

## RESEARCH PAPER

# Bupropion in breast milk: an exposure assessment for potential treatment to prevent post-partum tobacco use

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**Objectives:** To assess potential infant exposure to bupropion and its active metabolites in breast milk such as would occur during treatment to prevent post-partum relapse to tobacco use, and to compare the concentrations of bupropion in urine and saliva with plasma and breast milk.

**Design and setting:** Cohort study, outpatient clinical research centre.

**Subjects:** Ten healthy post-partum volunteers who agreed to take bupropion for seven days, pump and discard their breast milk, and have samples of breast milk, plasma, saliva, and urine analysed.

**Intervention:** Bupropion 150 mg a day for three days and then 300 mg a day for four days.

**Main outcome measures:** Concentrations of bupropion and its active metabolites (hydroxybupropion, erythrohydrobupropion, threo hydrobupropion) in breast milk, plasma, saliva, and urine. Determination of average infant exposure.

**Results:** The calculated average dosage of bupropion in breast milk was 6.75 µg/kg/day. Therefore, the average infant exposure is 0.14 % of the standard adult dose of bupropion, corrected for the difference in body weight. Considering the sum of bupropion and its active metabolites, the average infant exposure is expected to be 2% of the standard maternal dose on a molar basis. The concentration of bupropion and its active metabolites in breast milk was not associated with age, body mass index, use of oral contraceptive pills, age of infant, or the frequency of breast feeding at the time the study was initiated. The coefficient of determination ( $r^2$ ) between the concentration of bupropion in breast milk and in urine was 0.77 ( $p < 0.01$ ).

**Conclusions:** Bupropion and its active metabolites are present in the breast milk of lactating women. The concentrations of bupropion in breast milk and urine were highly correlated. These results indicate that the daily dose of bupropion and metabolites that would be delivered to an infant of a woman taking a therapeutic dose of bupropion is small. These results suggest that the effectiveness of bupropion to prevent post-partum relapse to tobacco use should be evaluated without excluding women who plan to breast feed.

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Cigarette smoking is the leading cause of preventable morbidity and mortality for women in the USA.<sup>1</sup> One estimate suggests that 13% of all deaths among women are a direct result of tobacco use, and that smoking shortens a woman's life by an average of 15 years.<sup>2</sup> Although tobacco use has been decreasing among women, a recent national report indicates that 24% of women still report current smoking.<sup>3</sup> Pregnancy is a pivotal event of young adulthood for many women. Women are much more likely to quit smoking around the time of pregnancy than at any other.<sup>4</sup> While the prevalence of smoking has also decreased among pregnant women, 12% of pregnant women report current smoking.<sup>3</sup> Unfortunately, women who quit during pregnancy have extremely high rates of relapse during the months immediately following delivery.<sup>5–9</sup> Behavioural interventions during pregnancy and the post-partum period have not been associated with an increase in post-partum tobacco abstinence.<sup>6 10 11</sup>

Medications are typically avoided in lactating women because of the potential exposure of their infants. Approximately 65% of women breast feed in the early post-partum period,<sup>12</sup> although the prevalence of breast feeding among women who quit smoking during pregnancy is probably lower than the general population.<sup>13</sup> Few studies have quantified the exposure of infants to medications consumed by their breast feeding mothers.<sup>14–19</sup> This practice leads women and their physicians to avoid medications, perhaps unnecessarily, or encourages women not to breast feed.

Bupropion is an effective therapy for smoking cessation and relapse prevention; it is as effective or more effective than nicotine replacement products.<sup>20–23</sup> Bupropion is an atypical antidepressant that has both dopaminergic and noradrenergic activity.<sup>24</sup> Bupropion is categorised for use in pregnancy by the US Food and Drug Administration as category B (that is, animal studies show no risk, or animal studies with minimal risk with no risk shown in humans). A slow release formulation became available in 1998, and this formulation is marketed for the treatment of smoking cessation. There are several reasons why bupropion may be particularly useful to prevent post-partum relapse, including mood stabilisation, decreased fatigue, decreased tobacco craving, and weight loss.<sup>20–22</sup> To date, there is no literature examining the use of bupropion or other antidepressants as part of an intervention to prevent post-partum relapse to tobacco use. Bupropion, like other psychotropic medications, is lipid soluble and therefore secreted into breast milk. Information about the use of bupropion by lactating women is limited. Case reports note non-detectable plasma concentrations of bupropion and its metabolites in three infants of breast feeding mothers.<sup>18 19</sup>

This study was designed to measure the amount of bupropion and its active metabolites in the breast milk of women who are lactating but not breast feeding to ascertain whether this drug might be given safely to post-partum women, who are or may be breast feeding, to prevent post-partum relapse to tobacco use. We also examined concentrations of bupropion in urine and saliva compared to plasma

and breast milk. If highly correlated, saliva or urine measurement would allow for less invasive monitoring of lactating women taking bupropion in the post partum period.

## METHODS

### Subjects

Ten healthy, paid volunteers were recruited through advertisements posted in clinic waiting rooms, and advertisements in parent periodicals. Women over the age of 18 years were eligible to participate if they were currently breast feeding at least three times per day and planned to discontinue breast feeding in the next few weeks. We excluded women who: (1) were currently using any psychoactive medications; (2) had current major depression, schizophrenia, or bipolar disorder; and (3) had a history of a seizure disorder, anorexia or bulimia, or intolerance to bupropion.

### Protocol

Subjects were studied as outpatients at the clinical study centre at San Francisco General Hospital. An eligible woman was scheduled for an initial study visit at the time that she intended to stop breast feeding. At this visit eligibility was confirmed, informed consent was obtained, a health history was performed and blood pressure, weight and height were measured. At this visit, women were also instructed on the use of a breast pump, and provided with one if they did not already have one available. Women were instructed to stop breast feeding on that day and to begin pumping, and discarding, their breast milk at least three times per day. The following day, women were instructed to initiate bupropion SR 150 mg orally once a day. Women were instructed to increase the dosage to 300 mg a day after three days. Phone contact was maintained with women during this period to facilitate compliance. On the seventh day of the protocol, women came in for a second study visit. At this visit, a single sample of plasma, saliva, urine, and breast milk were each obtained. The initial 3 ml of breast milk was obtained with the use of electric breast pump. Pill bottles were collected to ensure compliance with the medication dosing. We calculated an approximate time since the last dose ingestion by

calculating the time elapsed between the start of the clinic visit and the scheduled time of the last pill ingestion.

### Analytical chemistry

Measurement of bupropion and its active metabolites, hydroxybupropion, erythrohydrobupropion, and threohydrobupropion were quantitated in breast milk, plasma, saliva and urine using liquid chromatography-tandem mass spectrometry (LC-MS/MS). The method is similar to the one reported by Hsyu *et al*, but is capable of measuring the erythrohydrobupropion and threohydrobupropion individually.<sup>25</sup> Deuterium labelled internal standards, which were synthesised in our laboratory, were used as internal standards. The lower limit of quantitation of the bupropion assay (LLOQ) is 1 ng/ml. Samples were frozen and assayed in one batch at the completion of the study. There was no significant change in the concentration of bupropion and metabolites stored for one month in a freezer at  $-20^{\circ}\text{C}$ . Quality control procedures that are appropriate for pharmacokinetic studies were utilised.

### Data analysis

An average daily dose of bupropion and each of its active metabolites in breast milk was calculated. An average infant milk consumption of 0.15 l/kg/day was assumed.<sup>26</sup> Since bupropion metabolites are pharmacologically active,<sup>24</sup> the exposure of the infant to the sum of bupropion and its metabolites was estimated, and compared (on a molar basis) to the typical maternal weight-normalised exposure to bupropion. The Pearson correlation coefficients ( $r$ ) was used to calculate a coefficient of determination ( $r^2$ ) to compare the plasma, saliva, and urine concentrations of bupropion with breast milk concentration to determine whether saliva or urine measurement could be used (instead of plasma) to monitor bupropion concentrations in breast milk.

## RESULTS

The median age of the 10 women who participated in this protocol was 29 years (range 22–37 years). Their median weight was 59.4 kg (range 54.1–95.5) and their median body

**Table 1** Concentrations of bupropion and active metabolites in breast milk, plasma, urine, and saliva

	Breast milk	Plasma	Urine	Saliva
Mean (SD) bupropion*	45.2 (49.5)	25.0 (24.6)	1042.0 (2139.0)	68.5 (131.4)
Range	4.2–168.3	2.9–84.5	32.7–7056.4	3.2–439.0
Mean (SD) hydroxybupropion	104.6 (62.2)	940.2 (697.7)	2026.4 (1873.0)	184.5 (143.9)
Range	9.0–242.1	64.8–2672.8	125.7–5032.8	25.1–522.3
Mean (SD) erythrohydrobupropion	72.1(38.3)	84.1 (46.1)	2396.2 (1857.0)	202.9 (131.1)
Range	25.4–142.9	19.9–196.5	370.1–5972.1	71.7–491.6
Mean (SD) threohydrobupropion	459.0 (278.4)	370.2 (182.9)	18791.3 (16227.0)	1229.5 (794.1)
Range	192.7–1052.1	121.4–746.6	2484.5–45625.7	469.3–3089.1

\*ng/ml.

**Table 2** Infant dose of bupropion and metabolites

	Mean milk concentration (ng/ml)	Mean milk* concentration (nM/ml)	Infant dose† (µg/kg/day)	Infant dose (nM/kg/day)	Infant dose‡ (% maternal bupropion dose)
Bupropion	45	0.19	6.75	28.1	0.13
Hydroxybupropion	105	0.41	15.75	61.5	0.30
Erythrohydrobupropion	72	0.30	10.8	44.6	0.21
Threohydrobupropion	459	1.90	68.85	284.5	1.37
Total	–	–	–	418.7	2.01

\*Molecular weights: bupropion 240; hydroxybupropion 256; erythrohydrobupropion and threohydrobupropion 242.

†Infant dose based on breast milk concentration and infant consumption of 0.15 l/kg/day.

‡Maternal bupropion dose based on 300 mg/day = 5 mg/kg/day = 20833 nM/kg/day.

Metabolite percentages based on bupropion molar equivalents.

**Table 3** Coefficient of determination ( $r^2$ ) of plasma, breast milk, saliva, and urine concentrations of bupropion and metabolites

	Plasma bupro	Plasma hydroxy	Plasma erythro	Plasma threo	Breast milk bupro	Breast milk hydroxy	Breast milk erythro	Breastmilk threo	Saliva bupro	Saliva hydroxy	Saliva erythro	Saliva threo
Plasma bupro	1.00											
Plasma hydroxy	0.11 (0.35)	1.00										
Plasma erythro	0.10 (0.39)	<b>0.89</b> ( <b>&lt;0.01</b> )	1.00									
Plasma threo	0.06 (0.51)	<b>0.57</b> (0.01)	<b>0.82</b> ( <b>&lt;0.01</b> )	1.00								
Breast milk bupro	0.03 (0.65)	0.01 (0.79)	0.01 (0.85)	0.08 (0.43)	1.00							
Breast milk hydroxy	0.15 (0.27)	<b>0.88</b> ( <b>&gt;0.01</b> )	<b>0.82</b> ( <b>&gt;0.01</b> )	<b>0.66</b> ( <b>&gt;0.01</b> )	0.08 (0.43)	1.00						
Breast milk erythro	0.01 (0.74)	<b>0.47</b> (0.03)	<b>0.71</b> ( <b>&lt;0.01</b> )	<b>0.76</b> ( <b>&lt;0.01</b> )	0.004 (0.87)	<b>0.45</b> (0.03)	1.00					
Breast milk threo	0.04 (0.57)	0.16 (0.25)	0.40 (0.05)	<b>0.73</b> ( <b>&lt;0.01</b> )	0.06 (0.48)	0.22 (0.17)	<b>0.78</b> ( <b>&lt;0.01</b> )	1.00				
Saliva bupro	<b>0.73</b> ( <b>&lt;0.01</b> )	0.003 (0.88)	0.001 (0.93)	0.01 (0.83)	0.02 (0.71)	0.0001 (0.97)	0.12 (0.33)	0.13 (0.30)	1.00			
Saliva hydroxy	<b>0.53</b> (0.02)	0.04 (0.58)	0.03 (0.61)	0.0001 (0.99)	0.09 (0.41)	0.04 (0.57)	0.01 (0.76)	0.09 (0.40)	<b>0.75</b> ( <b>&lt;0.01</b> )	1.00		
Saliva erythro	<b>0.15</b> (0.02)	0.07 (0.45)	0.10 (0.36)	0.02 (0.70)	0.16 (0.26)	0.04 (0.58)	0.01 (0.84)	0.02 (0.68)	<b>0.67</b> ( <b>&lt;0.01</b> )	<b>0.85</b> ( <b>&lt;0.01</b> )	1.00	
Saliva threo	<b>0.50</b> (0.02)	0.02 (0.67)	0.06 (0.49)	0.02 (0.70)	0.11 (0.34)	0.10 (0.79)	0.001 (0.93)	0.01 (0.78)	<b>0.75</b> ( <b>&gt;0.01</b> )	<b>0.80</b> ( <b>&gt;0.01</b> )	<b>0.95</b> ( <b>&gt;0.01</b> )	1.00
Urine bupro	0.05 (0.54)	0.002 (0.90)	0.03 (0.61)	0.01 (0.77)	<b>0.77</b> ( <b>&gt;0.01</b> )	1.0 (0.10)	0.08 (0.37)	0.04 (0.76)	0.002 (0.90)	0.04 (0.33)	0.04 (0.22)	1.1 (0.34)
Urine hydroxy	0.03 (1.6)	0.01 (0.76)	0.05 (0.54)	0.03 (0.64)	0.10 (0.37)	1.0 (0.0)	0.05 (0.52)	0.02 (0.68)	0.07 (0.45)	0.03 (0.62)	0.03 (0.17)	0.28 (0.12)
Urine erythro	0.05 (0.54)	0.01 (0.76)	0.01 (0.81)	0.01 (0.82)	0.10 (0.37)	1.0 (0.78)	0.10 (0.89)	0.03 (0.66)	0.10 (0.39)	0.22 (0.17)	0.22 (0.17)	1.0 (0.18)
Urine threo	0.06 (0.48)	0.04 (0.58)	0.01 (0.79)	0.01 (0.59)	0.20 (0.20)	0.002 (0.92)	0.01 (0.92)	0.13 (0.30)	0.10 (0.38)	0.27 (0.12)	0.20 (0.19)	1.0 (0.19)

Numbers displayed are the coefficient of determination ( $p$  value). Bolding indicates associations that are significant ( $p < 0.05$ ).  
 Bupro, bupropion; erythro, erythrohydrobupropion; hydroxy, hydroxybupropion; threo, threohydrobupropion.

mass index was 25.3 kg/m<sup>2</sup> (range 20.9–38.4). At the time of participation, the average age of the infants of these women was 12.5 months. Half of the women were taking an oral contraceptive pill. No other medications were being used by any of the participants. The median number of hours since the last dose of bupropion was 2.5 hours (range 1–12 hours). The concentrations of bupropion and its active metabolites in breast milk, plasma, urine, and saliva are shown in table 1. The average (SD) breast milk to plasma (M/P) bupropion ratio was 2.8 (3.7). The average M/P ratios of hydroxybupropion, erythrohydrobupropion, and threo-hydrobupropion were 0.1 (0.03), 0.9 (0.3), and 1.2 (0.3), respectively. Since on average an infant drinks 0.15 l/kg/day,<sup>26</sup> the calculated dosage of bupropion in breast milk is 6.75 µg/kg/day (table 2). The estimated daily infant dosages of the metabolites were: hydroxybupropion 15.75 µg/kg/day, erythrohydrobupropion 10.80 µg/kg/day, and threo-hydrobupropion 68.85 µg/kg/day.

The concentration of bupropion and its active metabolites in breast milk was not associated with age, body mass index, age of infant, use of oral contraceptive pills, or the frequency of breast feeding at the time the study was initiated.

The coefficient of determination between the concentration of bupropion in breast milk and in urine was 0.77 ( $p < 0.01$ ) (table 3). There was no significant association between saliva or plasma bupropion concentrations and the concentration of bupropion in breast milk, although there were significant correlations between plasma and saliva bupropion. No side effects were noted by any of the mothers.

## DISCUSSION

Bupropion and its active metabolites are present in the breast milk of lactating women. These results indicate that the daily dose of bupropion and metabolites that would be delivered to an infant of a woman taking a therapeutic dose of bupropion is small. The estimated dose of bupropion taken up by the infant milk was less than 0.2 % of the weight normalised dose of an adult woman. The major metabolites of bupropion are active, producing equal or weaker inhibition of neurotransmitter uptake compared to bupropion.<sup>24</sup> Since the metabolites of bupropion have pharmacologic activity, the exposures of the metabolites should be considered as part of the infant drug exposure as well. If one conservatively assumes equimolar pharmacologic potency of the hydroxybupropion, erythrohydrobupropion, and threo-hydrobupropion metabolites to the parent bupropion, and assumes complete oral bioavailability in the infant, the total exposure to bupropion and metabolites would be 2% of the weight normalised maternal bupropion dose. This dose in the infant is lower than 10% of maternal dose that has been used as a guideline for drug safety during breast feeding.<sup>26</sup> The failure to detect bupropion in three other breast fed infants whose mothers were taking bupropion in doses of 150–300 mg daily doses supports the idea that infants are exposed to a very low concentration of the drug.<sup>18 19</sup>

The coefficients of determination for breast milk with urine, saliva, and plasma concentrations of bupropion and its active metabolites were not high (with the exception of breast milk and urine bupropion concentrations). This suggests that future studies should not rely on these other body fluids as surrogate markers for breast milk.

The concentration of bupropion and its metabolites were measured in breast milk and in other body fluids at one point in time. Sampling at multiple times was not performed. Although the half life of bupropion is relatively long, there is an absorption peak after ingestion of the sustained release preparation, peaking at 1–4 hours.<sup>27</sup> Most of our subjects had blood and milk samples taken around the time of the peak.

## What this paper adds

Although women are much more likely to quit smoking around the time of pregnancy than at any other time, women who quit during pregnancy have extremely high rates of relapse during the months immediately following delivery. While bupropion has been shown to be effective in smoking cessation and delaying relapse, it has not been evaluated as a treatment to prevent post-partum relapse because of concerns over potential exposure by an infant who is breast fed. This study examines the potential exposure of an infant breast fed by a woman taking bupropion, and determined that infant exposure to bupropion and its active metabolites in breast milk is low. These results are important for designing clinical trials to prevent post-partum relapse that incorporate bupropion.

Therefore our estimates of exposure to bupropion are likely to be high; the actual exposure to bupropion would be even less than what we have estimated. Since the metabolites have longer half lives than bupropion and are generated slowly from bupropion, these concentrations are expected to be at or near steady state. Thus, the estimates of exposure to metabolites based on a single sample should be representative of the exposure over the day.

The women who participated had been breast feeding for an average of 12.5 months. It is possible that the milk composition after this length of breast feeding may be different than that in the immediate post-partum period. Although our results suggest that bupropion taken by a breast feeding mother should not present a concern for most infants, exposure may be greater for some infants—for example, premature infants.

Medications are typically avoided in lactating women because of the potential exposure of their infants. Few studies have quantified the true exposure of infants to medications consumed by their breast feeding mothers.<sup>14–17</sup> This practice leads women and their physicians to avoid medications, perhaps unnecessarily, or encourages women not to breast feed.

Pregnant women have been extensively targeted for interventions to reduce prenatal tobacco use, primarily to protect the health of their unborn child. These efforts have been successful. Women are three times more likely to quit smoking during their first pregnancy and the year preceding this pregnancy than at any other time.<sup>4</sup> Estimates suggest that approximately 30–50% of women who smoke spontaneously quit either immediately before or during pregnancy.<sup>5 28 29</sup> Prenatal educational and behavioural interventions have been shown to increase cessation rates during pregnancy up to 50%.<sup>29–32</sup> However, despite a high likelihood of quitting around the time of pregnancy, many women relapse following delivery. Several studies have demonstrated high rates of smoking relapse post-partum, ranging from 40–90% within six months.<sup>5–8 28</sup> Bupropion has been shown to delay relapse to smoking in non-pregnant adults.<sup>22</sup> Bupropion is generally safe and well tolerated, with relatively rare adverse effect.<sup>21</sup> Our results suggest that bupropion taken by a breast feeding mother should not present a concern for most infants. Particularly given the lack of success of behavioural therapies in promoting post-partum relapse,<sup>11 33–37</sup> the effectiveness of bupropion to prevent post-partum smoking relapse should be evaluated in clinical trials without excluding women who are or may be breast feeding. During such studies, however, it would be advisable to measure bupropion and metabolites in infants, to confirm that the exposure is as low as expected.

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