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RetroDUR Criteria: Chronic benzodiazepine use in children and adolescents

Background

Reports from the literature suggest a nearly three-fold increase in use of anxiolytics for children and adolescents during the past decade. Despite this trend, the literature supporting the therapeutic role of benzodiazepines in children is sparse. In this age group, benzodiazepines are used primarily to treat seizures (partial, absence, myoclonic, atonic, and infantile spasms) and sleep disorders. Benzodiazepines are also employed for anxiety, especially dental procedures. Very often the benzodiazepine is given along with other central nervous system (CNS) depressants for short-term use. Use of benzodiazepines in children is often off-label. No firmly established indications exist for benzodiazepines for either children or adolescents with psychiatric disorders. No benzodiazepine has FDA approval for pediatric insomnia. Furthermore, basic information such as drug half-life for some benzodiazepines have not been established for infants and children.

Reviews generally support use of benzodiazepines for seizures, although alternatives exist. A Cochrane review concluded that there was no evidence to show intravenous lorazepam should be preferred to diazepam in tonic-clonic seizures. One evidenced-based review found the limited evidence did not allow for a recommendation for use in infantile spasms. Inhibitory effects of benzodiazepines at both the spinal cord and supra-spinal levels and binding near GABA receptors has made these ideal antispasmodics, particularly diazepam. Double-blind studies have shown mild improvement in children with cerebral palsy using diazepam. A randomized, control trial in children with cerebral palsy concluded that bedtime diazepam produced less wakefulness during the night, made passive stretching easier, sustained muscle relaxation the following day, and improved behavior with less irritability and crying. The authors recommended short courses of 6-12 weeks with a 3-4 week drug holiday to preclude tolerance.

The role of benzodiazepines for anxiety disorders in children is unclear. Similar to adult anxiety disorders, antidepressants are considered first line agents when pharmacotherapy is required. Benzodiazepines may be helpful for controlling severe symptoms while longer acting antidepressants take effect. 1, 3 Specific studies of benzodiazepines have been small and of short duration. Alprazolam and clonazepam have been shown to be ineffective in separation anxiety. 3 A study of social phobia in children and adolescents did not support use of benzodiazepines due to lack of efficacy.

Similar to the adult populations, benzodiazepines have a number of well documented adverse effects. Central nervous system depression, impaired psychomotor performance, amnesia, respiratory depression, and dependence and abuse potential are among the most commonly reported or concerning adverse effects.

Questions:

1) What is the prevalence of chronic benzodiazepine use among children and adolescents (<19 years of age)
2) What are the demographic and diagnostic characteristics of children and adolescents with chronic benzodiazepine
3) What are the characteristics of these two groups of benzodiazepine users with respect to demographics, Medicare eligibility, long-term care residence, etc.

Methods

- Among FFS Medicaid clients <19 years of age, Identify clients using benzodiazepines for greater than 59 days (sum of day supply >=60 and prescription service date difference >=60 and ratio of two is within 25% of 1)
- Quantify drug type, sex, race, age characteristics
- Quantify major diagnostic classification of group
- What proportion of chronic benzodiazepine users also have prescription fills for stimulant medication (i.e. methylphenidate, amphetamine)
- Period of evaluation 05/1/06 – 10/31/06

Results

During the evaluation period at total of 1205 children had at least one prescription fill for a benzodiazepine during the 6 month sample period. Of these, 141 (11.7%) subjects had at least 60 days of continuous treatment with one or more benzodiazepine. The average length of therapy among these subjects was approximately 5 months (150 days). The most frequently dispensed benzodiazepine was clorazepate (43%), followed by lorazepam (25%), diazepam (16%), and alprazolam (13%). The average age among all chronic users was 12 years and similar among all drug types. Table 2 shows the use of benzodiazepines by all 1205 subjects with at least 1 fill. Over half of all clorazepate use was among subjects with chronic use.

Table 1: Benzodiazepine drug use among chronic users

Benzodiazepine	Count	%	Average Age	Average Days of Therapy
CLORAZEPATE DIPOTASSIUM	61	43.0%	13.9	170.5
LORAZEPAM	36	25.4%	14.0	120.8
DIAZEPAM	22	15.5%	10.2	167.0
ALPRAZOLAM	19	13.4%	11.4	127.9
OXAZEPAM	2	1.4%	14.7	131.0
TRIAZOLAM	1	0.7%	15.5	61.0
CHLORDIAZEPOXIDE HCL	1	0.7%	17.0	176.0
	141		12.2	150.2

Table 2: Benzodiazepine drug use among all users

Benzodiazepine	Count	%	Average Age
DIAZEPAM	513	42.6%	10.0
LORAZEPAM	435	36.1%	13.7
ALPRAZOLAM	108	9.0%	15.1
CLORAZEPATE DIPOTASSIUM	103	8.5%	9.6
TRIAZOLAM	19	1.6%	9.8
MIDAZOLAM HCL	9	0.7%	5.9
TEMAZEPAM	7	0.6%	17.0
OXAZEPAM	6	0.5%	13.5
CHLORDIAZEPOXIDE HCL	4	0.3%	16.3
FLURAZEPAM HCL	1	0.1%	17.0
	1205		11.8

Only 4 of the 141 chronic benzodiazepine users also had a prescription for a stimulant medication during the study period.

Table 3 presents other demographic characteristics of chronic use and any use population. There were was higher proportion of males among chronic users compared to the any use group. Racial groups were similar.

Table 3: Patient sex and race

	Chronic users		All users	
	Count	%	Count	%
Sex				
Female	57	40.4%	637	52.9%
Male	84	59.6%	568	47.1%
Race				
White	110	78.0%	945	78.4%
Hispanic	16	11.3%	161	13.4%
Native American	6	4.3%	24	2.0%
Other	9	6.4%	75	6.2%

Table 4 shows the major diagnostic categories present among subjects with chronic benzodiazepine use. The most prevalent diagnostic code was for a seizure disorder (43%). Patients with a diagnostic code for a paralysis condition (e.g. hemiplegia, quadraplegia etc.) were the next most prevalent disease condition (34%). Other diagnoses with a higher prevalence were those for developmental disorders, attention deficit disorder, and psychiatric conditions.

Table 4: Major Diagnostic Categories (not mutually exclusive)

Seizure Disorders	60	42.6%
Paralysis (e.g. hemiplegia)	48	34.0%
Developmental Disorders/Autism	20	14.2%
Attention Deficit Disorders	8	5.7%
Depression / Bipolar Disorders	6	4.3%
Anxiety Disorders	5	3.5%
Psychosis	2	1.4%

Discussion and Recommendations

This evaluation observed the chronic use of benzodiazepines among children and adolescents was relatively low. Among those identified, major diagnostic characteristics include seizure disorder, paralytic disorders, and developmental disorders. Given the relatively small number of subjects observed, the lack of objective data suggesting specific risks, and the severity of disease of affected subjects, we recommend no specific retrodur criteria for this group.