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Associations between Fracture Incidence and Use of Depot Medroxyprogesterone Acetate and Anti-Epileptic Drugs in Women with Developmental Disabilities

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Abstract

Purpose—To evaluate any association between incidence of osteoporotic fractures and use of depot medroxyprogesterone acetate (DMPA) and/or anti-epileptic drugs (AEDs) among women and girls with developmental disabilities.

Methods—Cross-sectional population-based observational study of all non-institutionalized females with developmental disabilities age thirteen and older who received fee-for-service Medicaid in Washington State during 2002 (N=6773), using administrative data.

Main Findings—In a sample of 6,773 females, 140 women (2%) had an osteoporotic fracture during 2002. Among 340 users of DMPA, 13 (3.8%) had an osteoporotic fracture with an odds ratio of 2.4 (CI 95%, 1.3–4.4) for fracture compared to non-users. Among 1909 users of AEDs, 60 (3.1%) had an osteoporotic fracture with an odds ratio of 1.9 (CI 95%, 1.3–2.6) for fracture compared to non-users. We controlled for age and race (as Caucasian or non-Caucasian).

Conclusions—Use of either AEDs or DMPA by women with developmental disabilities is associated with significantly increased incidence of fracture. Women and girls who have developmental disabilities may be poor candidates for DMPA use due to increased risk of fractures. Further research is indicated (1) to determine the specific risks profile of DMPA for this population, (2) to explore alternative means of managing significant menstrual problems and contraceptive needs in this population and (3) to screen current and previous users of DMPA and chronic users of AEDs for osteoporosis risk, regardless of age.

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People who have developmental disabilities (DD) are at increased risk of fractures due to co-occurrence of low BMD (Aspray et al. 1998; Jaffe, Timell, & Gulanski, 2001; Lohiya, Tan-Figueroa, & Iannucci, 2004) and increased incidence of falls and other trauma (Hsieh, Heller & Miller, 2001). Developmental disabilities are severe and chronic disabilities which begin before age 22 and are the result of mental retardation, cerebral palsy, epilepsy, autism or a similar condition (U.S. code Title 42, chapter 75, section 6001.5.1, 1992). They include a wide range of both physical and cognitive disabilities and many have associated health problems.

Documented risks for low BMD include limited mobility (Lohiya et al. 2004; Tyler, Snyder & Zyzanski, 2000; Jaffe, Timell, Elolia & Thatcher, 2005), use of anti-epileptic drugs (AEDs) (Ray, Papaioannou, Ioannidis & Adachi, 2002), and diagnosis of Down Syndrome (Tyler et al.; Center, Beange & McElduff, 1998; Angelopoulou, Souftas, Sakadamils & Mandroukas, 1999). Increased risk for falls may be related to ataxia, impaired cognition, medication side effects, and seizure activity.

Fracture rates have also been shown to be increased in people with DD related to use of AEDs (Tannenbaum, Lipworth, & Baker, 1989; Lohiya, Crinella, Tan-Figueroa, Caires & Lohiya, 1999). Increased incidence of fracture has been related to both increased levels of mobility (Glick, Fischer, Heisey, Levenson & Mann, 2004; Tannenbaum et al. 1989; Lohiya et al. 1999) and decreased levels of mobility (Peabody & Stasikelis, 1999), depending on the population studied. Presumably, individuals who are confined to bed have lower risk for trauma in spite of lower BMD, and those who are more mobile have increased risk for falls and other trauma through use of assistive devices and during transfers. In addition, many individuals with DD have limited ability to communicate their discomforts, leaving them potentially vulnerable to undiagnosed and untreated fractures.

Problems with menstrual hygiene are reported for a subgroup of women with DD, including menorrhagia, cyclic increases in behavioral problems or self-injurious behavior (Taylor, Rush, Hedrick, & Sandman, 1993; Carr Smith, Giacini, Whelan & Pancari, 2003), cyclic increases in seizure activity (Quint, Elkins, Sorg, & Kope, 1999; Molsa, 1986; Chamberlain, Rauh, Passer, McGrath, & Burket, 1984; Grover, 2002; Servais, et al. 2002) and limited or no ability to self-manage menstruation. Surgical means to address problems with menstruation have included hysterectomy and endometrial ablation (Amesse, Boyce, & Pfaff-Amesse 2006; Wingfield, McClure, & Mamers, et. al., 1994). Pharmacological strategies historically included the oral progestins lynestrenol and norethisterone (Molsa, 1986; Huovinen, 1993), but these have been replaced over time by use of intramuscular depot medroxyprogesterone acetate (DMPA) (Chamberlain, Rauh & Passer, et. al., 1984; Servais, Jacques, & Leach, et. al., 2002; Grover, 2002; Dizon, Allen, & Ornstein, 2005). DMPA is a progestin-only drug which is given to women and girls with DD for either menstrual suppression, contraception, or both. It is used at a higher rate among women with disabilities than women in the general population (Servais, Jacques, & Leach, et. al., 2002). DMPA is administered by intramuscular injection every 90 days in a long-acting depot form. It works by suppressing the pituitary gonadotrophins, leading to hypoenestrogenemia, anovulation, endometrial atrophy, and in many women, cessation of menses. DMPA became available world-wide as a contraceptive in the 1970's, however, it was not approved for that purpose in the United States until 1992 due to concerns about possible cancer risks. Though not then approved as a contraceptive, DMPA was available in the U.S. prior to 1992 and was felt to have distinct advantages for adolescents in need of contraception, particularly those with mental retardation, due to the fact that it need only be administered every three months and was very reliable (AAP, 1980). Once concerns about cancer risks were dispelled, DMPA was considered to have no significant risks and few side effects other than possible weight gain and menstrual irregularities (Fredriksen, 1996). DMPA has continued to be a recommended choice for women with disabilities for whom estrogen is contraindicated due to thrombotic risks, for those who have increased seizures related to their menstrual cycles,

and for women who are unable to self-manage menstrual care. (Penovich, Eck, & Economou, 2004; Grover, 2002; Servais, Jacques, & Leach, et al. 2002). It is a highly reliable contraceptive for women who are not able use barrier methods of contraception and may be at increased risk of sexual exploitation or abuse due to physical or cognitive limitations.

Concerns about effects of DMPA on BMD have increased over the years. Use of DMPA in the general population has been associated with significant decreases in BMD (Berenson, Radecki, Grady, Rickert & Thomas, 2001; Scholes, LaCroix, Ott, Ichikawa & Barlow, 1999; Scholes, LaCroix, Ichikawa, Barlow & Ott, 2002; Scholes, LaCroix, Ichikawa, Barlow & Ott, 2005) and rates of bone resorption that are higher than rates of bone formation (Ott et al. 2001). In the only reported study to prospectively measure baseline BMD on all participants prior to initiation of DMPA (Clark, Sowers, Nichols & Levy, 2004), first-time DMPA users experienced bone loss which began with the first injection and continued through at least two years of continuous use. There appears to be recovery of BMD beginning immediately following discontinuation, but how much recovery can be expected and over what period of time remain to be determined (Scholes, et al. 2005).

Long-term use of DMPA for menstrual suppression and contraception is a modifiable risk factor for osteoporosis. This is of particular concern in women who also take AEDs, which are known to be associated with decreased BMD (Jaffe et al. 2005; Ray, et al. 2002) and increased fracture risk in people with DD (Bischof, Basu, & Pettifor, 2002; Tannenbaum et al. 1989; Lohiya et al. 1999). Women with DD are likely to begin DMPA at a young age, often near menarche, and to continue its use over a long period of time without opportunity for recovery of bone loss. Decrease in bone mass during adolescence is of particular concern because adolescents are normally gaining bone density during these years. Losses at this time likely affect peak bone mass, thus increasing fracture risk later in life.

While it is generally known that DMPA is given to women with DD, there are no published protocols for prescribing it in this population, and no population data on prevalence of use or outcomes of long-term use. This study was initiated to obtain data on associations between fracture incidence and drug use (DMPA, AEDs) in women with DD in Washington State.

MATERIALS AND METHODS

This was a descriptive cross-sectional population-based study including all females age thirteen and older who 1) received fee-for-service Medicaid in Washington State in 2002, 2) had an indicator code in their Medical Assistance Administration (MAA) record for DD, and 3) were eligible for services as indicated by Washington State Division of Developmental Disabilities (DDD) for the year 2002. The study was approved by the Washington State Institutional Review Board. Not included in this data extraction were males, those on managed care Medicaid, and those residing in large institutions for persons with DD or mental illness.

Data were extracted from DDD and MAA records of females thirteen years of age and older who were listed in both programs. Data were received in two files: one file contained demographic data from DDD and the other claims data from MAA. Each individual was identified by an encrypted number for matching the two files. Claims data file included encrypted ID, diagnostic and procedure codes, drug class, national drug codes and drug quantities. An individual could have multiple records in each file. For data analysis, a file was created with a single record for each individual that included both demographic and claims data. Records were excluded for fifteen individuals for whom there were Medicaid claims data, but no corresponding demographic data from DDD.

Incidence of osteoporotic fracture (yes or no for the year) was the outcome measure. The number of individuals who sustained at least one fracture is reported. Fractures were counted

if they fit the criteria for osteoporotic fracture as described by Kanis, et.al. (2001). This method includes fractures which have been shown to be associated with decreased BMD and which increase in incidence with age in the general population. For women, this algorithm includes all fractures except those of skull, face, hands and feet, fingers and toes, ankles and patellae.

An algorithm was developed for fracture in which fracture was presumed if there was a diagnostic code for fracture or if there were both a procedure code for fracture treatment and an x-ray. A variable for confirmed fracture indicated whether the algorithm for fracture was met for each individual. Variables were also created to indicate whether each subject had any procedure for treatment of fracture, any x-ray, any diagnosis of osteoporosis, or any BMD test during the year.

Drug information in the claims data was indicated by a variable for drug class and a variable for the specific drug indicated by its national drug code. Women were counted as taking a drug if they had any claim for it during the year. All AEDs were included, whether or not they have been shown to be associated with decreased BMD, based on the likelihood that any individual currently receiving any AED for seizures would likely have a past history of using either enzyme-inducing AEDs or valproate, both of which have been shown to affect BMD. Use of AEDs does not necessarily indicate a seizure disorder, since some are now routinely given for behavior stabilization as well, meaning an unknown segment of the sample may not have been life-long users of AEDs.

Because age and race are predictors of BMD and fracture rates, they were included as confounding variables. Because 83% of the sample was white and the 'other' and 'unknown' categories accounted for 5% of the sample, numbers in the remaining race categories were small. For this reason, race was recoded to 'white' or 'non-white'. The category of 'other' was included in 'non-white' and 'unknown' was included in 'white'. Age was calculated by subtracting the year of birth from 2002.

Data were analyzed using descriptive statistics and logistic regression. For logistic regression we controlled for age and race (as white or non-white), use of DMPA, and use of AEDs. The alpha was .05. We tested for interaction between DMPA and AEDs using Chi square.

RESULTS

The sample consisted of 6,773 women, ages 13 to 94 with a mean age of 36. Eighty-three percent of the sample was white. Of the 6,773 women in the sample, 360 (5.3%) received DMPA, 1909 (28.2%) received AEDs, and 152 (2.2%) received both during 2002. One hundred forty women (2.1%) experienced at least one osteoporotic fracture during the year.

Among the 360 women using DMPA, 13 (3.6%) experienced at least one osteoporotic fracture (See Table 1). The odds ratio of fracture for users of DMPA compared to non-users, controlling for age, race and use of AEDs, was 2.5 (CI 95%, 1.3–4.5). To get a better comparison group for DMPA users, we next divided the sample into two groups at age 55 based on the idea that DMPA use would cease after the age of menopause. Odds ratio for fracture among DMPA users when compared only to non-users age 55 or younger was 2.6. The absolute rate of fracture among these pre-menopausal age women was also significant at 3.6 fractures per 100 person years, compared to only 1.3 per 100 person years in women 50–55 years of age in a population sample taken in Olmstead County, Minnesota (Melton III, Crowson & O'Fallon, 1999).

Among the 1909 women using AEDs, 60 women (3.1%) experienced at least one osteoporotic fracture (See Table 2). The odds ration for fracture among those receiving AEDs compared to non-users, controlling for age, race and use of DMPA, was 1.9 (CI 95%, 1.3–2.6). An interaction term for DMPA and AEDs was not significant and the data are thus consistent with

the two effects being additive. When the sample was divided into those 55 and younger vs. those older than 55, there was significant increase in fracture incidence with age among those using AEDs. In the older group, the osteoporotic fracture rate was 8.5 per 100 person years.

Of the entire sample, 39 (0.6%) had been given a test for BMD during 2002, 216 (3.2%) had received bone ossification drugs, and 55 (0.8%) had a diagnosis of osteoporosis recorded for at least one medical encounter during the year. Bone ossification drugs included bisphosphonates, serum estrogen receptor modulators and salmon calcitonin. When the sample was divided at age 55, 2% of those age 55 or less and 12.3% of those over age 55 had used bone ossification drugs during the year. Similarly, 0.5% of those age 55 or less and 1.1% over age 55 had been given bone density testing during the year. Rates of supplementation with calcium and vitamin D were also very low, but may not represent actual rates of use due to the fact that they are available over the counter and may not have been charged to Medicaid. Among those 140 who had osteoporotic fractures, seven (5%) had a diagnosis of osteoporosis recorded, five (3.6%) had been given tests for bone density, and 23 (16.4%) were receiving bone ossification drugs.

DISCUSSION

This is the first population-based study to examine association between fracture and use of DMPA in women with DD. This study includes a large percentage of the non-institutionalized women with DD identified in our state and offers previously unpublished information on rates of use of DMPA among this population as well as rates of use of AEDs. It is also a community-based sample in that it does not include women currently living in large institutions. Due to extensive deinstitutionalization in Washington State, this community-dwelling population can be expected to include individuals with a full range of disability severity.

The results of this study demonstrate that women with DD who receive DMPA, AEDs, or both are at significantly increased risk of osteoporotic fracture compared to those who do not. They also suggest that this high-risk population is being under-screened and under-treated when they demonstrate risk factors or experience fractures.

Few data are available on fractures associated with DMPA in the general population as BMD change is the variable most commonly used in studies of DMPA and bone health. One well-controlled study of 3758 female U.S. Army recruits (Lappe, Stegman Recker, 2001), designed to determine risk factors for stress fractures during basic training, found that use of DMPA for contraception significantly increased the relative risk for stress fracture among non-Hispanic white recruits, but not among recruits of other races (RR 1.71, CI 1.01–2.90; $p=.04$). This risk no longer reached significance when the investigators controlled for BMD, suggesting that the risk of fracture associated with use of DMPA was related to a decrease in BMD.

It has been established in institutionalized populations that people with severe DDs have decreased bone density and high rates of fracture. Sample sizes are often too small to compensate for the fact that a large percentage of the sample is non-ambulatory and/or taking AEDs, thus limiting the ability to distinguish between the relative contributions of those risk factors. Studies in community-dwelling adults are limited in number, but have confirmed decreased BMD and increased fracture rates in samples with less severe disabilities. Among a sample of 94 predominately community-dwelling adults with DD (Center, et al 1998), small body size, hypogonadism, and Down Syndrome were predictive of low BMD. For females in that sample, low BMD was also associated with history of fracture, high phosphate and low Vitamin D levels.

The Surgeon General's Report on Bone Health and Osteoporosis (U.S. Department of Health and Human Services, 2004) suggests that a significant part of the problem with osteoporosis

in the United States lies in failing to apply what is already known about prevention, diagnosis and treatment. Similarly, the Surgeon General's report on Health Care Disparities and Mental Retardation addresses the poor health and lack of quality health care for people with mental retardation. These issues are reflected in this data in the fact that only 0.6% of this sample was tested for BMD during 2002 and only 3.2% were being treated with bone ossification drugs. Although the first symptom of osteoporosis is fracture and this population has multiple risk factors it appears many do not receive a diagnosis of osteoporosis or treatment with bone ossification drugs even with fracture occurrence. Undiagnosed fractures, especially those of the vertebrae, can lead to significant deterioration and decreased quality of life. One stark example was an investigation of unexplained declines in function in 48 adults in an intermediate care facility. Clinical records indicated that the level of mental retardation of the 48 adults ranged from mild to severe. Investigation of functional decline of these individuals led to identification of previously undiagnosed spinal cord compromise in 30 residents (Curtis et al, 2004). This compromise was attributed in each case to either spinal stenosis/degenerative disease, prolapsed disc, or spinal cord compression. Each of these conditions was significantly related to both use of AEDs and age. Curtis reports that many of these residents improved behaviorally after their conditions received appropriate treatment, whether surgical, non-surgical or conservative, suggesting the presence of undiagnosed pain prior to treatment. Treatment decisions must be based on clinical judgment and weighing of risks of

The current study is limited by its cross-sectional nature and the fact that it utilized administrative data. Relevant clinical information such as specific diagnosis, severity of disability, and ambulatory status were not available. No information was available on past drug use or reason for use of current drugs. Many may be recent or previous users of DMPA or AEDs. The error rate for the data, such as the accuracy of diagnostic and procedure codes, is not known.

CONCLUSIONS

In spite of the cross-sectional nature of this study and the limitations of administrative data, these findings point to the need for extremely judicious use of DMPA for menstrual suppression or contraception in women who have developmental disabilities. In our data, not only is the risk for fracture high, but the absolute rate of fracture is also high. Our conclusion is reinforced by a black box provider alert issued by the FDA and Pfizer November 18, 2004, indicating that Depo-Provera should be used for contraception for less than two years, if feasible, due to bone loss which is more significant with longer use and may not be completely reversible, particularly when used in adolescence and early adulthood. In spite of this warning, DMPA is still being recommended for adolescents when associated risks are weighed against risks of teen pregnancy (Cromer, Scholes, Berenson, et. al., 2006).. This may be justified in the general population based on the high risks of adolescent pregnancy, the fact that this group tends to use DMPA for short periods of time and the evidence of recovery of BMD after discontinuation. DMPA is also an important drug for use as a contraceptive in women with disabilities, a group at increased risk of manipulation or abuse and for whom pregnancy may pose significant risks. (Cromer, et.al., 2006). However co-occurring risks for low BMD in this population should be included in the risk-benefit analysis. Of concern is the fact that women with more severe disabilities, and therefore more risk factors for low BMD, are also more likely to be given DMPA for menstrual suppression and/or contraception over extended periods of years. Clinical and epidemiological research is needed to determine the risk profile for this drug for women with disabilities and to explore alternative treatment protocols for girls or women who need safe and reliable contraception or are experiencing significant menstrual problems related to their disabilities. Current or past use of DMPA should be considered a risk factor for fracture and be taken into account in decisions regarding screening for risk factors and bone density among women who have DD. While use of AEDs for seizures is unavoidable, our findings

reinforce previous work such as that of Curtis et al. (2004) which points to the need for earlier screening of bone density in those using AEDs. Risk for fracture among this group is high, particularly among those older than 55 years of age. The high rate of use of AEDs among those with DD also increases the likelihood of dual use of medications that may decrease bone density.

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Table 1

Fracture incidence and DMPA use

	Women using DMPA		Women not using DMPA		Odds ratio *	(95% CI)	p-value
	Total N	N (%) with fracture	Total N	N (%) with fracture			
All women	360	13 (3.6)	6413	127 (2.0)	2.5	(1.3-4.5)	.003
Women < age 55	359	13 (3.6)	5615	89 (1.6)	2.6	(1.4-4.7)	.002
Women > age 55	1	0	798	38 (4.8)	0	--	1.0

* Controlled for age and race.

Table 2

Fracture incidence and AED use

	Women using AEDs		Women not using AEDs		Odds ratio [*]	(95% CI)	p-value
	Total N	N (%) with fracture	Total N	N (%) with fracture			
All women	1909	60 (3.1)	4864	80 (1.6)	1.9	(1.3–2.6)	.000
Women < age 55	1696	42 (2.5)	4278	60 (1.4)	1.7	(1.1–2.5)	.013
Women > age 55	213	18 (8.5)	586	20 (3.4)	2.7	(1.4–5.2)	.004

^{*} Controlled for age and race.