Bupropion for Major Depressive Disorder and Smoking Cessation in Pregnancy: A Systematic Literature Review

Sally Lambert[1], Adrian J Dunlop[1,2]

1 Drug & Alcohol Clinical Services, Hunter New England Local Health District, Newcastle, NSW, Australia

2 School of Medicine & Public Health, University of Newcastle, & Hunter Medical Research Institute, Newcastle, NSW, Australia

Paper 179

Introduction & Aims

Bupropion is an antidepressant repurposed to support nicotine cessation. Both nicotine use and depressive disorder are high prevalence disorders in pregnancy, with known adverse maternal and fetal outcomes (1). This review evaluates the effectiveness of bupropion for smoking cessation and depression in pregnancy and on birth outcomes following bupropion exposure during pregnancy.

Method

A systematic literature review was performed in February 2018 for published clinical studies investigating bupropion use in pregnancy following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines with Premedline, MEDLINE, EMBASE, PsychINFO, Cochrane Central, and PubMed search engines.

Results

Ten studies reported on adverse fetal outcomes: negative findings include a slightly elevated risk of ventricular septal defect and a slightly elevated risk of left outflow tract heart defects, however, most studies found no elevated risk of malformations (2-11). One study reported increased risk of attention deficit hyperactivity disorder with bupropion (11), another no adverse associations related to birthweight and prematurity, however did report an increased rate of spontaneous abortion (2). Four studies measured effectiveness for nicotine cessation in pregnant women, all found indicators that smoking was reduced, but none found an association with sustained tobacco abstinence (10, 12, 13, 14). While there were no studies primarily measuring the effectiveness of bupropion for depression for pregnant women, one small study (n=56), did show promising results (13).

Table 1: Birth Abnormalities & Developmental Sequelae

Study	Study Type	Sample	Outcome	Limitations
Chun-Fai Chan 2005	Prospective Cohort	N = 136 First trimester bupropion exposure N = 133 No medication N= 89 Other antidepressant	No major malformations Rate of spontaneuos Abortion in bupropion group was comparable to rate of general population, but significantly higher (14.7%) than the no medication group (4.5%).	Small Sample size Controls not matched for depression, confounding by indication
Cole 2007	Retrospective Cohort	N = 1213 First trimester bupropion exposure N= 1049 Second and third trimester bupropion exposure N = 4743 Other antidepressant exposure	Normal cardiac malformation rates in all three groups	Potential recall bias May exclude those of lower socio-economic status
GlaxoSmithKline 2008	Prospective Case Series	N = 869 bupropion exposure	No elevated defect rates	High lost-to-follow-up rate No control group Small sample size Conducted by manufacturer
Einerson et al 2009	Prospective Cohort Study	N = 113 first trimester bupropion exposure N = 1243 matched comparison	No malformations with bupropion	Small sample size
Alwan et al 2010	Retrospective case-control study	N= 6853 first trimester bupropion exposure N= 5869 controls	No increased risk of cardiac malformation amongst with bupropion Increased risk of left ventricular outflow tract obstruction compared to controls (odds ratio 2.2).	Low power Possible confounding by indication (depression or smoking)
Louik et al 2014	Retrospective case-control study	N = 65 first trimester bupropion exposure N = 65 controls with no antidepressant exposure	Slight increased risk of ventricular septal defects amongst bupropion exposed (odds ration 1.6)	Small sample size Confounding variables not controlled for Recall bias Possible selection bias
Huybrechts et al 2014	Prospective Cohort Study	N = 64, 389 exposed to antidepressant Of which N= 8856 Bupropion N = 885115 no antidepressant exposure	No association between exposure to Bupropion and cardiac malformation or ventricular septal defects	Only live births accepted
Berard 2016	Prospective Cohort Study	N = 1288 pregnant smokers: N=72 bupropion exposure N= 316 NRT exposure N= 512 no pharmacotherapy	Bupropion associated with lower risk of premature birth (rate 2.8%) compared with NRT (rate 7.9%) and no pharmacotherapy (rate 26.7%)	Recall bias Lacking statistical power
Chun-Fai Chan 2005	Prospective Cohort	N = 136 First trimester bupropion exposure N = 133 No medication N= 89 Other antidepressant	No increase in rates low birth weight and premature birth	Small Sample size
Stotts 2015	Randomised Prospective Double Blind Pilot	N= 11 pregnant smokers N= 5 bupropion N= 6 placebo	The mean birth weight of infants in the bupropion group was slightly higher, (3,127g) than the placebo group, (2,983g).	Small sample size
Figueroa 2010	Case Control	N= 114 bupropion exposed N=5 ADHD cases (4.39%) N= 916 SSRI exposed N=23 ADHD cases (2.51%) N= 3532 depression, no antidepressant N=88 (2.49%)	Exposure to bupropion strongly associated with ADHD compared to SSRIs or no antidepressants	Variability in diagnosing ADHD Maternal smoking not identified as a confounder.

Table 2: Effectiveness for Cessation of Nicotine Use

Author	Study Type	Sample	Outcome	Limitations
Chan 2005	Prospective Matched Controlled Observational	N = 22 bupropion N = 22 controls	45% ceased smoking in Buproprion group vs 14% in control group	Small Sample size Relied on self-report
Chisholm	Randomised Control Trial	N= 56 pregnant smokers with substance dependence N= 28 with depression N= 11 bupropion N= 28 citalopram/escitalopram N= 28 Non-depressed without antidepressant	Bupropion group reported mean cigarette per day reduced from 14.6 on the initial visit to 8.2 on the final visit. Escitalopram/citalopram group reported reduction from 14.5 to 14.1 and the non-depressed controls reported a reduced mean cigarette per day from 14.9 to 9.6	Potential recall bias May exclude those of lower socio-economic status
Stotts 2015	Randomised Prospective Double Blind Pilot	N= 11 pregnant smokers N= 5 bupropion N= 6 placebo	2 women in the placebo group reported abstinence, none in the Buproprion group Results not statistically significant	Small sample size
Nanovskaya 2017	Randomised Prospective Double Blind Trial	N = 65 pregnant smokers receiving counselling N= 30 bupropion N= 35 placebo	Buproprion shown to reduce cravings, nicotine withdrawal symptoms and tobacco exposure. No difference in abstinence rates after medication stopped.	Small sample size

Table 3: Effectiveness for depression

Author	Study Type	Sample	Outcome	Limitations
Chisholm	Randomised Control Trial	N= 28 with depression N= 11 bupropion N= 28 citalopram/escitalopram N= 28 Non-depressed without antidepressant	Greater improvement in mood rating for the Buproprion group	Small sample size Rating of depression and mood was broad and crude.

Conclusion

Overall, the literature comprised of small sample size studies which utilised different methodologies and included multiple variables, making between group comparisons difficult. Only three studies were randomised controlled trials (n=156) (10, 13, 14). Future prospective controlled cohort studies may be able to determine the causality and temporality of observed fetal malformations, and larger randomised controlled trials may elucidate effectiveness of bupropion as an intervention for smoking cessation and depression in pregnant women.

Implications for Practice

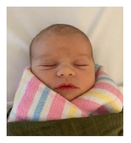
While there are possible risks with its use in pregnancy, bupropion may be considered for smoking cessation during pregnancy where other approaches (e.g. nicotine replacement therapy) have failed or are not clinically appropriate and the benefits outweigh the risks. Disclosure of Interest Statement: No grants were received and there were no conflicts of interest in the development of this study.

References

1. Benowitz NL, Dempsey DA, Goldenberg RL, et al. The use of pharmacotherapies for smoking cessation during pregnancy. Tob Control 2000;9(Suppl 3):III91-4.
2. Chun-Fai-Chan, B., Koren, G., Fayez, I., Kalra, S., Voyer-Lavigne, S., Boshier, A., Shakir, S. and Einarson, A., 2005. Pregnancy outcome of women exposed to bupropion during pregnancy: a prospective comparative study. Am J Obs & Gyne, 192(3), pp.932-936
3. Cole JA, Modell JG, Haight BR, Cosmatos IS, Stoler JM, Walker AM. Bupropion in pregnancy and the prevalence of congenital malformations. Pharmacoepidemiol Drug Saf 2007;16:474-84
4. GlaxoSmithKline Bupropion Pregnancy Registry. Final report: 1 September 1997 through 31 March 2008. Registry Report. Wilmington, NC, 2008
5. 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;54:242-6.
6. Alwan S, Reefhuis J, Rasmussen SA, Olney RS, Friedman JM. National Birth Defects Prevention Study. Use of selective serotonin- re-uptake inhibitors in pregnancy and the risk of birth defects. N Engl J Med 2007;256:2684-92.
7. Louik C, Lin AE, Werler MM, Hernández-Díaz S, Mitchell AA. First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. N Engl J Med 2007;356:2675-83.
8. Huybrechts, K.F., Palmsten, K., Avorn, J., Cohen, L.S., Holmes, L.B., Franklin, J.M., Mogun, H., Levin, R., Kowal, M., Setoguchi, S. and Hernández-Díaz, S., 2014. Antidepressant use in pregnancy and the risk of cardiac defects. N Engl J Med, 370(25):2397-2407
9. Berard A, Ramos E, Rey E, Blais L, St-Andre M, Oraichi D. First trimester exposure to paroxetine and risk of cardiac malformations in infants: the importance of dosage. Birth Defects Res B Dev Reprod Toxicol 2007;80:18-27
10. Stotts AL, Northrup TF, Cinciripini PM et al. Randomized, controlled pilot trial of bupropion for pregnant smokers: challenges and future directions. Am J Perinatol 2015;32:351-6
11. Figueroa R. Use of antidepressants during pregnancy and risk of attention-deficit/hyperactivity disorder in the offspring. J Dev Behav Pediatr 2010;31:641-8
12. Chan B, Einarson A, Koren G. Effectiveness of bupropion for smoking cessation during pregnancy. J Addict Dis 2005;24:19-23.
13. Chisolm MS, Brigham EP, Tuten M, Strain EC, Jones HE. The relationship between antidepressant use and smoking cessation in pregnant women in treatment for substance abuse. Am J Drug Alcohol Abuse 2010;36:46-51.
14. Nanovskaya TN, Oncken C, Fokina VM et al. Bupropion sustained release for pregnant smokers: a randomized, placebocontrolled trial. Am J Obstet Gynecol 2017;216:420.e1-420.e9.

Acknowledgements

Sally Lambert had a beautiful baby girl Edith on 3rd October
Mother and baby are well.



For further information contact:
Adrian.Dunlop@hnehealth.nsw.gov.au

NSW GOVERNMENT Health
Hunter New England Local Health District