Drug Metabolism and Disposition

Supplementary Information

Gene variants in *CYP2C19* are associated with altered *in vivo* bupropion pharmacokinetics but not bupropion assisted smoking cessation outcomes

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Supplementary Table S1. Baseline demographics of Study 1.

	White (n=21)	African American (n=14)	Asians (n=7)
Sex (% male)	62	50	86
Age in years (mean, range)	29 (19, 51)	33 (22, 64)	37(22, 60)
BMI (mean, range)	24 (19, 33)	26 (20, 34)	29 (21, 54)
CYP2C19 genotype			
**1/*1*	n=7	n=7	n=3
**1/*2*	n=5	n=2	n=3
**1/*17*	n=5	n=4	
**17/*17*	n=1		
**2/*17*	n=3	n=1	n=1

We also genotyped for *CYP2C19*3* in this study, but did not find any participants with the *CYP2C19*3* allele.

Supplementary Table S2. Plasma pharmacokinetic parameters and urinary bupropion and metabolite recovery for bupropion and metabolites by *CYP2C19* genotype

	All (n=42)	No variant (n=17)	with *2 (n=15)	with *17 (n=15)
Plasma	**Mean (95%CI)**	**Mean (95%CI)**	**Mean (95%CI)**	**Mean (95%CI)**
BUP				
AUC_{24} (h ng/ml)	685 (631,739)	670 (585,754)	**771 (694,848)**	663 (550,775)
Cmax (ng/ml)	58 (52,63)	58 (49,67)	66 (56,77)	54 (41,67)
Css (ng/ml)	29 (26,31)	28 (24,31)	32 (29,35)	28 (23,32)
OH-BUP				
AUC_{24} (h ng/ml)	9524 (8319,10729)	9401 (7686,11115)	9929 (7971,11887)	9558 (6982,12135)
Cmax (ng/ml)	464 (405,524)	463 (380,546)	476 (377,576)	470 (338,601)
Css (ng/ml)	397 (347,447)	392 (320,463)	414 (332,495)	398 (291,506)
AUC OH-BUP/BUP	14.4 (12.6,16.2)	14.7 (12,17.5)	13.2 (10.2,16.2)	14.7 (11.1,18.3)
EB				
AUC_{24} (h ng/ml)	772 (689,856)	732 (618,846)	**947 (802,1093)**	714 (573,854)
Cmax (ng/ml)	38 (35,42)	37 (31,42)	**47 (40,53)**	35 (28,42)
Css (ng/ml)	32 (29,36)	31 (26,35)	40 (33,46)	30 (24,36)
AUC EB /BUP	1.2 (1,1.3)	1.1 (1,1.3)	1.2 (1.1,1.4)	1.1 (0.9,1.3)
TB				
AUC_{24} (h ng/ml)	4209 (3612,4807)	3867 (3134,4601)	**5427 (4168,6686)**	3669 (2927,4411)
Cmax (ng/ml)	208 (180,236)	193 (155,231)	**267 (211,323)**	183 (147,219)
Css (ng/ml)	175 (150,200)	161 (131,192)	226 (174,279)	153 (122,183)
AUC TB/BUP	6.2 (5.5,6.9)	5.9 (4.9,6.9)	7.1 (5.6,8.6)	5.7 (4.8,6.6)
Urinary 24 hours recovery (nmol)	**Mean (95%CI)**	**Mean (95%CI)**	**Mean (95%CI)**	**Mean (95%CI)**
Total	67824 (51128,84520)	74825 (48476,101173)	71393 (33478,109309)	52890 (38439,67341)
BUP	2087 (1512,2662)	2465 (1196,3735)	1762 (1072,2452)	1896 (1204,2587)
BUP/Total Recovery (%)	0.07 (0.04,0.10)	0.09 (0.04,0.14)	0.03 (0.00,0.06)	0.06 (0,00,0.12)
OH-BUP-free	3672 (2782,4561)	4420 (2555,6284)	2941 (1889,3993)	3234 (2042,4426)
OH-BUP-glucuronide	12283 (10393,14173)	12249 (10042,14457)	13574 (9081,18067)	11041 (8406,13676)
OH-BUP/Total Recovery (%)	28.8 (25,32.6)	27.5 (21.5,33.5)	27.8 (22.8,32.8)	31.3 (23.3,39.4)
EB-free	4872 (3753,5991)	5574 (3751,7396)	4564 (2258,6870)	4111 (2704,5519)
EB- glucuronide	1718 (1438,1998)	1759 (1432,2086)	1982 (1284,2679)	1592 (1141,2042)
EB/Total Recovery (%)	10.3 (9.8,10.9)	10.5 (9.5,11.4)	10.1 (8.9,11.3)	10.9 (9.9,11.9)
TB-free	38376 (27180,49572)	43345 (25732,60957)	39718 (14184,65251)	28779 (18908,38649)
TB- glucuronide	4778 (2539,7017)	4946 (1476,8417)	6839 (1722,11957)	2217 (805,3629)
TB/Total Recovery (%)	57.8 (54.1,61.4)	58.9 (52.9,65)	59.4 (54.2,64.7)	54.3 (47.1,61.5)
% daily dose recovered	**Mean (95%CI)**	**Mean (95%CI)**	**Mean (95%CI)**	**Mean (95%CI)**
BUP	0.3 (0.2,0.4)	0.4 (0.2,0.6)	0.3 (0.2,0.4)	0.3 (0.2,0.4)
OH-BUP-free	0.6 (0.4,0.7)	0.7 (0.4,1.0)	0.5 (0.3,0.6)	0.5 (0.3,0.7)
OH-BUP-glucuronide	2.0 (1.7,2.3)	2.0 (1.6,2.3)	2.2 (1.5,2.9)	1.8 (1.3,2.2)
EB-free	0.8 (0.6,1.0)	0.9 (0.6,1.2)	0.7 (0.4,1.1)	0.7 (0.4,0.9)
EB- glucuronide	0.3 (0.2,0.3)	0.3 (0.2,0.3)	0.3 (0.2,0.4)	0.3 (0.2,0.3)
TB-free	6.1 (4.3,7.9)	6.9 (4.1,9.8)	6.4 (2.3,10.4)	4.6 (3,6.2.0)
TB- glucuronide	0.8 (0.4,1.1)	0.8 (0.2,1.3)	1.1 (0.3,1.9)	0.4 (0.1,0.6)

There were five individuals with **2/*17* genotype.

Bolded values indicate statistical significance compared with no variants using linear regression analyses as presented in Table 1.

Supplementary Table S3. Baseline demographics of Study 2.

	Placebo	Bupropion
% African American	100%	100%
Sex (% male)	68%	64%
Age (years) (mean, range)	46.2 (19, 80)	46.8 (22, 73)
BMI (mean, range)	31 (15, 68)	31 (16, 63)
CYP2C19 genotype		
**1/*1*	n=104	n=93
**1/*2*	n=60	n=60
**2/*2*	n=6	n=8
**1/*17*	n=60	n=77
**17/*17*	n=10	n=10
**2/*17*	n=27	n=20