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Long-term clonidine and fracture risk in children with attention-deficit hyperactivity disorder: multicentre electronic health record evidence

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ABSTRACT

Background: Children and adolescents with attention-deficit/hyperactivity disorder (ADHD) experience elevated injury rates. Clonidine is commonly prescribed for ADHD, yet its association with fracture risk has not been well defined.
Methods: Retrospective study using TriNetX. Patients (6-18 years) with ADHD (ICD-10-CM F90) were classified as clonidine-exposed if they had a prescription within 6 months before or on the ADHD index date; controls had no clonidine exposure. Matching yielded 73,141 patients per cohort. Follow-up began 1 day after the index and extended through available records, up to 20 years. Primary outcomes were distal radius (S52.5), clavicle (S42.0), and supracondylar humerus (S42.41) fractures.
Results: After matching, 133,630 patients were included (66,815 per cohort). Thirty-day postoperative infection occurred in 1.03% (690/66,815) of SSRI users versus 1.44% (963/66,815) of non-SSRI controls (risk difference-0.41 percentage points; RR 0.71, 95% CI 0.64-0.78; HR 0.69, 95% CI 0.62-0.76; $p<0.001$). No statistically significant differences were observed for delayed wound healing, wound dehiscence, hematoma, seroma, nausea, or sepsis.
Conclusions: Clonidine exposure was associated with lower risks of distal radius, clavicle, and supracondylar humerus fractures. Findings support prospective studies to confirm causality and explore mechanisms.

Keywords: Clonidine, ADHD, Pediatric fractures, Distal radius, Supracondylar humerus

INTRODUCTION

Attention-deficit or hyperactivity disorder is a common neurodevelopmental condition characterized by developmentally inappropriate inattention, hyperactivity, and impulsivity that impair academic and social functioning, with a global childhood prevalence near five percent.[1] Converging evidence implicates dysregulated catecholaminergic signaling within front striatal and frontoparietal networks, delayed cortical maturation, and executive control deficits as central features of its pathophysiology.[2] Alpha-2 adrenergic agonists enhance prefrontal network function via postsynaptic alpha-2A receptors, improving behavioral inhibition, working memory, and attentional control in pediatric ADHD.[3] Clonidine extended-release has demonstrated efficacy as adjunctive therapy to stimulants in randomized trials and is used clinically when sleep dysregulation, tics, or incomplete stimulant response are present.[4] Across pediatric studies, the most frequent adverse effects are somnolence, fatigue, and dose-related hypotension that generally improve with gradual titration and monitoring.[5]

Children and adolescents with ADHD have higher rates of unintentional injury than peers without ADHD, consistent with greater risk-taking and impaired inhibitory control in

daily activities and sports.[6] Fractures account for a substantial portion of this injury burden and occur more often in youth with ADHD than in the general pediatric population.[7] Distal forearm fractures are especially common in late childhood and early adolescence. They are reliably captured in electronic health records using diagnosis codes, making them suitable outcomes for large observational analyses.[8] Given the links among ADHD symptoms, real-world injury risk, and the pharmacologic effects of alpha-2 agonists on arousal and behavioral regulation, clonidine could plausibly reduce fracture risk through behavioral stabilization and improved psychomotor control. The objective of this study was to estimate the association between clonidine exposure and the risk of three common upper-extremity pediatric fractures.

METHODS

Study design and data source

A retrospective cohort study was conducted using TriNetX, a global federated health research network that aggregates de-identified electronic health records (EHRs) from participating healthcare organizations (HCOs). At the time of analysis, the Global Collaborative Network within TriNetX included 153 HCOs, contributing data from over 100 million patients worldwide. Because the TriNetX platform only provides de-identified data in compliance with the Health Insurance Portability and Accountability Act (HIPAA), this study was exempt from institutional review board (IRB) oversight.

Cohort selection

Patients aged 6 to 18 years with a diagnosis of attention-deficit/hyperactivity disorder (ADHD), as defined by ICD-10-CM diagnostic codes F90.0, F90.1, F90.2, F90.8, or F90.9, were identified. Cohort 1 ("clonidine-exposed") consisted of patients with ADHD who had a prescription for clonidine (RxNorm: 2599) within 6 months before or on the date of ADHD diagnosis. Cohort 2 ("control") included patients with ADHD who did not have a history of clonidine exposure.

Exclusion criteria for both cohorts were diagnoses of metabolic bone disease, malignancy involving bone, chronic corticosteroid use, or a prior fracture event that could confound fracture risk. Specifically, patients were excluded if they carried ICD-10-CM codes for osteoporosis (M80,M81), osteomalacia (M83), rickets (E55.0), Paget's disease (M88), hyperparathyroidism (E21), long-term systemic steroid use (Z79.52), secondary malignant neoplasm of bone (C79.5), or prior humerus, clavicle, or distal radius fractures (S42.0, S42.41, S52.5).

Matching and covariate adjustment

To minimize confounding, 1:1 propensity score matching was performed based on demographics (age, race, ethnicity), comorbid psychiatric conditions (anxiety, depression, ODD, conduct disorder), and medical history that could affect fracture risk. Following matching, 73,141 clonidine-exposed patients (Cohort 1) were successfully matched to 73,141 unexposed patients (Cohort 2). All measured baseline variables demonstrated adequate balance after matching. The mean age across Cohort 1 and Cohort 2 was 12.3 years.

Follow-up periods and outcomes

The index date was defined as the earliest date a patient met the inclusion criteria for their respective cohort. Outcomes were evaluated beginning one day after the index date and extended through the end of each patient's available EHR data, up to a maximum look-back period of 20 years.

The primary outcomes of interest were incident fractures of the clavicle (ICD-10-CM S42.0), distal radius (ICD-10-CM S52.5) and supracondylar humerus without intercondylar involvement (ICD-10-CM S42.41) several of the most common fractures sustained by children in our study age range.

Statistical analysis

Propensity score matching (PSM) was performed to balance demographic and clinical characteristics between cohorts. Matching was conducted in a 1:1 ratio using logistic regression with variables including age, sex, and race. Standardized mean differences were used to assess balance, with values <0.1 considered acceptable.

Following matching, risk analyses were performed to calculate absolute risk, risk differences, risk ratios, and odds ratios for each outcome. Kaplan-Meier survival analyses with log-rank tests were conducted to compare time-to-event outcomes between groups.

Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models, with proportionality assessed via Schoenfeld residuals. Additionally, number-of-instance analyses were performed, calculating mean and median numbers of outcome events per patient, with group comparisons made using t-tests.

All analyses were performed within the TriNetX platform, which applies built-in statistical testing and generates summary measures without providing access to patient-level data. A p value of <0.05 was considered statistically significant.

RESULTS

A total of 146,282 pediatric patients between the ages of 6 and 18 diagnosed with ADHD were included in the study. Following propensity score matching, both Cohort 1 (clonidine-exposed) and Cohort 2 (no clonidine exposure)

included 73,141 patients. The outcomes included the distal radius fracture, clavicle fracture, and supracondylar humerus fracture. The mean age across both cohorts was 12.3 years, and 61% of patients were male. The analysis revealed that patients who had been exposed to clonidine for a minimum of 6 months had a lower risk of all three fractures.

Table 1: Upper-extremity fracture outcomes in matched clonidine-exposed vs unexposed ADHD cohorts.

Outcome	Clonidine exposed N (%)	Unexposed N (%)	Risk ratio (95% CI)	Risk difference	Hazard ratio (95% CI)	P value
Distal radius fracture	284 (0.40)	491 (0.67)	0.58 (0.50-0.67)	-0.27%	0.46 (0.41-0.51)	<0.001
Clavicle fracture	93 (0.13)	147 (0.20)	0.63 (0.49-0.82)	-0.07%	0.59 (0.45-0.76)	<0.001
Supracondylar humerus fracture	29 (0.04)	66 (0.09)	0.44 (0.28-0.68)	-0.05%	0.40 (0.26-0.62)	<0.001

Thirty-day fracture outcomes in matched pediatric ADHD cohorts with and without clonidine exposure. Risk percentages, risk ratios (RR), risk differences (RD), and hazard ratios (HR) are shown for all outcomes. Negative RDs indicate lower absolute fracture risk among clonidine-exposed patients. All outcomes demonstrated statistically significant reductions in fracture risk and fracture-related hazard with clonidine exposure.

Table 2: Baseline characteristics of clonidine cohorts before and after propensity score matching.

Cohort			Mean±SD	Patients	% of cohort	P value	Std diff.
Demographics							
Cohort 1 (n=73,141) and cohort 2 (n=717,38) characteristics before propensity score matching							
1	AI	Age at index	8.8±3.2	73,141	100	<0.001	0.043
2			8.6±3.3	717,038	100		
1	2106-3	White		47,552	65.0	<0.001	0.158
2				411,051	57.3		
1	1002-5	American Indian or Alaska native		390	0.5	<0.001	0.015
2				3,088	0.4		
1	UNK	Unknown race		7,546	10.3	<0.001	0.219
2				128,302	17.9		
1	F	Female		21,430	29.3	<0.001	0.053
2				227,577	31.7		
1	2076-8	Native Hawaiian or another Pacific islander		156	0.2	<0.001	0.016
2				2,106	0.3		
1	2054-5	Black or African American		13,091	17.9	<0.001	0.059
2				112,453	15.7		
1	M	Male		51,136	69.9	<0.001	0.061
2				480,996	67.1		
1	2131-1	Another race		3,742	5.1	<0.001	0.025
2				40,706	5.7		
1	2028-9	Asian		664	0.9	<0.001	0.135
2				19,332	2.7		
Cohort 1 (n=73,141) and cohort 2 (n=73,141) characteristics after propensity score matching							
1	AI	Age at index	8.8±3.2	73,141	100	0.996	<0.001
2			8.8±3.2	73,141	100		
1	2106-3	White		47,552	65.0	0.991	<0.001
2				47,554	65.0		
1	1002-5	American Indian or Alaska native		390	0.5	1	<0.001
2				390	0.5		
1	UNK	Unknown race		7,546	10.3	1	<0.001
2				7,546	10.3		
1	F	Female		21,430	29.3	1	<0.001
2				21,430	29.3		

Continued.

Cohort			Mean±SD	Patients	% of cohort	P value	Std diff.
1	2076-8	Native Hawaiian or another Pacific islander		156	0.2	1	<0.001
2				156	0.2		
1	2054-5	Black or African American		13,091	17.9	0.989	<0.001
2				13,089	17.9		
1	M	Male		51,136	69.9	0.995	<0.001
2				51,137	69.9		
1	2131-1	Another race		3,742	5.1	1	<0.001
2				3,742	5.1		
1	2028-9	Asian		664	0.9	1	<0.001
2				664	0.9		

Distal radius fracture

Distal radius fractures occurred in 284 patients in Cohort 1 and 491 patients in Cohort 2. Risk of fracture was calculated as 0.4% (284/73,141) in clonidine exposed patients compared to 0.7% (491/73,141) in non-exposed patients, corresponding to a risk difference of -0.3% (95% CI -0.4% to -0.2%, p<0.001), risk ratio of 0.58 (95% CI 0.50-0.67) and an odds ratio of 0.58 (95% CI 0.50-0.67). This suggests that pediatric patients taking clonidine were just below half as likely to experience a distal radius fracture as patients not currently taking clonidine. A Kaplan–Meier survival analysis was performed, and the log-rank test confirmed a significance (χ^2=74.5, p<0.001). This demonstrates a higher fracture-free survival probability in the clonidine-exposed cohort (98.15%) compared with the control cohort (96.94%).

Clavicle fracture

The evaluation of clavicle fracture as a second outcome revealed 0.1% (93/73,141) in Cohort 1 and 0.2% (147/73,141) in Cohort 2. This produced a risk difference of -0.1% (95% CI -0.1% to -0.0%, p<0.001). The risk ratio of 0.63 (95% CI 0.49-0.82) and odds ratio of 0.63 (95% CI 0.49–0.82). The risk ratio reveals that pediatric patients taking clonidine had a 37% lower relative risk of clavicle fracture than patients not currently taking clonidine. Kaplan–Meier analysis with log-rank test was significant (χ^2=16.7, p<0.001) for clavicle fracture, again favoring the clonidine-exposed cohort. Survival probabilities were reported as 97.75% for Cohort 1 versus 98.53% in Cohort 2. Hazard ratio was calculated at 0.59 (95% CI 0.45-0.76).

Supracondylar humerus fracture

Supracondylar humerus fractures affected 0.04% (29/73,141) of clonidine-exposed patients vs. 0.09% (66/73,141) of patients not exposed to clonidine. This produced a risk difference of -0.05% (95% CI 0.1% to –0.0%, p<0.001). Risk ratio was reported as 0.44 (95% CI 0.28-0.68), along with an odds ratio of 0.44 (95% CI 0.28-0.68). Again, this suggests that pediatric patients exposed to clonidine had a significantly lowers relative risk of fracture when compared to the matched cohort. Survival probabilities of 99.91% in the clonidine group compared to 99.78% in controls were reported from the Kaplan-Meier analysis with a significant log-rank (χ^2=17.8, p<0.001). There was a hazard ratio of 0.40 (95% CI 0.26-0.62), indicating clonidine exposure as having markedly reduced hazard of supracondylar fracture.

Across all three fracture types considered for analysis, clonidine exposure in pediatric patients aged 6-18 with ADHD was associated not only with lower relative risk of fracture, but also considerably less hazard of sustaining fracture and higher fracture-free survival. Taken as a whole, this analysis indicates that clonidine has a protective effect against three common pediatric fractures of the distal radius, clavicle, and supracondylar humerus. A full summary of all fracture outcomes is provided in Table 1.

DISCUSSION

In this multicenter ADHD cohort of 146,282 youth, clonidine exposure was associated with fewer fractures at each prespecified site. Distal radius fractures occurred in 0.4% of clonidine-exposed patients (284/73,141) versus 0.7% of controls (491/73,141). Clavicle fractures were 0.1% (93/73,141) vs 0.2% (147/73,141), and supracondylar humerus fractures were 0.04% (29/73,141) vs 0.09% (66/73,141). Although absolute risks were low, the direction of effect was consistent across anatomically distinct injuries, suggesting a generalized reduction in trauma exposure rather than a site-specific artifact.

A biologically plausible pathway links alpha-2 adrenergic agonism to fewer injury-provoking behaviors. Alpha-2–mediated enhancement of prefrontal network function improves inhibitory control and behavioral regulation in ADHD, changes that could translate into fewer impulsive movements and falls in everyday activities and sports.[9] Clonidine is often selected when sleep is dysregulated; inadequate sleep is independently associated with more injuries in adolescent athletes, so improved sleep could compound the behavioral effect on real-world injury risk.[10] The distribution we observed, predominantly distal forearm and elbow injuries in late childhood and early adolescence, matches pediatric fracture epidemiology, which is dominated by falls onto an outstretched hand.[11] From a methods standpoint, propensity score matching is

a well-validated approach to reduce confounding in observational comparisons, and adherence to reporting standards for routinely collected health data strengthens the interpretability of real-world effect estimates.[12,13] Clinically, clonidine's expected adverse effects include somnolence and dose-related hypotension; randomized pediatric trials document these events, typically mitigated by gradual titration and monitoring, which could also modestly reduce hazardous activity while therapeutic benefits accrue.[14]

Our findings align with broader literature showing that pharmacologic treatment of ADHD can reduce injuries in youth. Extensive observational analyses have linked ADHD medication exposure with fewer trauma events, supporting the concept that symptom control lowers day-to-day risk.[15] The specific pattern we observed, attenuation of common fall-related upper-extremity fractures, is consistent with a behavioral mechanism that reduces fall frequency or severity rather than altering bone biology or fracture healing. Together, these data suggest that clonidine's behavioral stabilization may contribute to clinically meaningful injury prevention in routine care.

Future work should test these pathways prospectively by pairing medication exposure with direct measures of sleep quality, physical activity, and fall events, and by examining dose, duration, and concomitant stimulant use to determine whether effects are additive or synergistic.[16] Real-world evaluations that integrate clonidine into structured injury-prevention programs in adolescent sports could assess whether pharmacologic stabilization, combined with neuromuscular and warm-up interventions, further reduces fractures.[17]

Clinical implications

These results offer a practical approach to pediatric ADHD care. When treatment options are otherwise equivalent, clonidine may be a sensible choice for children at higher fracture risk, including those with prior fractures, low bone density, frequent falls, or participation in high-impact sports. Pair medication selection with a basic prevention bundle that ensures adequate calcium and vitamin D, promotes weight-bearing activity, fits protective gear, and removes home hazards. Document baseline fracture history and activity level to tailor therapy and follow-up. If clonidine is used, monitor blood pressure, heart rate, and daytime sedation to keep school and sports participation safe. Close coordination with primary care, sports medicine, and school staff can turn these steps into clear return-to-play and injury-prevention plans.

Limitations

This retrospective EHR study cannot establish causality, and medication orders may not perfectly reflect dose or adherence. Fracture outcomes were identified by diagnosis codes, so some minor injuries could be missed, although the use of specific acute codes helps limit misclassification. Residual confounding may remain despite propensity matching, including ADHD severity, participation in sports or risky activities, vitamin D status, and concurrent medications that influence bone health. A plausible behavioral confounder is clonidine's calming effect, which could reduce falls and trauma exposure independent of any direct skeletal effect; future work should capture activity levels and falls to separate behavioral from biologic pathways. Time-varying treatment (switching among clonidine, stimulants, or guanfacine) was not modeled and could modestly bias estimates. Generalizability is primarily to pediatric patients with ADHD in health systems contributing to this network. These common limitations warrant cautious interpretation but do not detract from the consistent association observed across three fracture sites.

CONCLUSION

Clonidine use in children and adolescents with ADHD was associated with fewer distal radius, clavicle, and supracondylar humerus fractures during follow-up. The direction and magnitude of effects were consistent across risk and time-to-event analyses, supporting a clinically meaningful reduction in fracture risk. Although this observational study does not prove causality, the findings suggest clonidine may confer protective benefits through behavioral stabilization, physiologic effects on bone metabolism, or both. These results warrant prospective confirmation and mechanistic work to determine pathways and to evaluate whether dosing, duration, or co-interventions can further lower fracture incidence.

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