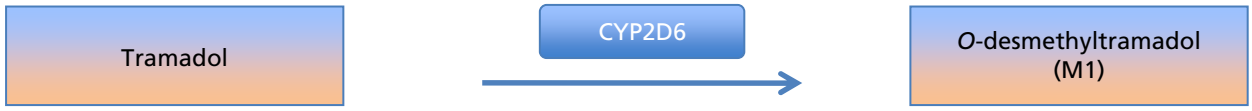
Appendix 1: Variation in cytochrome P450 isoenzyme 2D6 (CYP2D6) phenotype by ethnicity

Tramadol is converted by CYP2D6 to an active opioid metabolite (M1). The CYP2D6 phenotype varies greatly between individuals. The activity of CYP2D6 influences the amount of opioid produced. Even among patients with functional CYP2D6, concurrent use of strong CYP2D6 inhibitors (e.g., fluoxetine, paroxetine, bupropion and ritonavir) will render patients unable to convert tramadol to M1. Values in the table represent the estimated prevalence of CYP2D6 alleles in various ethnic groups. Phenotype results from the combination of alleles present in an individual. [Reprinted, with permission, from Ingelman-Sundberg M. Genetic polymorphisms of cytochrome P450 2D6 (CYP2D6): clinical consequences, evolutionary aspects and functional diversity. *Pharmacogenomics J* 2005;5:6-13. Copyright © 2005 Macmillan Publishers Ltd.]



Allele variant	Mutation	Consequence	Allele frequency, %			
			Caucasians	Asians	Black Africans	Ethiopians and Saudi Arabians
CYP2D6 *2xn	Gene duplication	Increased enzyme activity	1–5	0–2	2	10–16
CYP2D6 *4	Defective splicing	Inactive enzyme	12–21	1	2	1–4
CYP2D6 *5	Gene deletion	No enzyme	2–7	6	4	1–3
CYP2D6 *10	Point mutations	Unstable enzyme	1–2	51	6	3–9
CYP2D6 *17	Point mutations	Altered affinity for substrates	0	0	20–35	3–9

Appendix to: Young JWS, Juurlink DN. Tramadol. *CMAJ* 2013. DOI:10.1503/cmaj.121592.