Bupropion Use During Pregnancy: A Systematic Review

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ABSTRACT

Objective: To evaluate data on birth outcomes following bupropion use during pregnancy.

Data Sources: A systematic literature review of PubMed and PsycINFO was performed through June 2017 for clinical studies published in English. The following keywords were used: *bupropion*, *pregnancy*, *depression*, *smoking cessation*, *birth outcomes*, *miscarriage*, and *spontaneous abortion*. References and related articles were also searched to yield additional publications. With the exception of limiting the search to human subjects, no other limitations were applied in an effort to capture all relevant published studies.

Study Selection/Data Extraction: No studies were excluded. A total of 8 studies were included in this review.

Results: Bupropion's use in the first trimester has been linked with a small elevation in the risk of cardiovascular defects, although the absolute risk was low and confounding by indication (eg, use for smoking cessation) cannot be excluded. While the risk of miscarriage following prenatal bupropion exposure was higher than that of a control group of women in one study, it remained within the general population rate.

Conclusions: While more studies are needed, research to date suggests that bupropion may be a reasonable treatment option for depressed pregnant women who require pharmacotherapy, particularly when they also are attempting to reduce nicotine use during pregnancy.

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The pharmacologic treatment of depressed pregnant women presents a clinical dilemma for physicians and patients alike. Depression during pregnancy is associated with a number of adverse pregnancy outcomes including impaired fetal growth and preterm delivery.[1,2] Antidepressants can be helpful for these patients and are particularly valuable in cases when nonpharmacologic options have failed or are unavailable. Selective serotonin reuptake inhibitors (SSRIs) are the most widely prescribed antidepressants for pregnant women,[3] and an extensive literature now exists on their use prenatally. Findings are mostly reassuring,[4] although several studies[2,5,6] have reported troublesome outcomes in some exposed children. These outcomes have included neonatal symptoms, cardiovascular defects, and adverse developmental sequelae, including an elevated risk of autism spectrum disorders, although confounding factors may account for at least some of these findings.[2,5,6]

Further, SSRIs are ineffective for many patients or produce intolerable side effects.[7] It appears worthwhile, therefore, to broaden the pharmacologic treatment options for depressed pregnant women. Bupropion merits further study, as its mechanism of action, inhibiting norepinephrine and dopamine reuptake, appears to be distinctly different from that of SSRIs.[8] Bupropion's lack of serotonergic activity may be a valuable characteristic since alterations of serotonin systems in fetal brains have been linked to adverse developmental sequelae.[6,9] Serotonin plays an important role in fetal brain development, and "hyperserotonemia of autism" is considered a well-characterized biomarker in autism research.[10] While dopaminergic and noradrenergic antidepressants may also impact fetal brain development, little research has examined these effects. Of note, because of bupropion's distinctive mechanism of action, it is less likely than other antidepressants to produce common side effects, such as weight gain, sedation, and sexual dysfunction, and more likely to produce restlessness and reduce the seizure threshold.[8] To our knowledge, no data exist on newborns' risk of seizures following prenatal exposure to bupropion.

Bupropion also has a US Food and Drug Administration indication for smoking cessation and thus presents a reasonable option for pregnant depressed women wishing to reduce their nicotine use. Smoking cessation rates of women who use bupropion during pregnancy are significantly higher than those of untreated women.[11]

METHODS

A systematic literature review of PubMed and PsycINFO was performed through June 2017 for clinical studies

Clinical Points

- Bupropion may be a reasonable option for the treatment of depression among pregnant women.
- Bupropion can be especially helpful for pregnant women who need help with smoking cessation in addition to depression.

published in English. Keywords used were *bupropion*, *pregnancy*, *depression*, *smoking cessation*, *birth outcomes*, *miscarriage*, and *spontaneous abortion*. Resultant articles were cross-referenced for other relevant articles not identified in the initial search. With the exception of limiting the search to human subjects, no other limits were applied in an effort to capture all relevant published studies. No studies were excluded. A total of 8[11–18] studies were included in this review.

RESULTS

Birth Defects

To date, 7 studies have examined the rate of birth defects in children exposed prenatally to bupropion, including 3 prospective studies[12–14] and 4 retrospective studies.[15–18] In a prospective study[12] performed through a teratogen information service of 136 women who took bupropion in the first trimester, no major malformations were noted in any of the newborns. The study[12] included 2 matched comparison groups, one consisting of women taking other antidepressants (unspecified by the authors) and another of women exposed to no teratogens. Prospective data are also available from the Bupropion Pregnancy Registry,[13] which reported outcomes of 675 pregnancies with first-trimester bupropion exposure. The rate of birth defects was 3.6%, which is comparable to the general population rate.[13] The registry reported odds ratios of 0.95 and 0.97 for all congenital malformations and for cardiovascular malformations, respectively, and found no consistent pattern of defects. As participation in the registry was voluntary, the findings may have been biased or incomplete, and there were no data on a comparison group. Additional prospective data are available from a study[14] of 928 pregnant women taking antidepressants, 113 of whom took bupropion in the first trimester. The other antidepressants consisted of medications with serotonergic or mixed serotonergic/noradrenergic activity, namely citalopram (n = 184), escitalopram (n = 21), fluvoxamine (n = 52), nefazodone (n = 49), paroxetine (n = 148), mirtazapine (n = 68), fluoxetine (n = 61), trazodone (n = 17), venlafaxine (n = 154), and sertraline (n = 61). The study[14] included a matched comparison group of pregnant women taking no teratogenic medications. There were no defects reported in association with any of the antidepressants, including the bupropion exposures.[14]

The first of 4 retrospective studies[15–18] used medical and prescription claims data from a large managed care database (United Healthcare) over a nearly 10-year period. The study[15] compared infants whose mothers received prescriptions for bupropion in the first trimester (n = 1,213) with infants whose mothers received prescriptions for other antidepressants in the first trimester (SSRIs, serotonin-norepinephrine reuptake inhibitors [SNRIs], tricyclic antidepressants [TCAs], and monoamine oxidase inhibitors [MAOIs]) (n = 4,743) and with infants whose mothers received prescriptions for bupropion after the first trimester (n = 1,049). The authors found no evidence of a teratogenic effect from bupropion exposure in the first trimester: prevalence rates for congenital malformations were 2.31% for bupropion: first-trimester exposure, 2.32% for other antidepressants: first-trimester exposure, and 2.19% for bupropion: outside of the first-trimester exposure. Rates of cardiovascular malformations were also comparable among the 3 groups: 1.07% for bupropion: first-trimester exposure, 1.08% for other antidepressants: first-trimester exposure, and 9.5% for bupropion: outside of the first-trimester exposure.[15] While the use of prescription claims data has the advantage that it is unbiased by patient recall, drug exposure is not entirely certain.

A large retrospective case-control study[16] collected data on 6,823 infants with major heart defects and compared them with 5,869 control infants. Among all case and control mothers, 90 women took bupropion in the 1 month before to 3 months after conception. The study reported that mothers of infants with left outflow tract heart defects were more likely to have reported taking bupropion than mothers of control infants (adjusted odds ratio of 2.6). The authors[16] estimated an absolute risk of cardiovascular left outflow tract defects of approximately 2 of 1,000 pregnancies with first-trimester exposure. Of note, the number of exposed cases for this defect category was small (n = 10), thus the study was unable to stratify their analysis for type of bupropion prescription (Wellbutrin vs Zyban). As a result, the study could not control for confounding by indication (depression vs smoking cessation). This study[16] prompted a subsequent study[17] designed specifically to explore whether first-trimester bupropion exposure increases the risk of cardiovascular defects. The case-control study[17] included 39 exposures to bupropion and found no elevated rate of left outflow tract defects. However, a moderately increased risk of ventricular septal defects was observed (odds ratio of 2.5) among infants exposed to bupropion in the first trimester but only when bupropion was used alone; oddly, when bupropion was used with other antidepressants (SSRIs, venlafaxine, trazodone, and TCAs), there was no association with a higher risk for ventricular septal defects. The study[17] was also unable to control for confounding by indication (eg, smoking cessation) due to the small numbers of exposures. As the study[17] involved phone interviews of mothers several months after their children were born, recall bias could not be ruled out.

Finally, a group of epidemiologists[18] independently reexamined the data from the United Healthcare database described earlier.[15] Using a different classification system designed to facilitate the identification of isolated cardiac malformations, this reexamination reported an elevated risk

of left ventricular outflow tract obstructions associated with first-trimester exposure to bupropion, producing a risk of approximately 2.8 of 1,000 pregnancies.[18] In contrast, the prevalence of left ventricular outflow tract obstructions in the comparison group (ie, infants exposed to other antidepressants: SSRIs, SNRIs, TCAs, and MAOIs) was 0.7 (odds ratio of 4). Due to the small number of cases, this study[18] was unable to control for confounding by indication (eg, smoking cessation).

Miscarriage

The risk for miscarriage is high early in pregnancy, with a cumulative estimated overall risk of 14% to 22%,[19] and data on the impact of in utero bupropion exposure on the risk for miscarriage are limited. The Bupropion Pregnancy Registry,[13] which reviewed pregnancy outcomes from 1997 to 2008, did not calculate the risk of spontaneous pregnancy losses overall, as pregnancies were reported at variable times and any losses occurring early in gestation may not have been recognized or reported. However, in one prospective study[12] that followed 136 women exposed to bupropion during the first trimester of pregnancy, the authors found a significantly higher rate of miscarriages in the bupropion-exposed group compared to a control group of 133 women (14.7% vs 4.5%, $P = .009$). The authors[12] also compared outcomes for the subset of women taking bupropion for depression (n = 91) compared to women taking other antidepressants (n = 89) and the control group (n = 89) and found no significant differences among the 3 groups (15.4% vs 12.3% vs 6.7%, $P = .18$). In a third subanalysis of women taking bupropion for depression (n = 91) versus those taking bupropion for smoking cessation (n = 37) versus a control group of women (n = 133), the rates of miscarriages were comparable in the first 2 groups (15.4% and 16.2%), and both were significantly higher than the control group (4.5%, $P = .01$).[12] Subject groups were matched for confounding variables including age, alcohol and cigarette use, and gestational age at time of study contact. However, prenatal depression, also a potential risk factor for spontaneous abortion,[20] was not controlled between groups. Of note, rates of miscarriages associated with bupropion use were within the range for the general population, while rates in the control groups were unusually low.[12]

Gestational Age and Birth Weight

A study[12] that compared birth weights and gestational age of delivery among bupropion-exposed infants and controls found no differences between the groups. The mean birth weight among 136 newborns was 3,409 mg (7 lb 5 oz) compared to 3,446 mg (7 lb 6 oz) among controls, and the mean gestational age was 39.1 years compared to 39.3 years in the controls. Another study[11] compared 900 pregnant women who smoked during pregnancy with 72 women who smoked before gestation and used bupropion while pregnant and 316 women who smoked before gestation and used nicotine patches while pregnant. Adjusting for potential confounders, bupropion use was associated with a lower risk of prematurity compared to the smoking group (adjusted odds ratio of 0.12).[11]

Developmental Sequelae

To our knowledge, there are no data on developmental outcomes following prenatal exposure to bupropion.

CONCLUSION

Data on prenatal exposures to bupropion are gradually accumulating but remain sparse. Bupropion is not a widely used medication during pregnancy: approximately 0.7% of pregnant women take this medication at some time during pregnancy.[3] The available literature[12] shows that the rates of low birth weight and preterm births among bupropion-exposed pregnancies are comparable to general population rates. Three studies[12–14] found no increase in the rate of congenital defects, while 3 studies[16–18] reported elevated rates of cardiovascular defects, in particular, left ventricular outflow obstructions. The elevated risk of left ventricular outflow obstructions, if real, represents a 2 to 3 times higher rate than expected.[3] The overall absolute risk, however, remains small at 2.1–2.8 per 1,000 births. An additional finding of concern was the reported tripling in the rate of miscarriage linked with bupropion use in the first trimester. Notably, the rate remained within the general population range.

Several studies[16–18] were unable to control for confounding by indication (eg, use of bupropion for smoking cessation) due to the small numbers of exposures. Smoking may be a risk factor for cardiovascular defects[21] as well as for miscarriage.[22] Interestingly, many other antidepressants (including SSRIs, SNRIs, and TCAs) have also been linked with elevated rates of miscarriage,[23–26] suggesting that antidepressants as a group may increase this risk.

As bupropion affects different neurotransmitter systems compared to most other antidepressants, it presents an alternative option for depressed pregnant women who may require pharmacotherapy, particularly when they also are attempting to reduce nicotine usage. However, the number of reported prenatal exposures to bupropion remains small, and any conclusions regarding its use in pregnancy must be made with caution. While bupropion's use during the first trimester of pregnancy should be minimized, given the possible increased risk of miscarriage, further investigation into any association between bupropion and miscarriage is warranted. Additionally, more research is needed on cardiovascular health and developmental outcomes of exposed children.

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REFERENCES

1. Jarde A, Morais M, Kingston D, et al. Neonatal outcomes in women with untreated antenatal depression compared with women without

depression: a systematic review and meta-analysis. *JAMA Psychiatry*. 2016;73(8):826–837.
2. Chaudron LH. Complex challenges in treating depression during pregnancy. *Am J Psychiatry*. 2013;170(1):12–20.
3. Alwan S, Reefhuis J, Rasmussen SA, et al; National Birth Defects Prevention Study. Patterns of antidepressant medication use among pregnant women in a United States population. *J Clin Pharmacol*. 2011;51(2):264–270.
4. Yonkers KA, Blackwell KA, Glover J, et al. Antidepressant use in pregnant and postpartum women. *Annu Rev Clin Psychol*. 2014;10:369-92.
5. Jensen HM, Grøn R, Lidegaard Ø, et al. Maternal depression, antidepressant use in pregnancy and Apgar scores in infants. *Br J Psychiatry*. 2013;202(5):347–351.
6. Pedersen LH. Prenatal antidepressant exposure and childhood autism spectrum disorders: cause for concern? *Paediatr Drugs*. 2015;17(6):443–448.
7. Thompson C. Mirtazapine versus selective serotonin reuptake inhibitors. *J Clin Psychiatry*. 1999;60(suppl 17):18–22.
8. Stahl SM, Pradko JF, Haight BR, et al. A review of the neuropharmacology of bupropion, a dual norepinephrine and dopamine reuptake inhibitor. *Prim Care Companion J Clin Psychiatry*. 2004;6(04):159–166.
9. Whitaker-Azmitia PM. Behavioral and cellular consequences of increasing serotonergic activity during brain development: a role in autism? *Int J Dev Neurosci*. 2005;23(1):75–83.
10. Janusonis S. Origin of the blood hyperserotonemia of autism. *Theor Biol Med Model*. 2008;22:5–10.
11. Bérard A, Zhao JP, Sheehy O. Success of smoking cessation interventions during pregnancy. *Am J Obstet Gynecol*. 2016;215(5):611.e1–611.e8.
12. Chun-Fai-Chan B, Koren G, Fayez I, et al. Pregnancy outcome of women exposed to bupropion during pregnancy: a prospective comparative study. *Am J Obstet Gynecol*. 2005;192(3):932–936.
13. The Bupropion Pregnancy Registry. Final Report. Issued August 2008. A project conducted by GlaxoSmithKline. http://pregnancyregistry.gsk.com/documents/bup_report_final_2008.pdf. Accessed August 31, 2017.
14. Einarson A, Choi J, Einarson T, et al. Incidence of major malformations in infants following antidepressant exposure in pregnancy: results of a large prospective cohort study. *Can J Psychiatry*. 2009;54(4):242–246.
15. Cole JA, Modell JG, Haight BR, et al. Bupropion in pregnancy and the prevalence of congenital malformations. *Pharmacoepidemiol Drug Saf*. 2007;16(5):474–484.
16. Alwan S, Reefhuis J, Botto LD, et al; National Birth Defects Prevention Study. Maternal use of bupropion and risk for congenital heart defects. *Am J Obstet Gynecol*. 2010;203(1):52.e1–52.e6.
17. Louik C, Kerr S, Mitchell AA. First-trimester exposure to bupropion and risk of cardiac malformations. *Pharmacoepidemiol Drug Saf*. 2014;23(10):1066–1075.
18. Thyagarajan V, Clifford CR, Wurst KE, et al. Bupropion therapy in pregnancy and the occurrence of cardiovascular malformations in infants. *Pharmacoepidemiol Drug Saf*. 2012;21(11):1240–1242.
19. Kline J, Stein Z, Susser M. *Conception to Birth: Epidemiology of Prenatal Development*. New York, NY: Oxford University Press; 1989:43–68.
20. Marinescu I, Foarfa MC, Pirlog MC, et al. Prenatal depression and stress-risk factors for placental pathology and spontaneous abortion. *Rom J Morphol Embryol*. 2014;55(suppl 3):1155–1160.
21. Sullivan PM, Dervan LA, Reiger S, et al. Risk of congenital heart defects in the offspring of smoking mothers: a population-based study. *J Pediatr*. 2015;166(4):978–984.e2.
22. Pineles BL, Park E, Samet JM. Systematic review and meta-analysis of miscarriage and maternal exposure to tobacco smoke during pregnancy. *Am J Epidemiol*. 2014;179(7):807–823.
23. Einarson A, Fatoye B, Sarkar M, et al. Pregnancy outcome following gestational exposure to venlafaxine: a multicenter prospective controlled study. *Am J Psychiatry*. 2001;158(10):1728–1730.
24. Einarson A, Bonari L, Voyer-Lavigne S, et al. A multicentre prospective controlled study to determine the safety of trazodone and nefazodone use during pregnancy. *Can J Psychiatry*. 2003;48(2):106–110.
25. Kulin NA, Pastuszak A, Sage SR, et al. Pregnancy outcome following maternal use of the new selective serotonin reuptake inhibitors: a prospective controlled multicenter study. *JAMA*. 1998;279(8):609–610.
26. Almeida ND, Basso O, Abrahamowicz M, et al. Risk of miscarriage in women receiving antidepressants in early pregnancy, correcting for induced abortions. *Epidemiology*. 2016;27(4):538–546.