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Tramadol Therapy and *CYP2D6* Genotype

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Introduction

Tramadol is an analgesic used to treat moderate to moderately severe pain. It is a synthetic opioid, related to codeine, and is used to treat both acute and chronic pain. Tramadol is often prescribed for post-operative pain, and pain caused by cancer, osteoarthritis, and other musculoskeletal diseases (1).

The CYP2D6 enzyme metabolizes a quarter of all prescribed drugs, including tramadol. Individuals who carry two inactive copies of *CYP2D6* are known as poor metabolizers and have higher plasma concentrations of tramadol compared with individuals who have two copies of normal activity alleles (1). Individuals who carry one or more reduced or inactive copies of *CYP2D6* are known as intermediate metabolizers, and individuals who carry more than two active copies of *CYP2D6* are known as ultrarapid metabolizers.

The FDA states that the levels of tramadol are approximately 20% higher in poor metabolizers compared to extensive ("normal") metabolizers, while concentrations of the tramadol metabolite, M1, are 40% lower. Inhibitors of CYP2D6, such as fluoxetine and amitriptyline, also inhibit the metabolism of tramadol, and the full pharmacological impact of these alterations of tramadol dose in terms of either efficacy or safety is unknown (1).

A guideline from the Dutch Pharmacogenetics Working Group includes dose recommendations for poor metabolizers (either select an alternative drug—not oxycodone or codeine—or be alert to the symptoms of insufficient pain relief). It also contains dose recommendations for intermediate metabolizers (be alert to decreased efficacy of tramadol, consider increasing the dose and if the response is still inadequate, either select an alternative drug—not oxycodone or codeine, or be alert to the symptoms of insufficient pain relief) and ultrarapid metabolizers (either reduce the dose of tramadol by 30% and be alert to adverse drug events, or select an alternative drug e.g., acetaminophen, NSAID, morphine—not oxycodone or codeine) (see Table 1) (2).

Table 1. *CYP2D6* phenotypes and the therapeutic recommendations for tramadol therapy

Phenotype	Genotype	Therapeutic recommendation for tramadol
Ultrarapid metabolizer	More than two copies of functional alleles	Reduce dose by 30% and be alert to ADEs (e.g., nausea, vomiting, constipation, respiratory depression, confusion, urinary retention) or select alternative drug (e.g., acetaminophen, NSAID, morphine—not oxycodone or codeine)

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Table 1. continued from previous page.

Phenotype	Genotype	Therapeutic recommendation for tramadol
Intermediate metabolizer	One active allele and one inactive allele, or two decreased activity alleles, or one decreased activity allele and one inactive allele	Be alert to decreased efficacy. Consider dose increase. If response is still inadequate, select alternative drug—not oxycodone or codeine—or be alert to symptoms of insufficient pain relief
Poor metabolizer	Two inactive alleles	Select alternative drug—not oxycodone or codeine—or be alert to symptoms of insufficient pain relief

ADE: Adverse Drug Event
The strength of the tramadol therapeutic recommendations scored a maximum of 4/4 (the highest quality of evidence) for poor and intermediate metabolizers, and a score of 3/4 for ultrarapid metabolizers. Table is adapted from Swen J.J., Nijenhuis M., de Boer A., Grandia L. et al. Pharmacogenetics: from bench to byte - an update of guidelines. Clinical pharmacology and therapeutics. 2011;89(5):662–73 (2).

Table 2. Activity status of *CYP2D6* alleles

Allele type	Alleles
Active	**1, *2, *33, *35*
Decreased activity	****9**, ***10**, ***17**, *29, *36, ***41***
Inactive	****3**-***8**, *11-*16, *19-*21, *38, *40, *42*

Note: The most clinically significant variants are highlighted in bold.

Drug: Tramadol

Tramadol is an analgesic that is used to treat moderate to moderately severe pain. Tramadol is commonly prescribed for postoperative, cancer, and musculoskeletal pain. In the US, tramadol is classified as a Schedule IV controlled substance (1, 3).

Tramadol is a centrally acting analgesic that is structurally related to codeine and morphine, and belongs to the same drug class of opiate drugs. Tramadol, however, is a synthetic opioid, and it is administered as a racemic mixture of two enantiomers, (+) and (-) tramadol (4).

Although opiates have been used for pain control for several thousands of years, the receptors upon which they act were discovered relatively recently, in the 1960s. The exact mechanism of action of tramadol is not known, but it is thought that both enantiomers contribute to its analgesic effect in different ways. Tramadol has some activity at mu-opioid receptor (less than codeine) and it also inhibits the synaptic reuptake of serotonin and norepinephrine which inhibits pain transmission at the spinal cord (4, 5).

Tramadol is extensively metabolized within the liver and has one main major metabolite, O-desmethyltramadol, known as M1. Both the parent drug and M1 contribute to the analgesic effect, but M1 has a significantly higher affinity for opioid receptors than tramadol (6). The enzyme CYP2D6 catalyzes the production of M1, and other CYP enzymes (CYP2B6 and CYP3A4) catalyze the production of M2, an inactive metabolite (7).

The adverse effects of tramadol therapy are similar to that of other weak opioids. Common side effects include dizziness, nausea, constipation, and headache. But an additional risk of tramadol therapy is the risk of seizures, especially in patients who are already taking antidepressants or other drugs that decrease the seizure threshold. There is also an increased risk of suicide, and therefore tramadol should not be prescribed for patients who are suicidal or prone to addictions—the use of non-narcotic analgesics should be considered instead (1).

Because tramadol has mu-opioid agonist activity, there is a risk of abuse and addiction, even under appropriate medical use. Therefore, as for all patients treated with opioids, there should be careful monitoring of patients taking tramadol. In addition, the longer a patient is on continuous tramadol therapy, the greater the risk of

tolerance (the need to increase the dose of drug to maintain a defined level of analgesia in the absence of disease progression). Physical dependence upon tramadol is manifested by withdrawal symptoms after the use of tramadol is stopped abruptly. Symptoms include restlessness, rhinorrhea, lacrimation, and chills (1).

Serotonin syndrome is a potentially life-threatening syndrome that may occur with the use of tramadol, especially if other medications such as antidepressants or other drugs that impair the metabolism of tramadol (CYP2D6 and CYP3A4 inhibitors) are used concurrently. Symptoms include changes in mental status (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea) (1, 8).

Gene: *CYP2D6*

The cytochrome P450 superfamily (CYP450) is a large and diverse group of enzymes that form the major system for metabolizing lipids, hormones, toxins, and drugs. The *CYP450* genes are very polymorphic and can result in reduced, absent, or increased enzyme activity.

CYP2D6 is responsible for the metabolism of many commonly prescribed drugs, including antidepressants, antipsychotics, analgesics, and beta-blockers. The *CYP2D6* gene is highly polymorphic, with more than 100 star (*) alleles described (9).

*CYP2D6*1* is the wild-type allele and is associated with normal enzyme activity and the "extensive metabolizer" phenotype. The *CYP2D6* alleles **2*, **33*, and **35* are also considered to have near-normal activity.

Other alleles include variants that produce a non-functioning enzyme (e.g., **3*, **4*, **5,* and **6*) (10-13) or an enzyme with reduced activity (e.g., **10*, **17*, and **41*) (2, 14, 15) (see Table 2). There are large inter-ethnic differences in the frequency of these alleles, with **3*, **4*, **5*, **6,* and **41* being more common in Caucasians, **17* more common in Africans, and **10* more common in Asians (16).

Individuals who are intermediate or poor metabolizers carry copies of decreased-functioning and inactive *CYP2D6* alleles (see Table 1 and 2). In these individuals, the metabolic capacity of CYP2D6 is decreased which may result in higher levels of tramadol.

The FDA-approved drug label for tramadol includes a study where concentrations of tramadol were approximately 20% higher in "poor metabolizers" versus "extensive metabolizers", while M1 concentrations were 40% lower. The label also states that other factors, such as the concurrent use of CYP2D6 inhibitors (e.g., fluoxetine and its metabolite norfluoxetine, amitriptyline and quinidine) could also result in increases in tramadol concentrations and decreased concentrations of M1, and that the "full pharmacological impact of these alterations in terms of either efficacy or safety is unknown" (1).

The Dutch Pharmacogenetics Working Group recommendations state that for poor metabolizers, "either select an alternative drug (not oxycodone or codeine) or be alert to the symptoms of insufficient pain relief" (2).

Poor metabolizers are commonly found in European Caucasians (6-10%). The most common allele in this population is the functional *CYP2D6*1* (70%), and the most common nonfunctional alleles include *CYP2D6*4* and **5*, which largely account for the poor metabolizer phenotype in these populations (16). About 2% of African Americans are poor metabolizers, due to a wide ranges of variants that include the nonfunctional **4* and **5* alleles (17-19).

For intermediate metabolizers, the Dutch Pharmacogenetics Working Group recommendations state to be alert to decreased efficacy of tramadol. Consider increasing the dose of tramadol and if the response is still inadequate, either select an alternative drug (not oxycodone or codeine), or be alert to the symptoms of insufficient pain relief (2).

Approximately 30% of Asians and individuals of Asian descent are intermediate metabolizers. In these populations, only half of *CYPD6* alleles are fully functional, with the reduced function **10* variant being very common (~40%, compared to ~2% in Caucasians) (20). As a result, Asians are more likely to be intermediate metabolizers than Caucasians (16).

Individuals who have multiple functional copies of the *CYP2D6* gene are "ultrarapid metabolizers" (UM). Each allele contributes to the metabolism of tramadol. The Dutch Pharmacogenetics Working Group recommendations state that for ultrarapid metabolizers, either reduce the dose of tramadol by 30% and be alert to adverse drug events (e.g., nausea, vomiting, constipation, respiratory depression, confusion, urinary retention), or select an alternative drug (e.g., acetaminophen, NSAID, morphine—not oxycodone or codeine).

The ultrarapid metabolizer phenotype is estimated to be present in up to 28% of North Africans, Ethiopians, and Arabs; up to 10% in Caucasians; 3% in African Americans, and up to 1% in Hispanics, Chinese, and Japanese (16).

Genetic Testing

Genetic testing is available for many of the more common variant *CYP2D6* alleles. Results are typically reported as a diplotype, such as *CYP2D6 *1/*1* (21). A result for copy number, if available, is also important when interpreting *CYP2D6* results.

If the test results include an interpretation of the patient's predicted metabolizer phenotype, this should be confirmed by checking the diplotype and assigning an activity score to each allele (e.g., 0 for nonfunctional, 0.5 for reduced function, and 1 for each copy of a functional allele). The phenotype is defined by the sum of the two scores:

- An extensive (normal) metabolizer phenotype has an activity score of 1 to 2
- An intermediate metabolizer has an activity score of 0.5
- A poor metabolizer has an activity score of 0
- An ultrarapid metabolizer has an activity score greater than 2

Therapeutic Recommendations based on Genotype

This section contains excerpted[1] information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

Statement from the US Food and Drug Administration (FDA): Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P- 450. These individuals are "poor metabolizers" of debrisoquine, dextromethorphan, tricyclic antidepressants, among other drugs. Based on a population PK [pharmacokinetic] analysis of Phase I studies in healthy subjects, concentrations of tramadol were approximately 20% higher in "poor metabolizers" versus "extensive metabolizers", while M1 [tramadol metabolite] concentrations were 40% lower. Concomitant therapy with inhibitors of CYP2D6 such as fluoxetine, paroxetine and quinidine could result in significant drug interactions. In vitro drug interaction studies in human liver microsomes indicate that inhibitors of CYP2D6 such as fluoxetine and its metabolite norfluoxetine, amitriptyline and quinidine inhibit the metabolism of tramadol to various degrees, suggesting that concomitant administration of these compounds could result in increases in tramadol concentrations and decreased concentrations of M1. The full pharmacological impact of these alterations in terms of either efficacy or safety is

[1] The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt and may have inserted text in brackets, to explain some of the terms used. The FDA may not have labeled all formulations containing the generic drug.

unknown. Concomitant use of SEROTONIN re-uptake INHIBITORS and MAO INHIBITORS may enhance the risk of adverse events, including seizure and serotonin syndrome.

Please review the complete therapeutic recommendations that are located here: (1)

Summary of recommendations from the Pharmacogenetics Working Group of the Royal Dutch Association for the Advancement of Pharmacy (KNMP): For ultrarapid metabolizers, either reduce the dose of tramadol by 30% and be alert to adverse drug events (e.g., nausea, vomiting, constipation, respiratory depression, confusion, urinary retention), or select an alternative drug (e.g., acetaminophen, NSAID, morphine—not oxycodone or codeine).

For intermediate metabolizers, be alert to decreased efficacy of tramadol. Consider increasing the dose of tramadol and if the response is still inadequate, either select an alternative drug (not oxycodone or codeine), or be alert the symptoms of insufficient pain relief.

For poor metabolizers, either select an alternative drug (not oxycodone or codeine) or be alert to the symptoms of insufficient pain relief.

Please review the complete therapeutic recommendations that are located here: (2)

Nomenclature

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2D6*4*	1846G>A	NM_000106.4:c.506-1G>A	Not applicable—variant occurs in a non-coding region	rs3892097
*CYP2D6*5*	CYP2D6,DEL	NC_000022.10:g.(42534124_42531353)_(42521970_42519196)del	Not applicable—variant results in a whole gene deletion	
*CYP2D6*6*	1707 del T Trp152Gly	NM_000106.4:c.454delT	NP_000097.2:p.Trp152Glyfs	rs5030655
*CYP2D6*10*	100C>T Pro34Ser	NM_000106.4:c.100C>T	NP_000097.2:p.Pro34Ser	rs1065852
*CYP2D6*17*	Includes at least two functional variants*: 1023C>T (Thr107Ile) 2850C>T (Cys296Arg)	NM_000106.4:c.320C>T NM_000106.4:c.886T>C	NP_000097.2:p.Thr107Ile NP_000097.2:p.Cys296Arg	rs28371706 rs16947
*CYP2D6*41*	2988G>A	NM_000106.4:c.985+39G>A	Not applicable—variant occurs in a non-coding region	rs28371725

* In the literature, 1023C>T is also referred to as 1111C>T, and 2850C>T is also referred to 2938C>T.

Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS): http://www.hgvs.org/content/guidelines

Nomenclature for Cytochrome P450 enzymes is available from the Pharmacogene Variation Consortium database: https://www.pharmvar.org/

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References

1. TRAMADOL- tramadol hydrochloride tablet [package insert]. North Carolina, USA: Accord Healthcare, I.; 2014. Available from: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=052d06ef-4186-4ac1-9099-af05fa37c2f8
2. Swen J.J., Nijenhuis M., de Boer A., Grandia L., et al. Pharmacogenetics: from bench to byte--an update of guidelines. Clinical pharmacology and therapeutics. 2011;89(5):662–73. PubMed PMID: 21412232.
3. Drug Enforcement Administration, Department of Justice. Schedules of Controlled Substances: Placement of Tramadol Into Schedule IV. Federal Register 2014 [Last accessed: 3 June 2015]. Available from: https://www.federalregister.gov/articles/2014/07/02/2014-15548/schedules-of-controlled-substances-placement-of-tramadol-into-schedule-iv
4. Grond S., Sablotzki A. Clinical pharmacology of tramadol. Clin Pharmacokinet. 2004;43(13):879–923. PubMed PMID: 15509185.
5. Reeves R.R., Burke R.S. Tramadol: basic pharmacology and emerging concepts. Drugs Today (Barc). 2008;44(11):827–36. PubMed PMID: 19180260.
6. Gillen C., Haurand M., Kobelt D.J., Wnendt S. Affinity, potency and efficacy of tramadol and its metabolites at the cloned human mu-opioid receptor. Naunyn Schmiedebergs Arch Pharmacol. 2000;362(2):116–21. PubMed PMID: 10961373.
7. Subrahmanyam V., Renwick A.B., Walters D.G., Young P.J., et al. Identification of cytochrome P-450 isoforms responsible for cis-tramadol metabolism in human liver microsomes. Drug Metab Dispos. 2001;29(8):1146–55. PubMed PMID: 11454734.
8. Beakley B.D., Kaye A.M., Kaye A.D. Tramadol, Pharmacology, Side Effects, and Serotonin Syndrome: A Review. Pain Physician. 2015;18(4):395–400. PubMed PMID: 26218943.
9. CYP2D6 allele nomenclature. 2015 [Last accessed: 3 June 2015]. Available from: http://www.cypalleles.ki.se/cyp2d6.htm (now encompassed within the Pharmacogene Variation Consortium database: https://www.pharmvar.org/)
10. PharmGKB [Internet]. Palo Alto (CA): Stanford University. Haplotype CYP2D6*3. [Cited 3 June 2015]. Available from: http://www.pharmgkb.org/haplotype/PA165816578
11. PharmGKB [Internet]. Palo Alto (CA): Stanford University. Haplotype CYP2D6*4. [Cited 3 June 2015]. Available from: http://www.pharmgkb.org/haplotype/PA165816579
12. PharmGKB [Internet]. Palo Alto (CA): Stanford University. Haplotype CYP2D6*5. [Cited 3 June 2015]. Available from: http://www.pharmgkb.org/haplotype/PA165948092
13. PharmGKB [Internet]. Palo Alto (CA): Stanford University. Haplotype CYP2D6*6. [Cited 3 June 2015]. Available from: http://www.pharmgkb.org/haplotype/PA165816581
14. PharmGKB [Internet]. Palo Alto (CA): Stanford University. Haplotype CYP2D6*17. [Cited 3 June 2015]. Available from: http://www.pharmgkb.org/haplotype/PA165816583
15. PharmGKB [Internet]. Palo Alto (CA): Stanford University. Haplotype CYP2D6*41. [Cited 3 June 2015]. Available from: http://www.pharmgkb.org/haplotype/PA165816584
16. Bradford L.D. CYP2D6 allele frequency in European Caucasians, Asians, Africans and their descendants. Pharmacogenomics. 2002;3(2):229–43. PubMed PMID: 11972444.

17. Ingelman-Sundberg M., Sim S.C., Gomez A., Rodriguez-Antona C. Influence of cytochrome P450 polymorphisms on drug therapies: pharmacogenetic, pharmacoepigenetic and clinical aspects. Pharmacology & therapeutics. 2007;116(3):496–526. PubMed PMID: 18001838.
18. Sistonen J., Sajantila A., Lao O., Corander J., et al. CYP2D6 worldwide genetic variation shows high frequency of altered activity variants and no continental structure. Pharmacogenetics and genomics. 2007;17(2):93–101. PubMed PMID: 17301689.
19. Yokota H., Tamura S., Furuya H., Kimura S., et al. Evidence for a new variant CYP2D6 allele CYP2D6J in a Japanese population associated with lower in vivo rates of sparteine metabolism. Pharmacogenetics. 1993;3(5):256–63. PubMed PMID: 8287064.
20. Gaedigk A., Gotschall R.R., Forbes N.S., Simon S.D., et al. Optimization of cytochrome P4502D6 (CYP2D6) phenotype assignment using a genotyping algorithm based on allele frequency data. Pharmacogenetics. 1999;9(6):669–82. PubMed PMID: 10634130.
21. Crews K.R., Gaedigk A., Dunnenberger H.M., Klein T.E., et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Codeine Therapy in the Context of Cytochrome P450 2D6 (CYP2D6) Genotype. Clinical pharmacology and therapeutics. 2012;91(2):321–6. PubMed PMID: 22205192.

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