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Increasing Use of ADHD Medications in Pregnancy

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ADHD; medication use; pregnancy

To the Editor:

Attention-deficit hyperactivity disorder (ADHD) is one of the most common conditions of childhood^{1, 2} and is typically treated with medication. Once initiated, medication often becomes chronic therapy and approximately 30% of patients are estimated to continue pharmacologic treatment into adulthood³. As a result, these drugs are likely to be used by pregnant women, raising concerns about possible fetal exposure. A recent publication noted that premarket studies focused only on the short-term safety and efficacy of these medications in children⁴; further, no premarketing studies have focused on pregnant women and their offspring. To identify the prevalence of use of ADHD medications among pregnant women, we reviewed data from the Slone Epidemiology Center's Birth Defects Study (BDS), an ongoing case-control surveillance effort focused on birth defects in relation to antenatal medication use.

BDS methods have been described previously^{5–7}. Infants with any of a wide range of malformations (cases) are identified at hospital-based study centers and state-based birth defects registries; during the years of the present analysis, these include the areas surrounding Philadelphia, Toronto (through 2003), San Diego (initiated 2000), and Nashville (initiated 2012), as well as a portion of New York State and the state of Massachusetts. A sample of nonmalformed infants (controls) is identified at study hospitals in all centers; in 1998, enrollment in Massachusetts was expanded to include a population-based random sample of newborns. The current analysis was restricted to interviews conducted between 1998 (corresponding to women whose last menstrual period [LMP] was in 1997), and July, 2014 (LMPs in 2013).

To identify medication exposure, BDS uses a series of questions designed to maximize recall. We first inquire about specific illnesses and conditions that may have occurred during pregnancy, followed by questions about use of medications for specific indications; we then inquire about certain specifically-named medications. In July, 2013, we added a specific indication for ADD/ADHD ("attention disorder, [ex, ADD or ADHD]"). Prior to that, these

medications were typically reported in response to the indication “Other psychological condition” or “Medication for any other reason.” Because of this change in the specificity of the question, we examined trends separately for the interviews conducted before and after its introduction. We defined medications used to treat ADHD to be any of the following: amphetamine mixed salts (Adderall®/Adderall XR® and generics), methylphenidate HCl (Ritalin®, Concerta® and generics), lisdexamfetamine dimesylate (Vyvanse®), dextroamphetamine (Dexedrine® and generics), and atomoxetine (Strattera®). We included all exposures at any time from the LMP through the pregnancy.

This study has been approved by the institutional review boards of Boston University Medical Center and all participating institutions as appropriate.

There were 29,540 women who were interviewed between 1998 and 2014; 87 reported exposure to an ADHD medication. While the overall prevalence of use of any ADHD medication was 0.3%, there was a marked increase in the prevalence of use over the period of the study, from 0.2% for women with LMP dates in 1997–98 to 1.3% for women with LMP dates in 2013 (2-sided Cochran-Armitage test for trend: $p<.0001$), Figure 1). Because of the addition of a specific ADHD indication prompt in mid-2013, affecting women with LMP dates in 2012, we examined the prevalence of use for LMP year 2012 according to whether the interviews were conducted before or after the change. For subjects with LMPs in 2012, 902 were interviewed prior to the introduction of the new prompt and use was 0.9%; among the 1,352 interviewed with the new prompt, the prevalence was 1.0%. We therefore combined the pre- and post-modification data.

The most commonly-reported ADHD medication was amphetamine mixed salts (Adderall®/Adderall XR® and generics), which accounted for 57.5% of total exposures. Use of this product was not reported for LMP years 1997–98, while for LMP year 2013 the prevalence was 1.0% (2-sided Cochran-Armitage test for trend: $p<.0001$, Figure 1); this increase entirely accounts for the overall increase in ADHD medications. Other medications included methylphenidate (Ritalin®, Concerta® and generics), lisdexamfetamine dimesylate (Vyvanse®), and atomoxetine HCl (Strattera®), accounting for 29.9, 5.7, and 3.4% of total exposures, respectively.

Of the 87 women who were exposed to an ADHD medication, all but one used it during the first trimester; 18 (20.7%) continued use into the second trimester and 11 (12.6%) continued into the third trimester.

We examined trends separately for cases (19,811) and controls (9,729) and for each center (Boston, 9,476; Philadelphia, 7,970; Toronto, 3,323; San Diego, 4,969; New York, 3,531; Tennessee, 271). The secular trends were not explained by either factor; the trends were most striking in the centers with the largest sample sizes.

We observed a markedly increasing trend in the use of ADHD medications in pregnancy from 1998 through 2013. Given other reports documenting that use of these drugs is increasing in the adult population, this is not surprising^{2, 8}. To our knowledge, only one other study, conducted in Denmark, has examined trends in the use of ADHD medications specifically among pregnant women⁹. Our observation, together with similar findings from

Denmark through 2010⁹, raise particular concern because pregnant women constitute a special population for whom exposure carries a potential risk not only to the woman herself, but also to the fetus she is carrying. In animal studies, methylphenidate has not produced teratogenic effects in mice or rats; in rabbits, only doses that were about 40 times the maximum recommended human dose resulted in an increased risk of spina bifida¹⁰. Amphetamines given orally in doses approximately 1.5 and 8 times the normal human dose to both pregnant mice and rabbits had no apparent effects on fetal development, although parenteral doses at approximately 6 times the human dose resulted in fetal malformations in mice.¹¹ However, it is important to note that animal studies are not predictive of human effects¹²; teratogenicity in animals does not imply the same effect in humans, and lack of teratogenicity in animals does not ensure no effect in humans¹³.

The few human studies that have explored possible effects of these drugs on the fetus included only small numbers of subjects^{14, 15} or were primarily focused on methylphenidate¹⁵⁻¹⁷, while our experience indicates that amphetamine mixed salts is by far the most common (and most rapidly increasing) ADHD medication used by pregnant women in the United States.

With exposure prevalence now approximately 1%, these drugs rank among the most commonly used prescription medications in pregnancy,^{18, 19} and it is also possible that use will increase further as more women whose exposure began in childhood enter childbearing age. Additional exposures could occur from expanded indications as at least one medication is currently under review for a possible new indication to treat binge eating^{20, 21}.

This study relies on self-report, which represents both a potential limitation and a strength. The limitation relates to possible underreporting; however, our interview is designed to maximize recall²². A strength of our approach is that analyses based on exposures identified through other sources, e.g., medical records or claims data, may include prescriptions that are unfilled or unused and fail to capture medications that are borrowed²³, all of which can have a major impact on results.

The increase in use of ADHD medications in pregnancy, and particularly Adderall®/Adderall XR®, amphetamine mixed salts), together with the troubling lack of information regarding potential fetal risks in humans, indicate that this is an area where postmarketing studies are urgently needed.

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Key points

1. Use of ADHD medications is increasing among pregnant women.
2. This increase is entirely accounted for by increased use of Adderall[®]/Adderall XR[®].
3. There is little information on possible risks to the fetus from such exposure.

Figure 1.

Trends in the use of ADHD medications during pregnancy according to LMP year

*Interview modification introduced in 2013 affected this LMP year (see text).

**Adderall®/Adderall XR®=amphetamine mixed salts