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Prescription Benzodiazepine Use in Privately Insured U.S. Children and Adolescents

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Abstract

Introduction: Benzodiazepines are commonly prescribed in the U.S. but entail safety concerns including dependency. In pediatrics, many indications lack trial data. Authors aimed to describe youth initiating prescription benzodiazepine treatment, identify potential indications and prescribing concerns, estimate duration of treatment by potential indication, and identify factors that predict long-term use.

Methods: The study cohort included children (aged 3–12 years) and adolescents (aged 13–17 years) initiating prescription benzodiazepine treatment (≥3 days' supply) from January 2010 to September 2015 in a U.S. commercial claims database. Potential indications included selected ICD-9-CM diagnoses (≤30 days prior). Long-term (≥6 months) benzodiazepine treatment was estimated with Kaplan–Meier estimation and modified Poisson regression identified independent predictors of long-term benzodiazepine treatment (analysis completed in 2018).

Results: Of 24,504 children and 61,046 adolescents initiating benzodiazepines, 62% of children and 68% of adolescents had a potential indication. Anxiety disorders were the most common indication, with mental health indications more common among adolescents (45%) than children (23%) and epilepsy and movement disorders higher in children. Recent opioid prescriptions were common before benzodiazepine initiation (children, 22%; adolescents, 21%). Six percent of initiators became long-term benzodiazepine users. Potential indication, provider contact, psychotropic medication, and chronic conditions independently predicted long-term benzodiazepine treatment in adolescents and children.

Conclusions: U.S. children and adolescents are prescribed benzodiazepines for various mental health and other medical conditions, many lacking evidence of pediatric efficacy. Long-term

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benzodiazepine treatment, concurrent opioid prescriptions, psychotropic use, and prior substance use disorder diagnoses suggest safety risks among some youth prescribed benzodiazepines.

INTRODUCTION

Benzodiazepines are commonly prescribed in the U.S.,[1,2] with 62.6 million ambulatory care visits in which benzodiazepines were prescribed in 2015.[3] Use of benzodiazepines increases with age[1,4]; prescribing rates in young adults (aged 18–24 years) are approximately four to seven times those in children.[5] Still, in the past 30 days, 0.6% of U.S. children aged 0–19 years report prescription of benzodiazepines or other anxiolytics, sedatives, or hypnotics.[6] Considering cumulative exposure to prescribed medication and non-prescription use, a tenth of U.S. high school seniors report prior benzodiazepine exposure.[7]

There are safety concerns with benzodiazepine treatment, including mild memory impairment, decreased alertness, slowed reaction time,[8] and benzodiazepine dependence, prompting guidelines to confine use to the short term.[9] Nevertheless, longer-term benzodiazepine use is common, including in pediatrics.[10–15] Benzodiazepines, central nervous system depressants, are involved in drug overdose deaths,[16] including a third of opioid-related fatalities,[17] and have been associated with motor vehicle accidents and fractures in adults.[18–20] Among youth, nonmedical benzodiazepine use can follow prescription treatment, emphasizing the need for cautious and monitored use in young people.[7]

Despite safety concerns, benzodiazepines can be useful medications when prescribed appropriately.[21] Given sedative, anxiolytic, anticonvulsant, and muscle relaxation effects, adults are prescribed benzodiazepines for a range of clinical indications including anxiety disorders, sleep problems, and mood disorders.[2–4,11,22] Physicians also prescribe benzodiazepines as muscle relaxants for pain.[3,23] In older adults, benzodiazepines are commonly (42%) prescribed without a recommended indication.[24] Although the U.S. Food and Drug Administration approved benzodiazepines for treatment of selected conditions in adults, benzodiazepines remain unapproved for pediatric use outside of epilepsy and seizures. Benzodiazepines demonstrated efficacy for treating adult anxiety disorders, but failed to show efficacy over placebo in the few trials of pediatric anxiety disorders.[25–28] Similarly, evidence and recommendations for benzodiazepine treatment in sleep disorders varies for adults and pediatrics.[29,30]

Though there are no firmly established indications for benzodiazepines for the treatment of pediatric mental health disorders,[31] benzodiazepines are prescribed to children to treat mental health conditions including anxiety and sleep disorders.[15,32,33] A Swedish study revealed that half of adolescents prescribed benzodiazepines had a mental health disorder diagnosis in the months surrounding benzodiazepine initiation; anxiety and depression were the most frequent.[33] In the Swedish sample of children with new treatment periods, 29% lasted >6 months.[33] Recent publications provided important insights into prescription benzodiazepine use in U.S. adults.[3,34,35] In U.S. children, however, the treated conditions and duration of treatment across indications have not been described.

To define whether and where improvements in pediatric benzodiazepine prescribing are needed in clinical practice, it is important to understand why benzodiazepines are prescribed to this young population and to identify patient groups likely to receive long-term benzodiazepine treatment. Further, examining benzodiazepine prescribing practices separately in children and adolescents can be informative given results in other young populations[33] and the developmental changes occurring from childhood to adolescence.[36] Therefore, the authors aimed to describe children and adolescents who initiated prescription benzodiazepine treatment, potential indications and prescribing concerns, duration of treatment by potential indication, and predictors of long-term use.

METHODS

Study Sample

This study utilized the MarketScan administrative claims database using data from January 1, 2009 through December 31, 2015. The database covers individuals with employer-sponsored health insurance and their dependents. In 2016, >40 million lives were covered.[37] Patient-level details on insurance enrollment and insurance claims for outpatient and inpatient services and outpatient dispensed prescriptions are available. Service visits contain information on date, provider type, diagnostic codes, and procedure codes. Prescription drug data include dispensing dates, drug names, and days supplied.

The authors identified children (aged 3–12 years) and adolescents (aged 13–17 years) initiating benzodiazepines between January 1, 2010 and September 30, 2015 (before the switch from ICD-9-CM to ICD-10-CM codes). Benzodiazepine treatment was defined as dispensed prescriptions for alprazolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, quazepam, temazepam, and triazolam. Benzodiazepines taken orally were included, excluding other administrative routes. Authors identified the first prescription per individual during the study period and then restricted to new use. To identify new use, this study required a year of continuous prescription insurance enrollment before the individual's first benzodiazepine prescription. The cohort was restricted to youth initiating benzodiazepines with ≥3 days' supply, thereby excluding 45% of initiators. Youth with 1–2 days' supply likely include benzodiazepines prescribed in relation to a medical procedure. The study was submitted to the Rutgers University IRB and determined to be exempt.

Measures

To identify potential indications for benzodiazepine treatment, authors identified ICD-9-CM diagnostic codes ≤30 days before or upon benzodiazepine initiation (Appendix Table 1). Given limited pediatric approvals and recommendations for benzodiazepines, indications clinically suggested for adults were included. Primary potential indications included anxiety disorders, epilepsy or convulsions, and insomnia/sleep problems, for which there are limited pediatric recommendations.[8,28,30,38,39] Other mental health diagnoses considered potential indications were depression,[40,41] bipolar disorder, schizophrenia, and other psychotic disorders.[8,42,43] Diagnoses for conduct and disruptive behavior disorders (not including

attention-deficit hyperactivity disorder) were included.[24,44,45] Diagnostic codes for irritability and impulsiveness were included in a residual "other" group.

Given muscle relaxant effects of benzodiazepines, potential indications under "movement disorders, muscle spasm" included cerebral palsy, tics, muscular dystrophies and other myopathies, motor neuron diseases, abnormal movement disorders, muscle spasms, and abnormal involuntary movement diagnoses.[8,46–51] Also under "other" were alcohol withdrawal,[8,52] burning mouth syndrome,[53] and trigeminal neuralgia.[54] Based on preliminary results and broader use of benzodiazepines as muscle relaxants for muscle discomfort from acute injury or chronic musculoskeletal pain and musculoskeletal conditions,[55–57] the authors added potential indications for injury and "diseases of musculoskeletal system and connective tissue."

For the initial benzodiazepine prescription, agent, days supplied, and duration of action (long-acting: chlordiazepoxide, clobazam, clorazepate, diazepam, flurazepam, and clonazepam) were noted.

Factors potentially placing youth at heightened risk of benzodiazepine adverse effects were identified based on diagnoses in the ≤365 days before or on benzodiazepine initiation (Appendix Table 1). Cautions included diagnoses for drug or alcohol-related disorders,[28] suicidal ideation or suicide attempt/self-harm, and poisoning.[16] Diagnoses of sleep apnea, hypersomnia, respiratory failure, and hypoxemia were included given respiratory depressant effects of benzodiazepines.[9,30] Given strict warnings against concurrent benzodiazepine and opioid use,[58] opioid prescriptions dispensed within the 30 days before or on benzodiazepine initiation were identified.

Additional patient details included recent (≤30 days before or on benzodiazepine initiation) mental health diagnosis (ICD-9-CM: 290-319), psychiatric (primary/secondary diagnosis: 290-319) and non-psychiatric inpatient admission, and psychotropic prescriptions (selective serotonin reuptake inhibitor, other antidepressant, stimulant, atomoxetine, hydroxyzine, clonidine, guanfacine, antipsychotic). Recent contact with provider types included categories for mental health, general, and medical specialist provider types. The pediatric Complex Chronic Conditions classification system[59] was used to measure heightened medical complexity and morbidity (inpatient ICD-9-CM codes, year before benzodiazepine initiation).

Benzodiazepine treatment duration was estimated with prescription dispensing dates and days' supply information. If there was no benzodiazepine refill following the initial days' supply plus 30-day grace period, the patient was considered to have discontinued treatment (discontinuation date). Switching to a new benzodiazepine agent was considered treatment continuation. Treatment duration (days between initiation and discontinuation date) ≥6 months (180 days) was considered long-term benzodiazepine treatment. This definition was selected to be consistent with prior literature.[12] For a sensitivity analysis, treatment duration was defined using narrower (10-day) and broader (60-day) grace periods.

Statistical Analysis

This study described children and adolescents initiating benzodiazepine treatment and examined the proportion with each potential indication, prescribing caution, and other patient characteristic. Crude prevalence ratios (PRs) for child versus adolescent initiators highlighted relative differences. Potential indications were evaluated by sex and, for a sensitivity analysis, in youth without a recent inpatient hospitalization because prescriptions dispensed in hospital were unavailable in the data set. Initial benzodiazepine details were stratified by potential indication. Using Kaplan–Meier estimation, authors estimated treatment duration stratified by potential benzodiazepine indication, censoring at treatment discontinuation, insurance disenrollment, or end of data. Treatment duration was evaluated in youth with diagnoses for each potential indication (e.g., epilepsy) and in the subset of youth with only one potential indication (e.g., epilepsy and no other potential indication). To identify whether potential indications and other patient characteristics independently predicted long-term benzodiazepine treatment, the authors used modified Poisson regression with robust variance estimation, which allowed estimation of multivariable RRs and 95% CIs.[60] This analysis was restricted to youth with ≥6 months of follow-up with long-term treatment defined under a 30-day grace period. Separate models were constructed for children and adolescents. Analyses were completed in 2018 in SAS, version 9.4.

RESULTS

The cohort included 24,504 children (median age, 9 years) and 61,046 adolescents (median age, 16 years) initiating a benzodiazepine with ≥3 days' supply. Forty-six percent of child initiators and 60% of adolescent initiators were female. Diazepam, lorazepam, alprazolam, and clonazepam were the most common initial benzodiazepine agents (Table 1). The median initial prescription length was 10 days (IQR=5–30 days).

Overall, 67% of benzodiazepine initiators had at least one potential indication (Table 1). Anxiety disorders were the most prevalent potential indication, accounting for 28% of initiators (children, 17%; adolescents, 32%). In adolescents, 45% had a potential mental health indication, nearly twice as common as child initiators (23%), with few initiators having sleep problem diagnoses. Nineteen percent of adolescents had a recent depression diagnosis, half of these also having an anxiety diagnosis. Epilepsy and movement disorders were identified as potential indications in a greater proportion of child than adolescent initiators.

Considering sex, the largest absolute differences were seen in more female adolescent initiators with an anxiety or depression diagnosis and in more male adolescent initiators with an injury diagnosis (Appendix Figure 1). Among children, the largest difference was a higher proportion of female (5%) than male (2%) initiators with spine curvature diagnoses.

Benzodiazepine agent and days' supply varied by potential indication (Appendix Table 2). Initiators with potential indications of sleep problems, depression, bipolar disorder/schizophrenia, or conduct disorder received longer initial days' supply. Initiators with an injury or musculoskeletal condition were more likely to initiate on diazepam with shorter

days' supply. A majority (86%) of youth initiating triazolam had no potential indication, compared with 26%–36% for other common initial agents.

Eleven percent of adolescent benzodiazepine initiators had a diagnosis for one or more of the prescribing cautions, including drug- (4%) and alcohol-related (1%) disorder diagnoses (Table 2). A higher proportion of child than adolescent initiators had selected sleep- or respiratory-related prescribing cautions. Seventeen percent of benzodiazepine initiators had an opioid prescription dispensed the day of benzodiazepine initiation (Table 2). Recent opioid prescriptions were more prevalent in initiators with an injury or musculoskeletal condition diagnosis (children, 53%; adolescents, 48%) and in initiators with a recent inpatient admission (children, 65%; adolescents, 56%; data not shown).

Thirty percent of adolescents and 14% of children had a recent selective serotonin reuptake inhibitor prescription (Table 2). Recent non-psychiatric inpatient admissions and complex chronic conditions were relatively common in benzodiazepine initiators (children, 15%; adolescents, 7%). Only 18% of children and 28% of adolescents had recent contact with a mental health specialist before benzodiazepine initiation. In initiators with injury or musculoskeletal condition as a potential indication, 57% had recent contact with a provider in surgery, radiology, or anesthesiology (data not shown).

After excluding children (18%) and adolescents (12%) with a recent inpatient admission, the proportion with a potential benzodiazepine indication was similar (children, 58%; adolescents, 66%). Compared with the full cohort, youth without a recent hospitalization had a lower proportion with opioid prescriptions, musculoskeletal condition diagnoses, and complex chronic conditions (Appendix Table 3).

Overall, 6% (95% CI=6%, 7%) of children and 7% (95% CI=6%, 7%) of adolescents had long-term benzodiazepine treatment; 4% (children) and 3% (adolescents) with a 10-day grace period and 10% (children) and 12% (adolescents) with a 60-day grace period. By potential indication, the proportion with long-term use ranged from 3% of initiators with an injury or musculoskeletal condition to 15% with epilepsy, with variation by age (Table 3). Long-term use estimates were largely consistent when restricting to youth with only one potential indication (Table 3).

In multivariable models for children (n=20,386) and adolescents (n=51,390) with 6 months of follow-up, potential indications of anxiety, depression, and bipolar disorder/schizophrenia independently predicted long-term use in adolescents but not children (Table 4). Recent contact with a mental health specialist (children, RR=1.46; adolescents, RR=1.53), recent psychotropic prescriptions, and complex chronic conditions were associated with an increased risk of long-term benzodiazepine use. Alternatively, contact with a specialist in surgery, radiology, or anesthesiology was associated with a decreased likelihood of long-term use. Opioid prescriptions dispensed on day of benzodiazepine initiation (children, RR=0.12; adolescents, RR=0.16; ref, no recent opioid prescription) was also associated with a decreased likelihood of long-term use. A recent opioid prescription dispensed prior to benzodiazepine initiation was not associated with a decreased likelihood of long-term use in adolescents.

DISCUSSION

Privately insured U.S. children and adolescents initiate benzodiazepine treatment for a variety of mental health and other medical indications, with anxiety disorders as the most common. The vast majority of youth discontinued benzodiazepine treatment early. Yet, a substantial proportion continued benzodiazepine treatment for 6 months or longer, despite recommendations calling for short-term treatment.[28,29,61–64] Further, in young benzodiazepine initiators, the prevalence of opioid prescriptions, substance use disorder diagnoses, and concurrent psychotropic use raise potential safety concerns.

In this study, approximately one fourth of children and one half of adolescents initiating benzodiazepine treatment had a mental health condition as a potential indication, similar to children (17%) and adolescents (53%) in Sweden.[33] The true proportions are likely higher, as a potential indication was not identified in one third of initiators and the Swedish sample lacked diagnoses from primary care. Though sleep disorders are a prevalent indication of adult benzodiazepine use[3,11,65] and sleep disorders without anxiety are the most common preceding diagnosis in European databases,[4] few young initiators with sleep disorder diagnoses were observed. This may be due to differing clinical evidence and recommendations.[30,66] In keeping with other studies from the U.S.,[11,22] anxiety disorders were the most commonly observed potential indication, despite lack of supporting evidence in pediatric anxiety disorders[26,27].

In European databases, 22%–82% of benzodiazepine users had unknown indications.[4] The fact that one third of benzodiazepine initiators lack a potential indication in the present study is likely related to unrecorded diagnoses on patient claims, unconfirmed diagnoses, symptoms not meeting diagnostic criteria, and indications outside the included definitions. Benzodiazepines could also be prescribed for preoperative medical visits or dental procedures,[67,68] which are not captured consistently in claims data. Same-day opioid prescriptions and contact with providers in surgery, radiology, and anesthesiology suggest youth initiate benzodiazepines surrounding medical procedures. Attention-deficit hyperactivity disorder and its pharmaceutical treatments were relatively prevalent in this young sample; adverse effects of stimulants can include sleep disturbances.[69] Benzodiazepines could have been prescribed to treat medication side effects.

Most youth discontinued benzodiazepine treatment early. However, long-term use occurred, particularly in youth with epilepsy or mental health indications. There are clinical situations when long-term benzodiazepine treatment may be an important component of illness management; yet, questions remain over long-term use.[70,71] Under varying definitions, 6%–76% of use in adults involves long-term benzodiazepine treatment.[12] Importantly, many studies blend long-term use estimates from prevalent and incident users, which can vary substantially.[72] Incident long-term use estimates were lower than estimates from a recent study (29%) in youth initiating benzodiazepine treatment.[33] Still, the observed long-term use in youth with depression diagnoses is particularly concerning, as benzodiazepines are not recommended for pediatric depression.[73,74] Similar long-term treatment was observed in youth with anxiety (9%) and sleep disorder (12%) diagnoses despite recommendations.[28,29] Clinical guidelines on discontinuing long-term benzodiazepine treatment are available for

adults.[75,76] Based on findings, youth-specific guidelines are needed, which might involve determining whether benzodiazepine discontinuation interventions[77,78] are effective for young users.

Concurrent opioid and benzodiazepine use is strongly discouraged given increased mortality risk.[9,79,80] Still, a fifth of young benzodiazepine initiators had recent opioid prescriptions, higher than the 13% of Swedish adolescents dispensed opioids.[33] In pediatric intensive care units, concurrent benzodiazepine and opioid use is common, with clinicians likely accustomed to managing patients safely.[81] Opioid use was higher in recently hospitalized youth, suggesting a clinical need following hospital discharge. Relatedly, pediatric benzodiazepine initiators had relatively high morbidity with 15% of children having a past-year complex chronic condition. For comparison, 12% of children in an inpatient sample had a complex chronic comorbidity, as did 2% of children in an emergency department sample.[59]

Benzodiazepine–psychotropic polypharmacy occurred in most adolescent benzodiazepine users in Finland[82] and three fourths of children and young adults in Sweden had psychotropic medications surrounding benzodiazepine dispensing.[33] This polypharmacy and the concurrent psychotropic use in benzodiazepine initiators observed raises concerns owing to unclear efficacy and safety of benzodiazepines used with other psychotropics. Given the range of benzodiazepine indications, benzodiazepine prescribers may be unaware of prior psychotropic prescriptions, opioid prescriptions, and substance use disorders. Improved care coordination could inform treating physicians of prior prescriptions and diagnoses.

Limitations

This analysis has some limitations. The authors were unable to link patient diagnoses to prescriptions, resulting in uncertainty over the actual indication. The list of potential indications used in this study is not exhaustive given broad off-label use and ICD-9-CM code limitations. The prescriber and whether concurrent prescriptions came from multiple prescribers cannot be identified from the data; the data lack detailed clinical information. The data cover privately insured individuals and oversample individuals covered by large-sized employers. Different patterns of benzodiazepine use may occur among uninsured and Medicaid insured youth.[83] Results do not apply to non-benzodiazepine hypnotics or sedatives. Dispensed medications may not have been taken and youth may have access to benzodiazepines outside the prescription. Finally, long-term use estimates are dependent on days' supply values and selected grace period. Details on whether the benzodiazepine was prescribed for as-needed use is not available, which could allow for more flexible treatment duration definitions. The increase in long-term users under the extended grace period suggests some youth take benzodiazepines as needed.

CONCLUSIONS

Benzodiazepines can be clinically useful medications when prescribed carefully to appropriate patients.[21] However, they pose substantial risks.[9,84] The authors cannot determine whether a strong therapeutic rationale guided each pediatric benzodiazepine prescription, but by characterizing patterns of benzodiazepine prescriptions to U.S. children

and adolescents, this study identified areas of prescribing that can likely benefit from improvements. These areas include long-term benzodiazepine use, polypharmacy, prescribing cautions, and prescribing for conditions lacking empirical evidence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Potential Indications in Children and Adolescents Initiating Prescription Benzodiazepine Treatment

Variable	Total N=85,550	Children, 3–12 years N=24,504	Adolescents, 13–17 years N=61,046	Child vs adolescent
	%	%	%	Crude PR (95% CI)
Patient, prescribing characteristics				
Age at benzodiazepine start, median (IQR)	15.0 (12.0–16.0)	9.0 (7.0–11.0)	16.0 (15.0–17.0)	
Female	56.2	46.5	60.2	0.77 (0.76, 0.78)
Initial benzodiazepine				
Diazepam	30.0	42.0	25.1	1.67 (1.64, 1.71)
Lorazepam	24.2	21.8	25.1	0.87 (0.84, 0.89)
Alprazolam	18.5	9.9	22.0	0.45 (0.43, 0.47)
Clonazepam	21.5	20.4	22.0	0.93 (0.90, 0.95)
Triazolam	1.8	0.8	2.1	0.38 (0.33, 0.45)
Clobazam	0.8	2.2	0.3	7.70 (6.49, 9.14)
Other	3.2	2.9	3.4	0.86 (0.79, 0.93)
Potential indications, diagnoses prior 30 days				
Any potential indication	47.9	40.4	51.0	0.79 (0.78, 0.81)
Any potential indication including injury and musculoskeletal condition	66.6	62.0	68.4	0.91 (0.90, 0.92)
Mental health potential indication	39.0	23.0	45.4	0.51 (0.49, 0.52)
Anxiety disorder	27.6	17.2	31.7	0.54 (0.53, 0.56)
Unspecific anxiety	15.7	10.0	18.0	0.56 (0.53, 0.58)
Generalized anxiety disorder	7.9	5.0	9.1	0.55 (0.51, 0.58)
OCD	2.2	2.1	2.2	0.95 (0.85, 1.05)
PTSD	1.0	0.6	1.2	0.47 (0.40, 0.57)
Panic disorder	3.9	1.4	4.9	0.28 (0.25, 0.32)
Social phobia	1.0	0.4	1.3	0.31 (0.25, 0.39)
Other anxiety disorder[a]	2.7	2.3	2.9	0.81 (0.73, 0.89)
Sleep problems	3.1	2.7	3.3	0.80 (0.73, 0.87)
Bipolar disorder, schizophrenia, and other psychotic disorders	4.0	1.8	4.9	0.38 (0.35, 0.42)
Conduct/disruptive behavior disorders	2.2	2.7	2.0	1.38 (1.26, 1.51)
Depression	14.7	3.6	19.2	0.19 (0.17, 0.20)
Epilepsy, convulsions	6.3	12.5	3.8	3.33 (3.16, 3.51)
Movement disorders; muscle spasm[b]	5.9	9.8	4.4	2.23 (2.11, 2.35)
Other, uncommon[c]	0.2	0.2	0.2	0.95 (0.66, 1.37)
Injury[d]	12.5	12.9	12.4	1.04 (1.00, 1.08)
Musculoskeletal, connective tissue condition[d]	23.0	25.3	22.0	1.15 (1.12, 1.18)

[a]Other anxiety disorder includes: separation anxiety disorder, agoraphobia, other phobia, selective mutism, other anxiety, anxiety due to other conditions, acute stress disorder, nervousness/other anxiety.

[b] Movement disorder, muscle spasm: Muscle spasm, abnormal involuntary movement; cerebral palsy; tics; movement disorder; motor neuron diseases; muscular dystrophies/myopathies.

[c] Other uncommon: alcohol withdrawal, burning mouth syndrome, trigeminal neuralgia, irritability/impulsive.

[d] Injury(ICD-9-CM: 800-904, 910-957); Musculoskeletal, connective tissue condition (ICD-9-CM: 710-739.x); common diagnoses under 'musculoskeletal, connective tissue condition': spine curvature (3.4%, children=3.3%, adolescents=3.5%), pain in limb/joint (7.3%, children=7.2%, adolescents=7.3%), pain in neck/back (7.2%, children=7.1%, adolescents=7.3%).

OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder; PR, prevalence ratio.

Table 2.

Prescribing Cautions and Patient Characteristics of Children and Adolescents Initiating Prescription Benzodiazepine Treatment

Variable	Total N=85,550	Children, 3–12 years N=24,504	Adolescents, 13–17 years N=61,046	Child vs adolescent
	%	%	%	Crude PR (95% CI)
Prescribing cautions, prior year (unless specified)				
Drug-related disorder	2.8	0.5	3.8	0.12 (0.10, 0.15)
Alcohol-related disorder	0.8	0.1	1.1	0.08 (0.05, 0.12)
Suicidality (recorded self-harm, suicidal ideation)	3.7	0.7	4.9	0.15 (0.13, 0.17)
Poisoning	2.2	1.0	2.7	0.37 (0.32, 0.42)
Sleep apnea; hyposomnia	1.8	2.8	1.4	2.03 (1.84, 2.24)
Respiratory failure; hypoxemia (excludes day of BZD start)	1.2	2.4	0.7	3.29 (2.91, 3.72)
Any diagnosis above	9.8	6.7	11.0	0.61 (0.58, 0.64)
Opioid prescription				
Dispensed day of BZD start	16.9	17.9	16.5	1.08 (1.05, 1.12)
Dispensed in prior 30 days or day of BZD start	21.5	22.1	21.2	1.04 (1.01, 1.07)
>10 days supplied	4.4	5.3	4.1	1.28 (1.20, 1.37)
Provider contact, prior 30 days				
Mental health professional	25.5	18.2	28.4	0.64 (0.62, 0.66)
Psychiatrist	18.0	12.3	20.3	0.61 (0.58, 0.63)
Psychologist; therapist (supportive); psychiatric nurse	13.9	9.9	15.5	0.64 (0.61, 0.67)
General provider	50.4	49.6	50.8	0.98 (0.96, 0.99)
Pediatrician	24.6	33.1	21.3	1.55 (1.52, 1.59)
Family practice	17.4	10.5	20.1	0.52 (0.50, 0.54)
Internal medicine[a]	12.3	10.8	12.8	0.84 (0.81, 0.88)
Nurse practitioner; physician's assistant	3.6	3.4	3.6	0.96 (0.88, 1.03)
Specialist	30.1	37.5	27.1	1.38 (1.35, 1.41)
Neurology	7.6	11.6	6.0	1.94 (1.85, 2.03)
Surgery, radiology, anesthesiology	24.0	28.2	22.3	1.26 (1.23, 1.30)
Pediatrician specialty, other	8.0	11.9	6.5	1.83 (1.75, 1.92)
None of above	24.9	26.7	24.2	1.10 (1.07, 1.13)
Psychotropic prescription, prior 30 days[b]				
SSRI	25.2	14.1	29.7	0.48 (0.46, 0.49)
Other antidepressant	7.4	3.3	9.1	0.36 (0.34, 0.39)
Stimulant	9.2	9.6	9.1	1.06 (1.02, 1.11)
Antipsychotic	8.2	7.4	8.5	0.87 (0.82, 0.91)
Clonidine/guanfacine	3.8	6.7	2.6	2.54 (2.37, 2.72)
Additional characteristics				
Any mental health diagnosis, prior 30 days	48.2	36.3	53.0	0.68 (0.67, 0.70)

Variable	Total N=85,550	Children, 3–12 years N=24,504	Adolescents, 13–17 years N=61,046	Child vs adolescent
	%	%	%	Crude PR (95% CI)
ADHD diagnosis, prior year	15.9	17.4	15.3	1.13 (1.09, 1.17)
Inpatient admission, prior 30 days				
Psychiatric related	4.1	2.7	4.7	0.57 (0.53, 0.62)
Non-psychiatric related	9.7	15.1	7.5	2.02 (1.94, 2.10)
Discharged on BZD start date	7.5	10.0	6.5	1.56 (1.48, 1.63)
Complex chronic condition, prior year inpatient diagnoses[c]	9.4	14.6	7.4	1.97 (1.89, 2.06)
Neuromuscular, neurological	3.5	7.5	1.9	3.92 (3.65, 4.21)
Other congenital or genetic defect	3.2	3.8	3.0	1.25 (1.15, 1.35)
Malignancy	2.0	3.7	1.3	2.80 (2.55, 3.08)
Cardiovascular	1.6	2.0	1.4	1.38 (1.23, 1.54)

[a] Internal medicine and medical doctor not classified under another specialty.

[b] Hypnotic, z-drug (children=0.2%, adolescents=1.1%), Hydroxyzine (children=1.8%, adolescents=2.2%); Multiple psychotropic classes: antidepressant + antipsychotic (children=2.9%, adolescents=4.9%); antidepressant + stimulant (children=3.0%, adolescents=4.2%), antidepressant + another class (children=6.4%, adolescents=10.0%).

[c] Most common categories displayed (>1% of initiators).

BZD, benzodiazepine; PR, prevalence ratio; SSRI, selective serotonin reuptake inhibitor; ADHD, attention-deficit hyperactivity disorder.

Table 3.

Long-term Benzodiazepine Treatment (6+ Months) in Children and Adolescents by Potential Benzodiazepine Indication

Potential indication, diagnosis prior 30 days	Multiple potential indications allowed		Restricted to youth with one potential indication[a]	
	n (% of cohort)	% long-term BZD treatment (95% CI)	n (% of cohort)	% long-term BZD treatment (95% CI)
Children (n=24,504)				
Epilepsy	3,072 (13)	18.3 (17.0, 19.6)	1,939 (8)	18.4 (16.8, 20.1)
Bipolar; schizophrenia; conduct disorder	1,029 (4)	11.6 (9.8, 13.7)	392 (2)	9.3 (6.9, 12.6)
Sleep disorder	652 (3)	15.7 (13.2, 18.7)	284 (1)	15.3 (11.8, 19.8)
Depression	874 (4)	8.7 (7.0, 10.8)	230 (1)	10.2 (6.9, 15.0)
Anxiety disorder	4,218 (17)	7.1 (6.4, 7.9)	2,654 (11)	5.5 (4.7, 6.4)
Movement disorder, muscle spasm	2,395 (10)	9.4 (8.3, 10.6)	487 (2)	12.0 (9.5, 15.2)
Musculoskeletal condition	6,196 (25)	2.4 (2.1, 2.8)	2,873 (12)	0.8 (0.5, 1.2)
Injury	3,152 (13)	2.3 (1.8, 2.9)	1,094 (4)	1.2 (0.7, 2.0)
Any potential indication	15,204 (62)	7.3 (6.9, 7.7)	–	–
No potential indication	9,300 (38)	4.6 (4.2, 5.1)	–	–
Adolescents (n=61,046)				
Epilepsy	2,300 (4)	10.8 (9.7, 12.2)	1,157 (2)	10.0 (8.4, 11.8)
Bipolar; schizophrenia; conduct disorder	3,851 (6)	13.8 (12.7, 14.9)	1,286 (2)	14.6 (12.9, 16.7)
Sleep disorder	2,028 (3)	11.2 (9.9, 12.6)	651 (1)	10.3 (8.2, 12.8)
Depression	11,718 (19)	11.1 (10.5, 11.6)	4,077 (7)	10.5 (9.6, 11.5)
Anxiety disorder	19,374 (32)	9.0 (8.6, 9.4)	10,074 (17)	7.3 (6.8, 7.8)
Movement disorder, muscle spasm	2,680 (4)	7.3 (6.4, 8.4)	431 (1)	12.0 (9.4, 15.4)
Musculoskeletal condition	13,445 (22)	3.2 (2.9, 3.5)	5,500 (9)	1.9 (1.5, 2.3)
Injury	7,555 (12)	3.2 (2.9, 3.7)	1,894 (3)	1.7 (1.2, 2.4)
Any potential indication	41,783 (68)	7.4 (7.2, 7.7)	–	–
No potential indication	19,263 (32)	4.7 (4.4, 5.0)	–	–

[a]For example, 2,654 children (11% of children) had only a recent anxiety diagnosis and had no diagnosis for another potential indication (epilepsy, sleep disorder, bipolar/schizophrenia/conduct disorder, depression, muscle spasm/movement disorder, injury, musculoskeletal condition, other/uncommon) diagnosis in the prior 30 days; 'Other, uncommon' category is not displayed due to low numbers, but is an included category in restricted groups.

BZD, benzodiazepine.

Table 4.

Independent Predictors of Long-term Benzodiazepine Treatment (6+ Months) in Children and Adolescents[a,b]

Variable	Children (3–12 years)			Adolescents (13–17 years)		
	Total, N=20,386	Long-term use, (N=1,284)		Total, N=51,390	Long-term use, (N=3,477)	
		n	ARR (95% CI)		n	ARR (95% CI)
Female	9,441	580	1.05 (0.95, 1.17)	30,852	1,922	0.82 (0.76, 0.87)
Age at BZD start						
10–12 years (vs 3–9)	10,069	606	1.01 (0.91, 1.13)			–
16–17 years (vs 15–14)			–	29,058	2,092	1.14 (1.07, 1.22)
Potential indication, prior 30 days						
Epilepsy, convulsions	2,561	466	3.01 (2.61, 3.46)	1,952	217	1.70 (1.46, 1.98)
Bipolar disorder, schizophrenia, psychosis	387	44	1.02 (0.75, 1.39)	2,520	383	1.26 (1.12, 1.42)
Conduct/disruptive disorder	571	64	0.94 (0.74, 1.21)	1,026	125	0.95 (0.80, 1.13)
Sleep problems	544	86	1.72 (1.38,2.16)	1,677	191	1.40 (1.21, 1.61)
Depression	724	63	0.98 (0.76, 1.28)	9,849	1,140	1.13 (1.04, 1.23)
Anxiety disorder	3,487	252	0.92 (0.78, 1.08)	16,125	1,501	1.13 (1.06, 1.21)
Muscle spasm, movement disorder	1,958	184	1.47 (1.25, 1.73)	2,247	167	1.32 (1.12, 1.54)
Musculoskeletal condition	5,090	122	0.65 (0.53, 0.79)	11,301	362	0.82 (0.73, 0.92)
Injury	2,609	60	0.86 (0.66, 1.12)	6,335	216	0.82 (0.72, 0.94)
Prescribing cautions, prior year						
Drug-related disorder			_ [c]	1,910	247	1.16 (1.01, 1.33)
Alcohol related disorder			_ [c]	544	69	1.07 (0.84, 1.36)
Self-harm, suicidal ideation diagnosis	146	19	1.35 (0.86, 2.13)	2,484	329	1.00 (0.89, 1.14)
Poisoning	198	12	0.66 (0.38, 1.15)	1,389	163	1.02 (0.86, 1.20)
Sleep apnea, hypersomnia	582	90	1.58 (1.27, 1.95)	719	104	1.61 (1.34, 1.92)
Respiratory failure, hypoxemia	463	60	1.31 (1.00, 1.72)	364	38	1.83 (1.34, 2.49)
Opioid prescription, prior 30 day (ref=none)	15,918	1,244	ref	40,531	3,274	ref
Same day as benzodiazepine start	3,604	18	0.12 (0.08, 0.20)	8,387	52	0.16 (0.12, 0.21)
Prior 30 days (excluding day of BZD initiation)	864	22	0.50 (0.33, 0.76)	2,472	151	1.08 (0.92, 1.27)
Psychiatric inpatient admission, prior 30 days	544	71	1.16 (0.91, 1.47)	2,403	324	1.03 (0.90, 1.17)
Complex chronic condition	2,929	253	1.73 (1.48, 2.03)	3,765	188	1.18 (1.01, 1.38)
Health professional contact, prior 30 days						
Mental health specialist	3,760	368	1.46 (1.26, 1.69)	14,886	1,782	1.53 (1.42, 1.66)
General medical specialist	10,131	604	0.89 (0.80, 0.99)	26,217	1,675	0.91 (0.85, 0.97)
Neurology	2,406	312	1.19 (1.03, 1.38)	3,120	246	1.30 (1.12, 1.50)
Surgery, radiology, anesthesiology	5,773	200	0.68 (0.58, 0.80)	11,497	367	0.68 (0.60, 0.76)

[a]Model includes children and adolescents with at least 6 months of continuous insurance enrollment after benzodiazepine initiation.

[b] Variables not displayed but included in multivariable model (ARR, 95% CI): psychotropic prescriptions, prior 30 days for children [SSRI=1.23 (1.05, 1.45); other antidepressant=1.46 (1.18, 1.81); atomoxetine, hydroxyzine, clonidine, or guanfacine=1.46 (1.25, 1.69); stimulant=1.13 (0.96, 1.32); antipsychotic=1.45 (1.22, 1.72)] and adolescents [ARRs: SSRI=1.34 (1.25, 1.44); other antidepressant=1.52 (1.40, 1.66); hypnotic=1.60 (1.32, 1.95); atomoxetine, hydroxyzine, clonidine, or guanfacine=1.38 (1.24, 1.53); stimulant=1.25 (1.14, 1.37); antipsychotic=1.45 (1.32, 1.59)]; other specialized pediatrics provider contact: children=1.07 (0.91, 1.27), adolescents=0.94 (0.81, 1.09); Inpatient non-psychiatric hospitalizations not included in model given concordance with complex chronic condition.

[c] Not included in multivariable model given low number.

BZD, benzodiazepine; ARR, adjusted risk ratio.