Clinical and Practical **Psychopharmacology**

Gestational Exposure to Benzodiazepines and Z-Hypnotics and the Risk of Autism Spectrum Disorder and Attention-Deficit/Hyperactivity Disorder in Offspring

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Each month in his online column, Dr Andrade considers theoretical and practical ideas in clinical psychopharmacology with a view to update the knowledge and skills of medical practitioners who treat patients with psychiatric conditions.

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ABSTRACT

Two recent cohort studies, one from Norway and the other from Taiwan, examined for perhaps the first time whether gestational exposure to benzodiazepines and to z-hypnotics was associated with a clinical diagnosis of autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) in offspring. The studies had important methodological strengths that are not often seen; these included actual assessment during pregnancy of whether drugs prescribed were used, and, if so, when; adjustment of analyses for postbaseline time-varying covariates; inclusion of discordant sibling pair and paternal exposure analyses; inclusion of pre-pregnancy vs intrapregnancy analyses; and others. The studies also had important limitations; these included inadequate statistical power resulting in a failure to identify potential associations in even unadjusted analyses; lack of information on intermittent use vs daily dosing; and others. The strengths and limitations are identified and explained to empower readers to identify similar issues in other studies. Important findings apparent in these studies are that benzodiazepine exposure may be associated with an increased risk of both ASD and ADHD, regardless of the trimester of exposure. The magnitude of increased risk is small and diminishes to statistical nonsignificance in adjusted analyses. The risks appear elevated in association with paternal exposure. In discordant sibling pair analyses, risks do not appear to be significantly higher in the exposed sib relative to the unexposed sib. These findings imply that observed associations, if any, between gestational exposure to benzodiazepines and ASD or ADHD in offspring may be due to maternal and paternal genetic factors, to family environmental variables, and to confounding by indication, rather than to benzodiazepine exposure itself. Nevertheless, decision-making should be tailored to individual context and shared between prescriber and patient. Finally, no conclusions can be drawn regarding the neurodevelopmental safety of z-drug exposure during pregnancy.

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Maternal use of medications during pregnancy is often discouraged because of a possibly increased risk of a large number of adverse gestational outcomes, ranging from spontaneous abortion and preterm birth to major congenital malformations and poor neonatal adaptation syndrome. Very many studies have examined risks associated with psychotropic drug use during pregnancy, including the risk of impaired offspring neurodevelopment following gestational exposure to sodium valproate, antidepressant drugs, and antipsychotic drugs. Earlier articles in this column discussed gestational exposure to antidepressants and antipsychotics and the risk of neurodevelopmental disorders in offspring[1–4] as well as gestational exposure to benzodiazepines and the risk of spontaneous abortion and congenital malformations.[5–7] The present article examines the risk of gestational exposure to benzodiazepines and z-hypnotics (zopiclone, zolpidem) and the risk of neurodevelopmental disorders in offspring.

Background

Pregnancy is associated with psychological, physiological, and even physical stress, and so pregnant women may be as or more vulnerable to mental health disturbances, such as anxiety, as women in the general population. Sleep may be disturbed during pregnancy, either as an isolated symptom or in conjunction with a mental health disorder. Benzodiazepines and z-drugs are used to treat anxiety and sleep disturbances; so, these drugs may be prescribed to women who need them during pregnancy. These drugs may be used either daily, if symptoms reach diagnostic thresholds, or intermittently, for occasional anxiety and difficulties with falling or staying asleep.

In a systematic review and meta-analysis of 32 studies with data from 28 countries (pooled N = 7,343,571 pregnancies), the pooled prevalence of benzodiazepine use (or prescription) during pregnancy was 1.9%; this value was 3.1% in the third trimester.[8] In recently published studies, the exposure rate during pregnancy was 0.8% for benzodiazepines and z-drugs in Norway[9] and 5.0% for benzodiazepines in Taiwan.[10]

Systematic Reviews

In a systematic review, Wang et al[11] identified 19 cohort studies of neurodevelopmental outcomes following benzodiazepine and z-drug exposure during pregnancy. These studies had examined neurodevelopment in cognitive, emotional, behavioral, and motor domains. Almost all

Table 1. Strengths of the Study by Sundbakk et al[9]

1. Whether or not women took benzodiazepines and z-drugs during pregnancy was assessed using questionnaires that had been administered to and completed by the women during their pregnancies. This point is important because most studies on gestational exposure to psychotropic drugs assess exposure from medical records, in the form of prescriptions issued or medications dispensed. Records-based assessments can result in exposure misclassification because women may not necessarily use the drugs that were prescribed and dispensed.
2. The timing of exposure was assessed, as above, using questionnaires. This is important in benzodiazepine and z-drug exposure studies because these drugs are often used based on need, and not necessarily continuously, and may therefore be taken in a time window different from that in which they were prescribed.
3. ADHD was examined as actual diagnoses in children who were followed to a mean age of 11 years. This is important because most previous studies examined only clinical ratings of neurodevelopmental characteristics as proxies for ADHD; there is no assurance that elevations in ratings, if any were obtained, would reach clinically relevant thresholds.
4. Analyses were adjusted for important baseline covariates. These included usual covariates such as maternal age, marital status, parity, body mass index before pregnancy, education, income, whether or not the pregnancy was planned, whether or not folic acid supplementation was used, etc. These also included covariates that are not commonly available in studies of this nature, such as smoking, alcohol use, illicit drug use, history of major depression, history of sleeping difficulties, adverse life events, obstetric comorbidities, and use of medications for ADHD. This is important because it attempts adjustment for genetic and environmental risk factors for ADHD.
5. Analyses were adjusted for time-varying covariates. These included ratings of anxiety and depression during pregnancy and use of different categories of psychotropic and nonpsychotropic medications during pregnancy. This is important because most studies adjust analyses only for covariates that had been measured at baseline; such studies are unable to adjust for confounding that arises from postbaseline changes.

Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

Table 2. Strengths of the Study by Chen et al[10]

1. The sample was very large and the number of exposed pregnancies was also large. Thus, most if not all analyses were reasonably adequately powered or better.
2. ASD and ADHD were examined as actual diagnoses in children who were followed for a mean of 8.5 years. This is important because most previous studies examined only clinical ratings of neurodevelopmental characteristics as proxies for ADHD; there is no assurance that elevations in ratings, if any were observed, would reach clinically relevant thresholds.
3. The authors conducted a discordant sibling pair analysis. That is, they examined the risk of ASD and ADHD in siblings who did vs did not have gestational exposure to benzodiazepines. If the risk was greater in exposed vs unexposed sibs, it could indicate that exposure or confounding by indication (or both) drove the risk. If the risk was not greater in exposed vs unexposed sibs, it would suggest that the risk in exposed children observed in crude analyses was driven by parental genetic and family environmental variables that were shared by the sibs.
4. The authors conducted a paternal exposure analysis. That is, they examined the risk of ASD and ADHD in children whose fathers had been exposed to benzodiazepines during the mother's pregnancy. Because benzodiazepines used by fathers cannot directly affect gestational outcomes in the mothers, increased ASD and ADHD risks in offspring would suggest that paternal genetic characteristics could explain the risks.
5. The authors compared exposure during pregnancy with exposure in the window 90–270 days before pregnancy. There is no pharmacologic reason to expect that exposure in a time window so far before gestation could affect pregnancy outcomes; therefore, such an analysis could partly control for confounding by indication. So, if gestational exposure was found to be associated with greater risk, then either exposure or residual confounding (or both) would explain the risk. If gestational exposure was not associated with greater risks, it would suggest that genetic and shared family environmental variables may have been responsible for the increased risks observed in the crude analyses. This analysis is similar to the discordant sibling pair analysis; the only difference is that in this analysis the unexposed sib was "exposed" 90–270 days before pregnancy whereas in the discordant sibling pair analysis the unexposed sib was completely unexposed.

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ASD = autism spectrum disorder.

studies assessed outcomes using rating instruments rather than clinical diagnoses. Some studies found significant associations between medication exposure and impaired neurodevelopment in some domains; most studies, however, found no significant associations. These reassuring findings were supported by the possibility that the significant associations were driven by confounding by indication; that is, the maternal condition that necessitated treatment with benzodiazepines or z-drugs may have predisposed to the adverse neurodevelopmental outcomes rather than the medications themselves.

In another systematic review of much the same data, Jensen et al[12] identified 13 cohort studies of psychological, social, motor, and other neurodevelopmental outcomes in children who had had prenatal exposure to benzodiazepines or z-drugs. They found some evidence that exposure was associated with an increased risk of internalizing problems, gross motor skill impairments, academic underachievement, and attention-deficit/hyperactivity disorder (ADHD) traits in exposed children. However, they noted that the findings were inconsistent and of uncertain clinical relevance, that the persistence of the findings in later childhood remained to be demonstrated, and that confounding by indication and selection bias may have been responsible for significant associations.

Two new cohort studies have now been published.[9,10] Both studies had important methodological strengths (Tables 1 and 2) and are considered in the present article.

The Study From Norway[9]

Sundbakk et al[9] examined the risk of ADHD in children who had been gestationally exposed to benzodiazepines or z-drugs. The data were extracted from the population-based Norwegian Mother, Father, and Child Cohort Study. Subjects in the study were recruited during 1999–2008 and were assessed during pregnancy using questionnaires. The final

Table 3. Important Findings From the Study by Sundbakk et al[9]

1. In unweighted (crude) analyses, exposure to benzodiazepine or z-drugs was not associated with a diagnosis of ADHD in either the full sample (HR, 1.34; 95% CI, 0.91–1.99) or in the sample of women with mental health conditions (HR, 1.25; 95% CI, 0.82–1.89). The associations were smaller in the weighted analyses: HR, 0.85 (95% CI, 0.51–1.42) and HR, 0.91 (95% CI, 0.55–1.50), respectively.
2. In the full sample, among women who used these drugs in the 6 months before pregnancy (n = 637), in comparison with those who discontinued treatment, those who continued treatment during pregnancy (n = 220) were not at increased risk of the exposed child receiving a diagnosis of ADHD (HR, 1.26; 95% CI, 0.56–2.85).
3. In the full sample, relative to no exposure, neither exposure in early pregnancy nor exposure in middle/late pregnancy was associated with an increased risk of ADHD in offspring. This was so in both crude and weighted analyses.
4. In the full sample, relative to exposure in a single 4-week window, exposure in 2 or more 4-week windows was not associated with an increased risk of ADHD in offspring. This was so in both crude and weighted analyses.
5. In the subsample of women with mental health conditions, early pregnancy exposure, middle/late pregnancy exposure, and exposure in 2 or more 4-week time windows were not associated with an increased risk of ADHD in offspring. This was so in both crude and weighted analyses.
6. The results were consistent in sensitivity analyses.

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CI = confidence interval, HR = hazard ratio.

Table 4. Important Limitations of the Study by Sundbakk et al[9]

1. The cohort from which the study sample was drawn included only 41% of eligible women; the remaining women did not consent to participate. So, we do not know how representative of the population the study sample was.
2. In the full sample, only 681 women reported benzodiazepine or z-drug exposure; so, the main analysis, and especially many if not all of the subgroup analyses, were very likely to have been underpowered. This probably explains why even the crude analysis of even the main dataset failed to identify a significant association between exposure and attention-deficit/hyperactivity disorder.
3. No information was available on the number of days of benzodiazepine or z-drug exposure in the 4-week windows; if many of the women had only occasional exposure, then the number of women with clinically significant exposure would have been even smaller than 681, and the ability of the study to identify significant risks would have been even further diminished.

sample comprised 82,201 mother-child dyads among whom 19,585 had received treatment for mental health indications. The mean age of the women was about 30 years. Slightly more than half of the sample was primiparous. In the full sample, 681 (0.8%) children had been gestationally exposed to benzodiazepines or to z-drugs (or to both). In the sample of mothers with mental health conditions, 468 (2.4%) had been exposed.

Women who reported benzodiazepine or z-drug exposure had higher rates of smoking, alcohol use, and illicit drug use during pregnancy; their pregnancies were less likely to be planned. They were more likely to report sleeping problems and a history of major depression. They were more likely to have used psychotropic and nonpsychotropic medications during pregnancy. Interestingly, their husbands were also more likely to have a history of major depression.

Exposure to benzodiazepines or to z-drugs during early pregnancy (weeks 0–16) was more common than exposure in middle or late pregnancy, and exposure in a single 4-week window was more common than exposure in more than one 4-week window.

The sample was followed until 2016; the mean duration of follow-up of the children was 11 years. A diagnosis of ADHD was recorded in 2.7% of children (3.9% in the women with mental health conditions). The risk of ADHD was assessed in the children after adjusting for baseline and time-varying covariates (Table 1).

Important findings from the study are presented in Table 3. In summary, in none of the crude or weighted main, subgroup, and sensitivity analyses was exposure to benzodiazepines or z-drugs during pregnancy associated with a statistically significant risk of ADHD diagnosis in the offspring.

Despite its strengths, the study had many limitations. Important limitations are listed in Table 4. The most important limitation, one that was not acknowledged either by the authors of the study[9] or by the authors of a commentary[13] on the study, is subtle: the study failed to identify a statistically significant association between gestational drug exposure and ADHD in the crude (unadjusted) analyses not only in the main sample but even in the subsample of women with mental health conditions. Readers who are familiar with the research will be aware that there is an increased prevalence of genetic, environmental, behavioral, and other risk factors for adverse gestational outcomes among women who use psychotropic drugs during pregnancy and that, for this reason (confounding by indication), crude analyses almost always show relationships between gestational exposure to psychotropic drugs and adverse gestational outcomes. So, in the study by Sundbakk et al,[9] if the number of exposed pregnancies was too small to detect a combined confounding plus drug effect, it was too small to detect a drug effect, if any existed; this means that the adjusted analyses were perhaps unnecessary. Furthermore, if the main analysis was underpowered, then all subgroup and sensitivity analyses were also underpowered, and the study therefore cannot provide reassurances about the safety of benzodiazepine and z-drug exposure during pregnancy.

The Study From Taiwan[10]

Chen et al[10] examined the risk of autism spectrum disorder (ASD) and ADHD in children who had been

Table 5. Important Limitations of the Study by Chen et al[10]

1. Analyses were adjusted for potential confounds such as maternal and paternal age, parity, family income status, maternal and paternal history of mental illness, maternal smoking and opioid use during pregnancy, and offspring gestational age at birth. However, surprisingly, no adjustment was made for other important confounds, such as maternal body mass index, maternal medical comorbidities, and maternal alcohol, psychotropic drug, and nonpsychotropic drug use during pregnancy.
2. No data on dosing were available. This is of concern because some women may have needed daily dosing whereas others may have used benzodiazepines on an as-needed basis for situational anxiety or insomnia. It is important to understand risks associated with the context of use.

Table 6. Main Findings From the Study by Chen et al[10]

For ASD:
1. In crude analyses, the risk of ASD in offspring was significantly or near-significantly increased following first (HR, 1.13; 95% CI, 1.05–1.21), second (HR, 1.10; 95% CI, 0.98–1.22), as well as third (HR, 1.21; 95% CI, 1.00–1.47) trimester exposure to benzodiazepines.
2. In adjusted analyses, the risks were attenuated and were no longer statistically significant. The trimesterwise HRs for ASD were 0.96 (95% CI, 0.89–1.03), 0.91 (95% CI, 0.82–1.02) and 1.01 (0.83–1.23), respectively.
3. In sibling pair analyses, the trimesterwise HRs for ASD were 0.92, 0.97, and 1.07, respectively, with no significant differences between exposed and unexposed sibling pairs.
For ADHD:
1. In crude analyses, the risk of ADHD in offspring was significantly increased following first (HR, 1.24; 95% CI, 1.20–1.28), second (HR, 1.27; 95% CI, 1.21–1.34), as well as third (HR, 1.25; 95% CI, 1.14–1.37) trimester exposure to benzodiazepines.
2. In adjusted analyses, the risk of ADHD was marginally significantly elevated after first (HR, 1.06; 95% CI, 1.02–1.10) and second (HR, 1.07; 95% CI, 1.02–1.12) but not third (HR, 1.05; 95% CI, 0.95–1.15) trimester exposure to benzodiazepines.
3. In sibling pair analyses, the trimesterwise HRs for ADHD were 0.91, 0.89, and 1.08, respectively, with no significant differences between exposed and unexposed sibling pairs.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ASD = autism spectrum disorder, CI = confidence interval, HR = hazard ratio.

gestationally exposed to benzodiazepines. The data were extracted from the Taiwan National Health Insurance Research Database for the period 2004–2017. The study sample comprised 1,138,732 mothers and 1,134,320 fathers of 1,516,846 children aged < 14 years who had been followed for a mean of 8.5 years.

Five percent of the children (n = 76,411) had been exposed to benzodiazepines during pregnancy. Exposure was classified by trimester, with prescriptions for the previous 90 days plus prescriptions during the trimester qualifying for exposure during that trimester. Whereas this inevitably created overlap, it was intended to include the possibility that, because medications were typically prescribed for 28–90 days, women might use the medications distal from the date of prescription. Exposure was recorded as 4.6%, 2.2%, and 0.6% for the first, second, and third trimesters, respectively.

Exposed mothers were more likely to have used opioids and were far more likely to have had anxiety, major depressive disorder, or any mental disorder than unexposed mothers. Data were unavailable for other covariates of importance (Table 5).

Among exposed vs unexposed children, ASD was diagnosed in 1.1% vs 0.9% and ADHD in 4.9% vs 3.9% of children, respectively. Diagnoses were based on at least 1 inpatient record or at least 3 outpatient records in order to improve the likelihood of valid diagnoses. Strengths and limitations of the study are presented in Tables 2 and 5.

Important findings from the study[10] are presented in Tables 6 and 7. In summary, in almost all of the crude analyses, gestational exposure to benzodiazepines was associated with a small but significantly increased risk of ASD and ADHD regardless of trimester of exposure; these findings attenuated and even lost significance in adjusted analyses. There was no significant increase in risks in discordant sibling pair analyses or in analyses of exposure during pregnancy vs exposure before pregnancy. Risks were very slightly but significantly increased in association with paternal exposure to benzodiazepines during maternal pregnancy. These findings suggest that there is a small association between gestational exposure to benzodiazepines and ASD or ADHD and that the risk is probably driven not by benzodiazepine exposure but by maternal genetic factors, paternal genetic factors, confounding by indication, and/or shared family risk factors. The possible contribution of confounding by indication is underlined by the absence of adjustment for important risk variables (Table 5).

A puzzling contradiction appeared in the findings and was not discussed by the authors: the risks for ASD and ADHD appeared greater and were more likely to be statistically significant when short- and long-acting benzodiazepine exposures were considered separately in subgroup analyses than when they were considered together in the main analysis.

Concluding Notes

Despite its many strengths (Table 1), no reassurances can be drawn from the study by Sundbakk et al[9] because the number of exposed children (n = 681) was too small for even the main analyses to be adequately powered. This means that no conclusions are possible about the neurodevelopmental safety of z-drug exposure during pregnancy. Conclusions about benzodiazepines can be drawn from the study by Chen et al.[10]

Table 7. Other Findings[a] From the Study by Chen et al[10]

1. For both short- and long-acting benzodiazepines, the risk of ASD was marginally but significantly increased after third but not after first- and second-trimester exposure. For both short- and long-acting benzodiazepines, the risk of ADHD was marginally but significantly increased after exposure in each trimester. However, in discordant sibling pair analyses, for both short- and long-acting benzodiazepines there was no significant increase in the risk of either ASD or ADHD in any trimester.
2. When analyses were restricted to mothers with anxiety or depression, in no trimester of pregnancy was gestational exposure to benzodiazepines associated with an increased risk of either ASD or ADHD; this was true in the discordant sibling pair analyses, as well. Interestingly, after first and second trimester exposures, there was actually a statistically significant *decrease* in the risk of ASD.
3. In sensitivity analyses, benzodiazepine exposure was not associated with an increased risk of either ASD or ADHD regardless of the definition of exposure examined.
4. Paternal exposure to benzodiazepines was associated with a small but significantly increased risk of ASD only after third trimester exposure but not after first or second trimester exposures. Paternal exposure to benzodiazepines was associated with a small but significantly increased risk of ADHD in all trimesters. In discordant sibling pair analyses, however, there was an increased risk only for ASD and only with third trimester exposure.
5. Relative to pre-pregnancy exposure, in no trimester of pregnancy was exposure to benzodiazepines associated with an increased risk of either ASD or ADHD. This was so in discordant sibling pair analyses, as well, though statistical power was low.

[a]All findings were from adjusted analyses. Most of these findings were presented in the supplementary file.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ASD = autism spectrum disorder.

The number of exposed children in the study by Chen et al[10] was more than a hundredfold larger (n = 76,411) than that in the study by Sundbakk et al.[9] In crude analyses, this study[10] found that benzodiazepine exposure was associated with an increased risk of both ASD and ADHD, regardless of the trimester of exposure. The magnitude of increased risk was however small, and the hazard ratios further decreased and were mostly not statistically significant in adjusted analyses. Furthermore, risks were elevated in association with paternal exposure; and in discordant sibling pair analyses, risks were not significantly higher in the exposed sib relative to the unexposed sib. These findings suggest that the observed association between gestational exposure to benzodiazepines and ASD and ADHD in offspring may be more due to maternal and paternal genetic factors, to shared environmental factors, and to confounding by indication, than to benzodiazepine exposure itself.

This reassurance is not testimony that benzodiazepines can be safely used in pregnancy. For one, the neurodevelopmental safety of gestational exposure to benzodiazepines at present rests on the single cohort study by Chen et al.[10] For another, other gestational risks associated with benzodiazepines need to be examined in context.[14–19] Decision-making should therefore be both tailored to individual context and shared between prescriber and patient.

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