects up to 50% of hospitalized older adults and is estimated to cost the US health care system $150 billion per year.[1,2] Delirium is associated with poor outcomes, including prolonged hospitalization, institutionalization, dementia, and death.[3-5] Agitation due to delirium is often treated with antipsychotic medications, such as haloperidol or olanzapine,[6] and guidelines consider them the medications of choice.[7] However, antipsychotics are associated with an increased risk of death from respiratory and cardiac causes.[6,8] Alternative approaches to managing the behavioral manifestations of delirium are, therefore, greatly needed.

Alpha-2 receptor agonists reduce catecholamine outflow resulting in anxiolysis and sedation.[9-12] Both clonidine and dexmedetomidine are utilized to manage agitation or hyperactivity due to delirium but are associated with hypotension and bradycardia.[13,14] Furthermore, dexmedetomidine use is often restricted to the ICU.[11] Clonidine must be administered multiple times per day at varying doses to provide sedation without hemodynamic compromise,[15] and abrupt discontinuation may be associated with rebound sympathetic phenomena.[16-18]

Guanfacine is an oral alpha-2 receptor agonist commonly used to treat attention-deficit/hyperactivity disorder. Recently, guanfacine has been used off-label for the management of irritability, impulsivity, and agitation in hospitalized older adults with dementia.[19] The mechanism by which guanfacine exerts its effects are not fully understood; however, it is thought to reduce sympathetic outflow at post-synaptic alpha-2A receptors in the dorsolateral prefrontal cortex.[19,20] Guanfacine has a much higher affinity to the alpha-2A subtype versus alpha-2B compared with clonidine.[21] This mechanism, in addition to guanfacine's activity in the locus coeruleus, is thought to result in enhanced working memory, attention, and arousal control.[21,22]

In 2021, based on a case series describing its use in delirium,[23] the inpatient geriatrics consult service at our institution began administering guanfacine to manage the behavioral manifestations of delirium in older adults in an effort to reduce or prevent the use of antipsychotics. The dosing was typically started at 0.5 mg twice daily based on the case series referenced. There was no algorithm developed at this time, and dose changes, monitoring, and discontinuation of guanfacine was at the discretion of the provider. The objective of this study was to estimate guanfacine's effect on delirium resolution, need for other psychoactive medications, and clinically relevant safety events in hospitalized older adults experiencing agitated delirium.

Methods

Study Design

This single-center retrospective cohort study included patients 65 years of age or older who received guanfacine for the management of agitation due to delirium from January 2021 to April 2023. Patients had to have a positive Confusion Assessment Method (CAM) screening and/or evidence of delirium, such as acute development of confusion, mental status change, inattention, disorientation, hallucinations, or agitation based on medical record review.[24] Patients were excluded if they were admitted to the ICU prior to or at the time of guanfacine initiation, were admitted to the inpatient psychiatric unit, were taking guanfacine prior to hospital admission, or received guanfacine for an alternative indication (eg, hypertension). This study was reviewed as exempt by the MaineHealth institutional review board, and the need for informed consent was waived.

Demographics and Clinical Characteristics

Patient demographics included age, sex, race, primary care team, admitting diagnosis, comorbid conditions, and pertinent home medications. Clinical characteristics included delirium duration, delirium mitigation, hospital length of stay, and discharge location.

Effectiveness Outcomes

Data were collected for the 3 days before guanfacine initiation (days −3, −2, and −1), the day of guanfacine initiation (day 0), and up to six days afterward (days +1 through +6). Patients were included in the effectiveness analysis if they had recorded guanfacine and antipsychotic data on days −1, 0, +1, and +2. This time frame was chosen based on prior studies assessing medications for agitated delirium,[13,25] the assumption that peak antipsychotic administration would occur the day before guanfacine initiation, and an attempt to see if guanfacine had an effect earlier than the median duration of delirium symptoms in older adults of around 7 days.[26] Change in antipsychotic medication utilization from the day before guanfacine was initiated (day -1) to two days after it was initiated (day +2) was calculated using olanzapine equivalents (OE). According to the International Consensus Study of Antipsychotic Dosing, olanzapine oral/intramuscular 1 mg = haloperidol intravenous (IV)/oral 0.5 mg = quetiapine 37 mg = risperidone oral 0.3 mg.[27] Change in the proportion of patients with delirium on day −1 and day +2 was also calculated. Delirium was identified by a positive CAM score or, in the absence of CAM screening, by a validated chart review using published criteria.[23]

Adverse Drug Effects

All patients who received at least 1 dose of guanfacine were included in the safety analysis. Hypotension was defined as a mean arterial pressure (MAP)<65 mmHg or systolic blood pressure <90 mmHg. Bradycardia was defined as a heart rate <60 beats per minute. Subsequent interventions

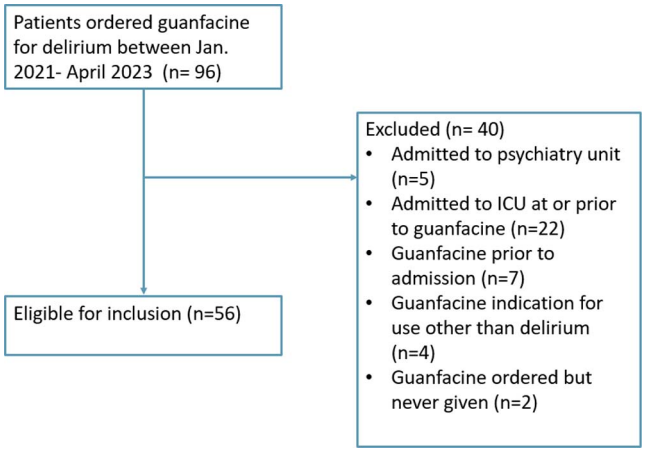

FIGURE: Study cohort and application of exclusion criteria

that were needed to correct blood pressure or heart rate were recorded, including drug discontinuation, transfer to ICU, oxygen supplementation, fluid resuscitation, atropine administration, or external heart pacing.

Statistical Analysis

We summarized data using descriptive statistics. Continuous data are reported as median (interquartile range) or mean ± SD as appropriate, and categorical data are reported as numbers (percentage). Differences in paired continuous data between day −1 and day +2 were evaluated using Wilcoxon signed rank test and differences in paired categorical data were analyzed by McNemar's test. Analyses were performed using SPSS Statistical Software Version 29 (IBM SPSS Inc, Armonk, NY) and significance was accepted at $p < 0.05$.

Results

Demographics and Clinical Characteristics

Ninety-six patients were ordered guanfacine during the study period, and 56 (58%) were included in the final analysis (Figure). Table 1 shows demographic data, and Table 2 provides details of hospital course. Mean age was 80.5 ±7.1 years, and most patients were male (40/56, 71%) and white (53/56, 95%). Most patients were admitted to a surgical service (32/56, 57%), and hypertension was the most common comorbidity (44/56, 79%). The median hospital length of stay was 17 (8.5 to 25.8) days, and 54/56 (96%) patients received a geriatrics consult. Patients were discharged to a variety of situations as seen in Table 2, and 4 (7.1%) patients expired during their hospitalization.

Guanfacine Administration

The median initial and ongoing guanfacine doses were both 1.0 (0.5 to 1.0) mg/day (range 0.5 to 2 mg/day).

TABLE 1: Baseline demographics and clinical characteristics of the study group

Variable	Measurement
n	56
Age (mean ± standard deviation)[a]	80.5 ± 7.1
Sex, n (%)	
Male	40 (71.4)
Female	16 (28.6)
Race, n (%)	
White	53 (94.6)
Other	3 (5.4)
Primary Team in Charge of Care, n (%)	
Surgery	32 (57.1)
Internal/Family Medicine	19 (33.9)
Cardiology	2 (3.6)
Other	3 (5.3)[b]
Admitting Diagnosis, n (%)	
Surgery/trauma	37 (66.1)
Neurologic	7 (12.5)
Sepsis/Infectious Disease	4 (7.1)
Gastrointestinal	3 (5.4)
Cardiovascular	2 (3.6)
Respiratory	1 (1.8)
Hepatic	1 (1.8)
Failure to Thrive	1 (1.8)
Comorbidities, n (%)	
Hypertension	44 (78.6)
Dementia	20 (35.7)
Arrhythmias	20 (35.7)
Underlying Psychotic Disorder	1 (1.8)
Home Medications, n (%)	
Antihypertensive	31 (55.4)
Heart Rate Control	29 (51.8)

[a]n = 10 patients had age >89 and were entered as age = 90 years for the purpose of calculation. Median age is 81 years.
[b]n = 1 each from oncology, neurosurgery, and orthopedics.

Twenty-three (52%) patients continued guanfacine at discharge, and 17/56 (39%) were discharged on a new antipsychotic.

Effectiveness Outcomes

Thirty-eight (68%) patients were included in the effectiveness analysis. The proportion of patients who received an antipsychotic medication on day −1 (before guanfacine initiation) was 58% (22 of 38 patients) and was 47% (18 of 38 patients) on day +2 after guanfacine was initiated (absolute difference 11%, $p = 0.5$). Patients received a median of 6.4 (3.3 to 16) OE on day −1 and 4.2 (1.7 to 10.0) OE on day +2 (absolute difference 2.2 OE; relative difference, 34%; $p = 0.8$). The proportion of patients with a positive delirium screen, either through CAM results or chart review, was 87% (33 of 38 patients) on day −1 before guanfacine initiation and 66% (25 of 38 patients) on day +2 after guanfacine initiation (absolute difference 21%; $p = 0.04$). The median duration of delirium in this subset of the study group was 11 (4 to 17) days.

TABLE 2: Characteristics of hospital course among the study group

Variable	Measurement[a]
n	56
Duration of Delirium (Days)	11 [4.0-17.8] (1-104)
Delirium Mitigation/Prevention Strategies, n (%)	
Geriatric Consult	54 (96.4)
Psychiatry Consult	21 (37.5)
Hospital Elder Life Program Consult	2 (3.6)
Hospital Length of Stay (Days)	17 [8.5-25.8] (3-110)
Discharge Location, n (%)	
Home	14 (25.0)
Skilled Nursing Facility	19 (33.9)
Long Term Care Facility	2 (3.6)
Rehabilitation Facility	7 (12.5)
Other Hospital	2 (3.6)
Hospice	8 (14.3)
Expired During Hospitalization	4 (7.1)

[a]Data are shown as median [interquartile range] (full range) or n (%).

Safety Outcomes

Twenty-one of 56 (38%) patients experienced at least 1 episode of hypotension (10/21, 48%, were taking an antihypertensive medication). Of these 21 patients, 7 (33%) required intervention, including decreasing the guanfacine dose, discontinuation of guanfacine or other antihypertensive, or IV fluid administration. Twenty-three (41%) patients experienced at least 1 episode of bradycardia (11/23, 48%, were taking concomitant heart rate controllers); of these 23 patients, 1 (4%) required transfer to an ICU due to high-grade atrioventricular block with subsequent pacemaker placement. Overall, 28 (50%) patients were receiving concomitant antihypertensives, and 31 (55%) were receiving concomitant heart rate controllers at the time of guanfacine administration.

Discussion

This is the first cohort study to describe the administration of guanfacine to manage the behavioral manifestations of delirium in hospitalized patients who were all 65 years of age or older. We found that guanfacine administration at a dose of 0.5 to 2 mg per day was associated with a significant decrease in the incidence of delirium by 21% over 72 hours. Furthermore, the need for antipsychotics decreased by 2.2 OE per day; however, this finding was not statistically significant, possibly due to the relatively small size of the subgroup in which we assessed efficacy. We also found a decrease in the number of patients requiring antipsychotics after administration of guanfacine that trended toward statistical significance. The lack of a protocol precluded the routine discontinuation of antipsychotics, and future studies should incorporate a discontinuation algorithm if the initial response to guanfacine is favorable in an effort to reduce risks associated with polypharmacy.[28] Bradycardia or hypotension occurred in about a third of patients and required intervention in 12% of all study participants. Based on other studies of guanfacine referred to in the following discussion, this was a larger than expected outcome for bradycardia and hypotension. Future prospective studies should evaluate whether this is clinically significant and if steps could be taken to mitigate this risk.

Three other studies describe the administration of guanfacine to manage the behavioral manifestations of delirium in adults. The first was a case series of 7 patients that included both ICU patients who were being weaned off a dexmedetomidine infusion (n = 4) and non-ICU (n = 3) patients.[23] They documented that delirium and concomitant psychoactive medication use decreased within 3 days of guanfacine initiation,[23] and our finding of a significant 21% decrease in delirium over 72 hours is consistent with this. In this study, no patient developed clinically relevant hypotension or bradycardia.[23] This was a small sample size of just 7 patients, which may not accurately reflect a larger population.[29]

The second study was a retrospective chart review and included 105 adult ICU patients (median age 59 years) who were being weaned off dexmedetomidine.[13] The reported median dose was 1.5 (1 to 2.2) mg/day. At the time of guanfacine initiation, 41% of patients screened positive for delirium using the CAM-ICU. Dexmedetomidine was discontinued within 48 hours in 58% of patients and in 71% of patients within 72 hours. Hypotension, defined as a systolic blood pressure <90 mmHg, MAP <65 mmHg, or need for vasopressors, occurred in 8% of patients. Bradycardia, defined as a heart rate <60 beats per minute, occurred in 2% of patients.[13] Eleven (10%) patients required vasopressors after developing hypotension, but these patients were critically ill.[13]

The third study was a retrospective chart review and included both ICU (n = 95; 64%) and non-ICU (n = 54; 36%) patients with a mean age of 58 years.[29] The majority (86%) of patients had hyperactive delirium. The guanfacine doses administered in the present cohort (daily and maximum doses of 1.0 [0.5 to 1.0] mg/day) were similar to those reported in this study of a mean initial dose of 1.82 mg/day with a mean maximum dose of 2.61 mg/day. These authors reported a 25% reduction in acute sedative use at 71.6 ± 39 hours,[27] which again is consistent with the 34% reduction in antipsychotic use at 72 hours that we documented. However, we cannot attribute these changes directly to guanfacine, and further work is needed to distinguish the effect of guanfacine from natural resolution of symptoms during a hospital stay. Hypotension, defined as a systolic blood pressure <90 mmHg requiring intervention, was not

observed, and 2 (1%) patients developed bradycardia, defined as a heart rate <50 beats per minute.[29] In contrast, approximately 13% of our patients developed hypotension that needed intervention, and 41% had at least 1 instance of bradycardia. This difference may be explained not only by our study participants' older age, differing diagnostic profiles, and high rates of concomitant antihypertensive and heart rate controller use, but also, it may be an artifact of our requiring only a single abnormal measurement to define either condition. Jiang et al[29] had the more stringent criterion of requiring 2 consecutive abnormal measurements to define either hypotension or bradycardia. A future opportunity includes proactively and temporarily reducing heart rate controllers or antihypertensives prior to guanfacine initiation.

Our study has several limitations. As the parameters needed for a power analysis were not available, this is an exploratory analysis, and significance should be interpreted in this context. This was a descriptive study that will be used to determine a sample size calculation for a prospective study as safety data in this patient population were not available prior to commencement. The retrospective design and lack of a comparator group limited our ability to determine if guanfacine affected delirium incidence or if it would have resolved via natural progression and whether adverse events such as hypotension or bradycardia were drug-related or associated with this older population. The single-center design means our results may not be generalizable to other settings. More than 90% of our population was white, and more than 70% male, which limits generalizability to other populations. Last, the involvement of the geriatric service, which focuses on nonpharmacologic interventions for delirium prior to medication intervention, may have introduced provider or selection bias into our findings.

In order to adjust for the above limitations, some of these authors are conducting another retrospective study of patients who received a geriatric consult for delirium comparing patients who received guanfacine with those who did not. In addition, plans are underway to conduct a prospective safety trial, which will help inform the risk of bradycardia and hypotension. A future efficacy trial comparing guanfacine to standard of care (antipsychotics) will help inform if there is a reduction in outcomes such as falls, pneumonia, or death. The study that informed the boxed warning for antipsychotics had an average duration of treatment of 10 weeks,[30] which may be longer than the duration used for symptoms of delirium. Studies show that inadvertent continuation of antipsychotics is common upon discharge,[31] which could lead to longer term use involving further harms.

Part of the explorations of future studies should include dose finding. This could determine if guanfacine follows a similar pattern to clonidine wherein higher doses cause more stimulation of alpha1-adrengeric receptors and maintenance of blood pressure, whereas lower doses maintain alpha2-adrengergic receptor selectivity and reduce blood pressure.[32] Until further studies are conducted, guanfacine could be considered if standard treatment of behavioral manifestations of delirium fail.

Conclusion

Guanfacine may reduce the behavioral manifestations of delirium in hospitalized patients who are 65 years of age or older albeit with some adverse effects. Future prospective controlled studies are needed to better evaluate the effectiveness and safety of guanfacine in this older population and to validate our findings.

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