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Tramadol Therapy and *CYP2D6* Genotype

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Introduction

Tramadol (brand names ConZip, Ultram, UltramER, Odolo) is an analgesic used to treat moderate to severe pain. It is used for a variety of pain conditions, including post-operative pain, cancer pain, and musculoskeletal pain. Tramadol is a centrally acting opioid analgesic with mu-opioid binding activity as well as weak inhibition of reuptake of norepinephrine and serotonin.

The CYP2D6 enzyme converts tramadol to the active metabolite, O-desmethyltramadol (M1), which has a significantly higher affinity for the mu-opioid receptor than tramadol. The M1 metabolite is up to 6 times more potent than tramadol in producing analgesia.

Individuals who have reduced CYP2D6 activity are known as "intermediate metabolizers" and those with absent CYP2D6 activity are known as "poor metabolizers." The standard recommended doses of tramadol may not provide adequate pain relief in these individuals because of reduced levels of M1. Whereas in individuals who have increased CYP2D6 activity ("ultrarapid metabolizers"), standard doses of tramadol may result in a higher risk of adverse events because of increased exposure to M1.

The 2021 FDA-approved drug label warns that individuals who are ultrarapid metabolizers (UMs) should not use tramadol because of the risk of life-threatening respiratory depression and signs of opiate overdose (for example, extreme sleepiness, confusion, or shallow breathing) (Table 1) (1).

The prevalence of CYP2D6 UM varies but is thought to be present in approximately 1–10% of Caucasians (European, North American), 3–4% of Blacks (African Americans), and 1–2% of East Asians (Chinese, Japanese, Korean). The frequency of UM phenotype has been reported to be even higher in some groups, including Ashkenazi Jews and regional populations in the Middle East.

Furthermore, tramadol is not recommended in nursing mothers due to the potential exposure to high levels of M1 causing life-threatening respiratory depression, if the mother is a UM. At least one death was reported in a nursing infant who was exposed to high levels of morphine in breast milk because the mother was an UM of codeine, which—similar to tramadol—is activated by CYP2D6 metabolism.

Tramadol is contraindicated for all children younger than age 12 and for all individuals under the age of 18 when being used for post-operative analgesia following tonsillectomy or adenoidectomy, or both. The label warns that

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life-threatening respiratory depression and death have occurred in children who received tramadol, and in at least one case, the child was an UM of tramadol.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) recommends that for an individual identified as a CYP2D6 UM, a different non-CYP2D6 dependent analgesic should be used to avoid the risk of severe toxicity with standard dosing of tramadol. The CPIC also recommends avoiding tramadol in individuals identified as CYP2D6 poor metabolizers (PMs) due to the possibility of lack of effect (Table 2) (2).

The Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP) provides dosing recommendations for tramadol based on CYP2D6 genotype (Table 3). The DPWG states it is not possible to calculate a dose adjustment for tramadol, because when the ratio of tramadol and M1 is altered, the nature and total analgesic effect of tramadol also changes. For CYP2D6 UM, DPWG recommends selecting an alternative drug to tramadol - but not codeine, which is also metabolized by CYP2D6. Alternative drugs include morphine (not metabolized by CYP2D6) and oxycodone (which is metabolized by CYP2D6 to a limited extent, but this does not result in differences in side effects in clinical practice). For CYP2D6 poor (PM) and intermediate metabolizers (IM), DPWG recommends increasing the dose of tramadol, and if this does not have the desired effect, selecting an alternative drug (not codeine) (Table 3) (3).

Table 1. The FDA Tramadol Dosing Recommendation based on CYP2D6 Genotype (2021)

	CYP2D6 ultrarapid metabolizers
All ultrarapid metabolizer individuals	Some individuals may be ultrarapid metabolizers because of a specific CYP2D6 genotype. These individuals convert tramadol into its active metabolite, O-desmethyltramadol (M1), more rapidly and completely than other people. This rapid conversion results in higher than expected serum M1 levels. Even at labeled dosage regimens, individuals who are ultrarapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing). Therefore, individuals who are ultrarapid metabolizers should not use tramadol hydrochloride tablets.
Ultrarapid metabolizer children	Life-threatening respiratory depression and death have occurred in children who received tramadol. Some of the reported cases followed tonsillectomy or adenoidectomy, or both; in at least one case, the child had evidence of being an ultrarapid metabolizer of tramadol due to a CYP2D6 polymorphism. Tramadol hydrochloride is contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy or adenoidectomy, or both. Avoid the use of tramadol hydrochloride tablets in adolescents 12–18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol
Infants nursing from ultrarapid metabolizer mothers	Tramadol is subject to the same polymorphic metabolism as codeine, with ultrarapid metabolizers of CYP2D6 substrates being potentially exposed to life-threatening levels of the active metabolite O-desmethyltramadol (M1). At least one death was reported in a nursing infant who was exposed to high levels of morphine in breast milk because the mother was an ultrarapid metabolizer of codeine. A baby nursing from an ultrarapid metabolizer mother taking tramadol hydrochloride tablets could potentially be exposed to high levels of M1, and experience life-threatening respiratory depression. For this reason, breastfeeding is not recommended during treatment with tramadol hydrochloride tablets.

Please see Therapeutic Recommendations based on Genotype for more information from the FDA. This table is adapted from (1).

Table 2. The CPIC Tramadol Therapy Recommendations Based on CYP2D6 Phenotype (2021)

Phenotype[a]	Activity score[b]	Implications	Genotype	Examples of diplotypes[b]	Recommendations for tramadol therapy[d]
Ultrarapid metabolizer	> 2.25	Increased formation of O-desmethyltramadol (active metabolite) leading to higher risk of toxicity	More than 2 copies of normal-function alleles	**1/*1xN*[c] **1/*2xN*	Avoid tramadol use because of potential for toxicity. If opioid use is warranted, consider a non-codeine opioid.

Table 2. continued from previous page.

Phenotype[a]	Activity score[b]	Implications	Genotype	Examples of diplotypes[b]	Recommendations for tramadol therapy[d]
Normal metabolizer	1.25–2.25*	Expected O-desmethyltramadol (active metabolite) formation	2 normal-function alleles, or one normal-function allele and one decreased-function allele, or combinations of duplicated alleles that result in an activity score of 1.25–2.25	**1/*10* **1/*41* **1/*9* **10/*41x3* **1/*1* **1/*2* **2x2/*10*	Use tramadol label-recommended age- or weight-specific dosing.
Intermediate metabolizer	0.25–1*	Reduced O-desmethyltramadol (active metabolite) formation.	One decreased-function allele and one no-function allele, or 2 decreased-function alleles	**4/*10* **4/*41* **10/*10* **10/*41* **41/*41* **1/*5*	Use tramadol label-recommended age or weight-specific dosing. If no response and opioid use is warranted, consider a non-codeine opioid
Poor metabolizer	0	Greatly reduced O-desmethyltramadol (active metabolite) formation leading to diminished analgesia.	2 no-function alleles	**3/*4* **4/*4* **5/*5* **5/*6*	Avoid tramadol use because of possibility of diminished analgesia. If opioid use is warranted, consider a non-codeine option.
Indeterminant metabolizer	n/a	n/a	An individual having one or 2 uncertain-function alleles	**1/*22* **1/*25* **22/*25*	No recommendation

[a] See the *CYP2D6* Frequency Table for race-specific allele and phenotype frequencies from PharmGKB and CPIC.
[b] Assignment of allele function and allele activity values including citations for allele function can be found at PharmGKB (*CYP2D6* Allele Definition Table and *CYP2D6* Allele Functionality Table) and CPIC.
For a complete list of *CYP2D6* diplotypes and resulting phenotypes, see the *CYP2D6* Genotype to Phenotype Table at PharmGKB and CPIC.
[C] Where xN represents the number of *CYP2D6* gene copies. For individuals with *CYP2D6* duplications or multiplications, see supplemental data in (2) for additional information on how to translate diplotypes into phenotypes.
[d] The strength of therapeutic recommendations is "moderate" for intermediate metabolizers, and "strong" for all other metabolizers. Table is adapted from (2).

Table 3. The DPWG Recommendations for Tramadol Dosing based on CYP2D6 Phenotype (2017)

CYP2D6 phenotype	Dosing recommendations
Poor metabolizer (gene dose 0, absent enzyme activity)	It is not possible to provide a recommendation for dose adjustment, because the total analgesic effect changes when the ratio between the mother compound and the active metabolite changes. 1. be alert to a reduced effectiveness 2. in the case of inadequate effectiveness: ◦ try a dose increase. ◦ if this does not work, choose an alternative* 3. if no alternative is selected: advise the individual to report inadequate analgesia
Intermediate metabolizer (gene dose 0.5-1, decreased enzyme activity)	

Table 3. continued from previous page.

CYP2D6 phenotype	Dosing recommendations
Ultrarapid metabolizer (gene dose ≥ 3) (enhanced enzyme activity)	As the total analgesic effect changes when the ratio between the mother compound and the active metabolite changes, the effect of a dose reduction cannot be predicted with certainty. 1. select an alternative* 2. if an alternative is not possible: ◦ use 40% of the standard dose ◦ advise the individual to report side effects (such as drowsiness, confusion, constipation, nausea and vomiting, respiratory depression or urine retention).

* Do not select codeine, as this is also metabolized by CYP2D6. Morphine is not metabolized by CYP2D6. Oxycodone is metabolized by CYP2D6 to a limited extent, but this does not result in differences in analgesia and side effects in clinical practice.
This table is adapted from (3).

Drug: Tramadol

Tramadol is a synthetic opioid used to treat moderate to severe pain. Tramadol is used for both acute and chronic pain, and is commonly prescribed for post-operative pain, pain caused by cancer, and musculoskeletal pain. In the USA, tramadol is classified as a Schedule IV controlled substance (1, 4). Drugs and other substances that are considered controlled substances under the Controlled Substances Act (CSA) are divided into 5 schedules based on whether they have an accepted medical indication and the potential for abuse or addiction. Schedule II drugs have a high potential for abuse that may lead to severe psychological or physical dependence, and schedule III have a lower potential for abuse. Schedule IV drugs have even further reduced potential for abuse relative to schedule III. (5)

Tramadol is structurally similar to codeine and morphine. Opioid prescriptions are common in the USA. One study estimated that between 2011 and 2012, nearly 7% of the adult population had taken an opioid in the 30 days before participation in the study (6). Opioid prescribing rates peaked in the USA in 2012, with over 255 million prescriptions annually and a prescribing rate of 81.3 prescriptions per 100 persons. Prescribing rates have consistently declined and in 2018, 51.4 prescriptions were written per 100 persons. (7)

As an opioid, tramadol is relatively weak. However, it is thought to have a unique mechanism of action involving different targets. Tramadol is administered as a racemic mixture of 2 enantiomers, (+) tramadol and (-) tramadol, which inhibit pain transmission at the spinal cord by inhibiting serotonin reuptake (+ tramadol) and noradrenaline reuptake (- tramadol). (2)

Both tramadol and its major active metabolite, M1, bind to the mu-opioid receptor. However, M1 has a significantly higher affinity (approximately 200 times greater) for the opioid receptor than tramadol and is thus more potent at providing analgesia. However, tramadol and its metabolites are proposed to exert their antinociceptive effect via a multimodal mechanism that includes serotonin and norepinephrine reuptake inhibition, as well as binding to the mu-opioid receptor. (8, 9, 10, 11, 12, 13)

Tramadol requires bioactivation in the liver to be converted to M1 and exert its full analgesic effect. This process is primarily mediated by the CYP2D6 enzyme, and the level of activity of the CYP2D6 enzyme influences the plasma concentration of M1. Other CYP enzymes (CYP2B6 and CYP3A4) catalyze the production of N-desmethyl tramadol (M2), an inactive metabolite (14). Other enzymes are involved in further metabolism, pharmacokinetics and pharmacodynamics of tramadol, but the clinical relevance of variants in those genes has yet to be determined (15).

Adverse effects of tramadol therapy include dizziness, nausea, constipation, and headache. Owing to its effects on serotonin and norepinephrine reuptake, additional risks of tramadol therapy include the risk of seizures, suicidal tendencies, and serotonin syndrome. Seizure risk is especially notable in individuals who are already

taking antidepressants or other drugs that decrease the seizure threshold. There is also an increased risk of suicide, therefore tramadol should not be prescribed for individuals who are suicidal or prone to addictions—the use of non-narcotic analgesics should be considered instead (1). Serotonin syndrome is a potentially life-threatening syndrome that may occur with the use of tramadol, especially if other serotonergic medications such as antidepressants (selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants) or other drugs that impair the metabolism of tramadol are used concurrently (for example, CYP2D6 and CYP3A4 inhibitors such as amiodarone, quinidine, erythromycin, or ritonavir). Symptoms of serotonin syndrome can variably include changes in mental status (for example, agitation, hallucinations, coma), autonomic instability (for example, tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (such as hyperreflexia, incoordination) and gastrointestinal symptoms (for example, nausea, vomiting, diarrhea) (1, 16).

Because tramadol has mu-opioid agonist activity, there is a risk of abuse and addiction, even under appropriate medical use. Therefore, as for all individuals treated with opioids, there should be careful monitoring of individuals taking tramadol. The longer an individual 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, 12). Concomitant medication with benzodiazepines or other CNS depressants is also discouraged due to the heightened risk of profound sedation, respiratory depression, coma, and death. Consider naloxone or nalmefene —opioid antagonists—prescription for emergency treatment of opioid overdose causing respiratory depression, but be aware that naloxone administration may increase the risk of seizure (1).

The drug label warns that women of reproductive age should be informed that tramadol can cause fetal harm, and women should inform their healthcare provider if they suspect or know they are pregnant. The prolonged use of tramadol during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life threatening if not recognized and treated. The signs are diverse, and include feeding difficulties, breathing problems, and seizures. Additionally, chronic use of opioids can reduce fertility in both females and males of reproductive potential; these effects may or may not be reversible (1). Breastfeeding is not recommended during tramadol treatment (1, 17).

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 in the liver. The *CYP450* genes are very polymorphic and can result in decreased, absent, or increased enzyme activity.

The CYP2D6 enzyme is responsible for the metabolism of many commonly prescribed drugs, including antidepressants, antipsychotics, analgesics, and beta-blockers (18).

The *CYP2D6* Alleles

The *CYP2D6* gene is highly polymorphic, as over 100 star (*) alleles have been described and cataloged at the Pharmacogene Variation (PharmVar) Consortium, and each allele is associated with either normal, decreased, or absent enzyme function (Table 4). (19)

The combination of *CYP2D6* alleles that a person has is used to determine their diplotype (for example, *CYP2D6 *4/*4*). Based on function, each allele can be assigned an activity score from 0 to 1, which in turn is often used to assign a phenotype (for example, CYP2D6 PM). However, the activity score system is not standardized across all clinical laboratories or *CYP2D6* genotyping platforms. The CPIC revised their activity scoring guidelines in

October 2019 to promote harmonization. The CYP2D6 phenotype is defined by the sum of the 2 activity scores, which is usually in the range of 0 to 3.0: (20)

- An ultrarapid metabolizer (UM) has an activity score greater than 2.25
- A normal metabolizer phenotype (NM) has an activity score of 1.25–2.25
- An intermediate metabolizer (IM) has an activity score of >0–<1.25
- A poor metabolizer (PM) has an activity score of 0

Table 4. Activity Status of Selected *CYP2D6* Alleles

Allele type	*CYP2D6* alleles	Activity score
Normal function	**1, *2, *27, *33*	1
Decreased function	**17, *41, *49*	0.5
Strongly decreased function	**10*	0.25
No function	**3, *4, *5, *6, *36*	0

For a comprehensive list of *CYP2D6* alleles, please See PharmVar. Activity scores from (20).

The *CYP2D6*1* allele is the wild-type allele when no variants are detected and is associated with normal enzyme activity and the "normal metabolizer" phenotype. The *CYP2D6*2*, **27*, and **33* alleles are also considered to have near-normal activity.

Other *CYP2D6* alleles include variants that produce a non-functioning enzyme (for example, **3*, **4*, **5*, and **6*) (21, 22, 23, 24) or an enzyme with decreased activity (for example, **10*, **17*, and **41*) (25, 26, 27) (see Table 4). There are large inter-ethnic differences in the frequency of these alleles, with **3*, **4*, **5*, **6*, and **41* being more common in individuals with European ancestry, **17* more common in Africans, and **10* more common in Asians. (28)

Larger structural variants at the *CYP2D6* locus have also been described, including gene duplications, deletions, tandem alleles, and gene conversions. As one might expect, deletions result in a no-function allele (for example, the **5* allele is a deletion). Duplications have been reported for alleles with normal function and decreased function, as well. In the case of allele duplications, the activity scores for the full complement of *CYP2D6* alleles are summed to determine the predicted metabolizer phenotype. Additional details on structural variants are available from PharmVar.

Allele Frequencies Vary between Populations

Among Asians and in individuals of Asian descent, only approximately 50% of *CYPD6* alleles are of normal function, and the frequency of *CYP2D6* duplications is as high as 45%, although this may have been overestimated by not accounting for tandem hybrid alleles (for example, **36+*10*). (29) Other studies on a USA population suggested less than 50% of alleles detected within Asian-descent individuals are normal-function alleles in a single copy, with 30% of alleles arising from structural variants (duplications or deletions). (30) Common no-function variants are *CYP2D6*36* and *CYP2D6*4.* (30) Both these alleles contain the variant "c.100C>T", which if present alone, results in *CYP2D6*10* (see Nomenclature table). (28, 29, 31, 32) The *CYP2D6*36* allele is the result of a gene conversion event with the pseudogene *CYP2D7* (33). This no-function allele is most commonly found in individuals of Asian ancestry (30).

Among Africans and African Americans, only approximately 50% of *CYP2D6* alleles are normal function. (21, 27, 28, 34) African Americans also have been found to have a higher frequency of no-function structural variants or decreased-function single-copy variant alleles versus Caucasian or Hispanic Americans. (30)

Middle-Eastern countries show a great diversity in phenotypic and allelic distribution for *CYP2D6* (35), though on average, these individuals show a lower frequency of PM phenotypes (0.91%) and higher ultrarapid

phenotypes (11.2%) than other ethnicities (Note: Oceania and Middle-Eastern ethnicities are combined in this study). (36)

Among European countries, there is diversity of allelic distribution. Gene duplications were more common in the south-eastern countries (Greece, Turkey: 6%) and less common in northern countries (Sweden and Denmark, <1%). Meanwhile, *CYP2D6*4* and *CYP2D6*5* alleles were more common in the north and less common in the south. (37) Worldwide *CYP2D6* genotype and phenotype frequencies have been catalogued and recently published (36).

CYP2D6 Phenotype

CYP2D6 Phenotype Frequencies Vary between Populations

Normal metabolizers: Between 43–67% of individuals have 2 normal-function alleles (**1* or **2*), or one normal-function allele and one decreased-function allele, resulting in a "normal metabolizer" phenotype based on the CPIC/PharmGKB activity scores (38). These individuals are most likely to have a phenotypically normal response to tramadol. However, there is a large amount of variability in tramadol response within individuals genotyped as normal metabolizers (NMs), and the causes of this variation, among individuals with the same diplotype, are unknown. (39)

Intermediate metabolizers: Between 10–44% of individuals are IMs—they have either 2 decreased-function alleles or one normal- or decreased-function and one no-function allele. (36, 38) These individuals may not respond as well to tramadol because the metabolism of tramadol to M1 is reduced. A study of a diverse USA urban population of children found that roughly 8% of subjects were IMs, though this may be higher due to the broader range for IM activity scores. (40) Within the USA, it has been observed that individuals of African or Asian descent were most likely to be classified as IMs (20–28% of population by ethnicity). (30) Similarly, PharmGKB reports that the highest frequency of IM activity scores are found in Sub-Saharan-African and East-Asian populations (38).

Poor metabolizers: Between 0.4–6.5% of individuals are PMs—they have 2 no-function alleles. (38, 41) In these individuals, tramadol will provide little or no pain relief. Poor metabolizers are more commonly found in European Caucasians and their descendants. The no-function *CYP2D6*4* and **5* alleles largely account for the PM phenotype in these populations (23, 26, 42). It should be noted that the frequency of PMs can be much lower in certain populations including East Asian, Oceania and Middle-Eastern (36). Studies of USA multi-ethnic populations have estimated the prevalence of PMs to be between 1.5–5.7% (30, 40).

Ultrarapid metabolizers: Individuals who are UMs have an enzyme activity score greater than 2.25, often due to an increased copy number of the *CYP2D6* gene. The UM phenotype has been estimated to be present in 1–2% of individuals, but the prevalence varies widely in different populations. It 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 (41, 43). PharmGKB reports that the Oceanian population has the highest prevalence of UM phenotype (38). Ultrarapid metabolizers made up 9% of subjects in an urban multi-ethnic population with a large portion of Hispanic/Latino subjects (40). A larger study of USA individuals predicted an UM phenotype in only 2.2% of individuals, regardless of ethnicity (30).

Pharmacologic Conversion of CYP2D6 Phenotype

Factors other than genotype can affect CYP2D6 enzyme activity and thus the metabolizer phenotype of any individual. Administration of multiple drugs, sometimes called polypharmacy or co-medication, can lead to a phenomenon called phenoconversion whereby an individual with one metabolizer genotype can have enzymatic activity of a different metabolizer group (higher or lower, depending on the medications). Enzymatic activity of CYP2D6 can be inhibited or reduced by medications including duloxetine, paroxetine, fluoxetine, bupropion,

amiodarone (note: this is a weak inhibitor), and quinidine (43, 44, 45, 46). This can result in NMs or IMs responding to medications as if they were PMs. Thus, co-medication with multiple CYP2D6 substrates may result in reduced metabolism of these drugs. In the case of tramadol, this may present as reduced analgesic effect. In contrast, discontinuing a co-medication can increase the rate of CYP2D6 metabolism to the genotype predicted activity level.

Other Genes of Note

OPRM1

The mu-opioid receptor is encoded by the *OPRM1* gene. The mu-opioid receptor is a G-coupled protein receptor and is a key signal transducer for the desired analgesic effect of opioids such as tramadol and codeine. There are more than 200 known variant alleles of *OPRM1*, and some variants have been suggested to have a role in opioid response or predisposition to opioid use disorders (47, 48). However, CPIC's expert review found inconsistent evidence linking any of these alleles to post-operative dose requirements for some opioids and the effect on morphine dose adjustment was deemed not to be clinically actionable (2).

COMT

Catechol-o-methyltransferase (COMT) is an enzyme involved in the methylation and degradation of adrenaline, noradrenaline, and dopamine. This enzyme regulates the concentration of catecholamines and thus is a key regulator of the pain perception pathways (49). The variant rs4680 (p.Val158Met) in *COMT* has been suggested to result in decreased levels of methylation activity (2, 49). However, CPIC's review found variable evidence associating this variant with analgesia response or opioid dose requirements and thus makes no recommendations based on *COMT* genotype (2).

CYP2B6 and *CYP3A4/5*

Other cytochrome P450 enzymes are involved in the metabolism of tramadol. The formation of the inactive metabolite M2 is mediated by CYP3A4 and CYP2B6. Variants leading to reduced function of these enzymes may lead to increased levels of tramadol, though there are no specific prescribing recommendations based on the presence of these alleles. (11, 50)

Linking Gene Variation with Treatment Response

It has been established that genetic variation in the *CYP2D6* gene can be responsible for the variability in CYP2D6 enzyme expression, and consequently, for variability in an individual's analgesic response to tramadol. Individuals with normal levels of CYP2D6 activity ("CYP2D6 normal metabolizers") are mostly likely to benefit from tramadol therapy (51).

The standard recommended doses of tramadol may lead to severe adverse effects in individuals who have increased CYP2D6 activity. In these individuals, tramadol is converted to M1 more rapidly and completely, leading to higher than expected levels of M1 and a higher risk of adverse events. In contrast, individuals who have absent CYP2D6 enzyme activity may have little analgesic effect from standard doses of tramadol and may request a stronger opioid. This is not drug seeking; this is an inability to benefit from tramadol therapy because of an inability to produce adequate levels of M1.

Therefore, clinicians should consider CYP2D6 testing in individuals who either have a minimal response to standard doses of tramadol (possible CYP2D6 PMs), or who have unexpected adverse effects (possible CYP2D6 UMs) (48, 52, 53). Several studies have investigated the feasibility and impact of pharmacogenetic testing for

CYP2D6 variation and have concluded that—in multiple care settings—this is both feasible and has the potential to improve pain management while decreasing adverse reactions (45, 54, 55, 56).

Tramadol should not be used in individuals with increased CYP2D6 activity. Even at labeled dosage regimens, individuals (especially children) may have life-threatening or fatal respiratory depression, or experience the signs of opiate overdose, such as extreme sleepiness, confusion, and shallow breathing.

There have been several cases of respiratory depression and death of children who have received tramadol. A case report describes a child with the *CYP2D6* ultrarapid genotype, who had severe respiratory depression after taking tramadol for pain relief following a tonsillectomy, a day case procedure (57, 58, 59).

Because of the risks of respiratory depression, tramadol is contraindicated for all children younger than age 12 years of age and is contraindicated in children of any age undergoing tonsillectomy or adenoidectomy, or both. Tramadol should also be avoided in children who are obese, have obstructive sleep apnea, have severe lung disease, or any other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol. This warning is similar to the drug label warning for codeine - a structurally similar opioid that is also bioactivated by CYP2D6.

For CYP2D6 intermediate and PMs, an increased dose of tramadol may be required. Alternatively, a different analgesic (a non-CYP2D6-dependent opioid or a non opioid) may be more appropriate. However, codeine as well as hydrocodone are not suitable alternatives to tramadol because they are also metabolized by CYP2D6. Oxycodone is to a lesser degree metabolized by CYP2D6 (it is primarily metabolized by CYP3A4), but neither the CPIC nor the DPWG find sufficient evidence to support a *CYP2D6* genotype correlation with altered analgesia or side effects, thus oxycodone can be considered as an alternate opioid. Opioids that are not primarily metabolized by CYP2D6 include morphine, oxymorphone, buprenorphine, fentanyl, methadone, and hydromorphone. (6, 12, 48, 60, 61, 62, 63, 64, 65, 66, 67, 68)

The enzymatic activity of CYP2D6 can also be affected by co-medications. The FDA-approved drug label does not specifically recommend adjusting dosage, but encourages close monitoring of individuals taking CYP2D6 inhibitors. (1) One recent study reported a higher incidence of breakthrough pain requiring additional medication in the hospital setting for tramadol individuals also taking fluoxetine and bupropion (69).

The *CYP2D6* Gene Interactions with Medications Used for Additional Indications

The CYP family of enzymes is involved in metabolism of many substances and CYP2D6 especially has been implicated in altered pharmacologic responses for many compounds. The drugs can be categorized into many different classes:

- Antipsychotics—for example, aripiprazole, risperidone, thioridazine and—to a lesser extent—clozapine is metabolized by CYP2D6. According to the FDA, aripiprazole dosage should be reduced for PMs and thioridazine is contraindicated for individuals who are known to have reduced CYP2D6 activity due to increased risk of potentially fatal side effects. Ultrarapid metabolizers may have a decreased plasma concentration of risperidone.
- Tricyclic antidepressants—for example, amitriptyline, and imipramine may require dosage adjustments, potentially guided by therapeutic drug monitoring, to achieve the desired therapeutic range in UMs or PMs. Ultimately, tricyclic antidepressants may be ineffective in CYP2D6 UMs
- Serotonin and norepinephrine reuptake inhibitors—for example atomoxetine and venlafaxine may have reduced efficacy in UMs at standard doses while PMs are at risk of elevated plasma concentrations for both medications. The DPWG advises against use of venlafaxine in CYP2D6 PMs and IMs.

- Cardiovascular dysfunction—for example, carvedilol, metoprolol, and propafenone are all metabolized by CYP2D6 and PMs will have higher plasma concentrations of these medications compared with NMs resulting in potentially undesired side effects or (in the case of metoprolol) extensive slowing of the heart rate.
- Anti-cancer medications—for example, tamoxifen is activated by CYP2D6 and IMs or PMs may have reduced benefit from tamoxifen therapy.
- Various therapies for genetic disorders—for example eliglustat used in the treatment of Gaucher disease, and deutetrabenazine used in the treatment of Huntington disease—have reduced dose recommendations for CYP2D6 PMs. The CYP2D6 UMs may not achieve adequate concentrations of eliglustat and therefore CYP2D6 genotyping is required before initiation of eliglustat therapy.

It is important to note that *CYP2D6* is the most common biomarker in drug responses for FDA drug labels, the list provided here is by no means exhaustive. Additional information on gene-drug interactions for *CYP2D6* are available from PharmGKB, CPIC and the FDA (search for "CYP2D6").

Genetic Testing

Genetic testing is available for many (~30) of the variant *CYP2D6* alleles. Usually, an individual's result is reported as a diplotype, which includes one maternal and one paternal allele, for example, *CYP2D6 *1/*2*. When individuals have more than 2 copies of the *CYP2D6*, the copies of the allele are denoted by an "xN", for example, *CYP2D6*1/*2x2*. Some laboratories also use the notation of DUP to indicate an increase in copy number, but the report does not specify the number of duplications nor the allele that has been duplicated.

Genetic tests for tramadol response and the *CYP2D6* gene can be found on the NIH Genetic Testing Registry. The available CYP2D6 tests include targeted single-gene tests as well as multi-gene panels or genome-wide sequencing tests. In addition, variant *CYP2D6* alleles to be included in clinical genotyping assays have been recommended by the Association for Molecular Pathology (70).

The test results may include an interpretation of the individual's predicted metabolizer phenotype, which can be confirmed by checking the diplotype and calculating the CYP2D6 activity score, as described in the "*CYP2D6* Alleles" section above.

Variants in other genes, such as *COMT*, *ABCB1*, *UGT2B7* and *OPRM1*, may also influence an individual's response to tramadol. However, evidence is lacking on whether genetic testing for these variants will aid optimum dosing. (71, 72, 73, 74)

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.

2021 Statement from the US Food and Drug Administration (FDA):

Ultra-Rapid Metabolism of Tramadol and Other Risk Factors for Life-threatening Respiratory Depression in Children

Life-threatening respiratory depression and death have occurred in children who received tramadol. Tramadol and codeine are subject to variability in metabolism based upon CYP2D6 genotype (described below), which

[1] The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labeled all formulations containing the generic drug. Certain terms, genes and genetic variants may be corrected in accordance to nomenclature standards, where necessary. We have given the full name of abbreviations, shown in square brackets, where necessary.

can lead to increased exposure to an active metabolite. Based upon post-marketing reports with tramadol or with codeine, children younger than 12 years of age may be more susceptible to the respiratory depressant effects of tramadol. Furthermore, children with obstructive sleep apnea who are treated with opioids for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to their respiratory depressant effect. Because of the risk of life-threatening respiratory depression and death:

- Tramadol hydrochloride extended-release tablets are contraindicated for all children younger than 12 years of age.
- Tramadol hydrochloride extended-release tablets are contraindicated for post-operative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy.
- Avoid the use of tramadol hydrochloride extended-release tablets in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol unless the benefits outweigh the risks. Risk factors include conditions associated with hypoventilation, such as postoperative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression.
- As with adults, when prescribing opioids for adolescents, healthcare providers should choose the lowest effective dose for the shortest period of time and inform patients and caregivers about these risks and the signs of opioid overdose.

Nursing Mothers

Tramadol is subject to the same polymorphic metabolism as codeine, with ultra-rapid metabolizers of CYP2D6 substrates being potentially exposed to life-threatening levels of the active metabolite O-desmethyltramadol (M1). At least one death was reported in a nursing infant who was exposed to high levels of morphine in breast milk because the mother was an ultra-rapid metabolizer of codeine. A baby nursing from an ultra-rapid metabolizer mother taking tramadol hydrochloride [extended-release] tablets could potentially be exposed to high levels of M1, and experience life-threatening respiratory depression. For this reason, breastfeeding is not recommended during treatment with tramadol hydrochloride extended-release tablets.

***CYP2D6* Genetic Variability: Ultra-rapid metabolizer**

Some individuals may be ultra-rapid metabolizers because of a specific *CYP2D6* genotype (e.g., gene duplications denoted as *1/*1xN or *1/*2xN). The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 1 to 10% for Whites (European, North American), 3 to 4% for Blacks (African Americans), 1 to 2% for East Asians (Chinese, Japanese, Korean), and may be greater than 10% in certain racial/ethnic groups (i.e., Oceanian, Northern African, Middle Eastern, Ashkenazi Jews, Puerto Rican). These individuals convert tramadol into its active metabolite, O-desmethyltramadol (M1), more rapidly and completely than other people. This rapid conversion results in higher than expected serum M1 levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing). Therefore, individuals who are ultra-rapid metabolizers should not use tramadol hydrochloride tablets.

[…]

Drug Interactions

Inhibitors of CYP2D6:

Clinical Impact: The concomitant use of tramadol hydrochloride tablets and CYP2D6 inhibitors may result in an increase in the plasma concentration of tramadol and a decrease in the plasma concentration of M1, particularly when an inhibitor is added after a stable dose of tramadol hydrochloride tablets is achieved. Since M1 is a more potent μ-opioid agonist, decreased M1 exposure could result in decreased therapeutic effects, and may result in signs and symptoms of opioid withdrawal in patients who had developed physical dependence to tramadol.

Increased tramadol exposure can result in increased or prolonged therapeutic effects and increased risk for serious adverse events including seizures and serotonin syndrome. After stopping a CYP2D6 inhibitor, as the effects of the inhibitor decline, the tramadol plasma concentration will decrease and the M1 plasma concentration will increase. This could increase or prolong therapeutic effects but also increase adverse reactions related to opioid toxicity, such as potentially fatal respiratory depression.

Intervention: If concomitant use of a CYP2D6 inhibitor is necessary, follow patients closely for adverse reactions including opioid withdrawal, seizures and serotonin syndrome. If a CYP2D6 inhibitor is discontinued, consider lowering tramadol hydrochloride tablets dosage until stable drug effects are achieved. Follow patients closely for adverse events including respiratory depression and sedation.

Examples: Quinidine, fluoxetine, paroxetine and bupropion

Inhibitors of CYP3A4:

Clinical Impact: The concomitant use of tramadol hydrochloride tablets and CYP3A4 inhibitors can increase the plasma concentration of tramadol and may result in a greater amount of metabolism via CYP2D6 and greater levels of M1. Follow patients closely for increased risk of serious adverse events including seizures and serotonin syndrome, and adverse reactions related to opioid toxicity including potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of tramadol hydrochloride tablets is achieved. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the tramadol plasma concentration will decrease, resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to tramadol.

Intervention: If concomitant use is necessary, consider dosage reduction of tramadol hydrochloride tablets until stable drug effects are achieved. Follow patients closely for seizures and serotonin syndrome, and signs of respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider increasing the tramadol hydrochloride tablets dosage until stable drug effects are achieved and follow patients for signs and symptoms of opioid withdrawal.

Examples: Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir)

CYP3A4 Inducers:

Clinical Impact: The concomitant use of tramadol hydrochloride tablets and CYP3A4 inducers can decrease the plasma concentration of tramadol, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to tramadol. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the tramadol plasma concentration will increase, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause seizures, serotonin syndrome, and/or potentially fatal respiratory depression.

Intervention: If concomitant use is necessary, consider increasing the tramadol hydrochloride tablets dosage until stable drug effects are achieved. Follow patients for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider tramadol hydrochloride tablets dosage reduction and monitor for seizures and serotonin syndrome, and signs of sedation and respiratory depression. Patients taking carbamazepine, a CYP3A4 inducer, may have a significantly reduced analgesic effect of tramadol. Because carbamazepine increases tramadol metabolism and because of the seizure risk associated with tramadol, concomitant administration of tramadol hydrochloride tablets and carbamazepine is not recommended.

Examples: Rifampin, carbamazepine, phenytoin

[….]

Special populations: Poor/Extensive Metabolizers, CYP2D6

The formation of the active metabolite of tramadol, M1, is mediated by CYP2D6, a polymorphic enzyme. Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P450 metabolizing enzyme system. These individuals are "poor metabolizers" of debrisoquine, dextromethorphan and tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase 1 studies with IR tablets in healthy subjects, concentrations of tramadol were approximately 20% higher in "poor metabolizers" versus "extensive metabolizers," while M1 concentrations were 40% lower.

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

2020 Statement from the Clinical Pharmacogenetics Implementation Consortium (CPIC)

For CYP2D6 normal metabolizers (i.e. CYP2D6 activity score 1.25 to 2.25), a label recommended age- or weight-specific starting dose of codeine or tramadol, as recommended in the product label, is warranted. A label recommended starting dosing is also recommended for intermediate metabolizers (i.e. activity score of 0.25 to 1); these patients should be monitored closely for less than optimal response and should be offered an alternative analgesic if warranted. For CYP2D6 poor metabolizers (i.e. activity score of 0), current evidence supports the avoidance of codeine and tramadol and the use of an alternative analgesics due to the likelihood of suboptimal or lack of effect. There is insufficient evidence in the literature to recommend a higher dose of codeine or tramadol in poor metabolizers, especially considering the evidence that some adverse events do not differ between poor and normal metabolizers (19). For CYP2D6 ultrarapid metabolizers (namely, activity score of >2.25), codeine or tramadol should not be used, in order to avoid the risk of severe toxicity with label-recommended dosing. Non-opioid analgesics and if needed, other opioids that are not affected by CYP2D6 phenotype, are potential alternatives for use in CYP2D6 poor and ultrarapid metabolizers based on the type, severity and chronicity of the pain being treated.

Please review the complete therapeutic recommendations that are located here: (2, 39).

2017 Summary of recommendations from the Pharmacogenetics Working Group of the Royal Dutch Association for the Advancement of Pharmacy (KNMP)

Ultra-rapid metabolizer (gene dose ≥ 3) (enhanced CYP2D6 enzyme activity)

The genetic variation increases the conversion of tramadol to a metabolite with a stronger opioid effect. This can result in an increase in potentially life-threatening side effects.

Recommendation:
As the total analgesic effect changes when the ratio between the mother compound and the active metabolite changes, the effect of a dose reduction cannot be predicted with certainty.

1 select an alternative

Do not choose codeine, as it is contra-indicated for CYP2D6 UM.
Morphine is not metabolized by CYP2D6.
Oxycodone is metabolized by CYP2D6 to a limited extent, but this does not result in differences in side effects in patients.

2. if an alternative is not possible:

- use 40% of the standard dose

- advise the patient to report side effects (such as drowsiness, confusion, constipation, nausea and vomiting, respiratory depression or urine retention).

Intermediate metabolizer (gene dose 0.5-1) (decreased CYP2D6 enzyme activity)

The genetic variation reduces the conversion of tramadol to a metabolite with a higher activity. This can result in reduced analgesia.

Recommendation:
It is not possible to provide a recommendation for dose adjustment, because the total analgesic effect changes when the ratio between the mother compound and the active metabolite changes.

1. be alert to a reduced effectiveness
2. in the case of inadequate effectiveness:
    - try a dose increase
    - if this does not work: choose an alternative

Do not select codeine, as this is also metabolized by CYP2D6.

Morphine is not metabolized by CYP2D6.
Oxycodone is metabolized by CYP2D6 to a limited extent, but this does not result in differences in analgesia in patients.

3. if no alternative is selected: advise the patient to report inadequate analgesia

Poor metabolizer (gene dose 0) (absent CYP2D6 enzyme activity)

The genetic variation reduces the conversion of tramadol to a metabolite with a higher activity. This can result in reduced analgesia.

Recommendation:
It is not possible to provide a recommendation for dose adjustment, because the total analgesic effect changes when the ratio between the mother compound and the active metabolite changes.

1. be alert to a reduced effectiveness
2. in the case of inadequate effectiveness:
    - try a dose increase.
    - if this does not work: choose an alternative
      Do not select codeine, as this is also metabolized by CYP2D6.
      Morphine is not metabolized by CYP2D6.
      Oxycodone is metabolized by CYP2D6 to a limited extent, but this does not result in differences in analgesia in patients.
3. if no alternative is selected: advise the patient to report inadequate analgesia

Please review the complete therapeutic recommendations that are located here: (3).

Nomenclature

Nomenclature of Selected *CYP2D6* Alleles

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2D6*2*	2851C>T (Arg296Cys)	NM_000106.6:c.457G>C	NP_000097.3:p.Arg296Cys	rs16947
*CYP2D6*3*	4181G>C (Ser486Thr)	NM_000106.6:c.886C>T	NP_000097.3:p.Ser486Thr	rs1135840

Nomenclature of Selected continued from previous page.

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2D6*4*	1846G>A	NM_000106.6:c.506-1G>A	Variant occurs in a non-coding region (splice variant causes a frameshift)	rs3892097
*CYP2D6*5*	Gene deletion			
*CYP2D6*6*	1707 del T Trp152Gly CYP2D6T	NM_000106.6:c.454delT	NP_000097.3:p.Trp152Glyfs	rs5030655
*CYP2D6*10*	100C>T (Pro34Ser)	NM_000106.6:c.100C>T	NP_000097.3:p.Pro34Ser	rs1065852
*CYP2D6*17*	1023C>T[1] (Thr107Ile)	NM_000106.6:c.320C>T	NP_000097.3:p.Thr107Ile	rs28371706
	2851C>T[2] (Cys296Arg)	NM_000106.6:c.886T>C	NP_000097.3:p.Cys296Arg	rs16947
	4181G>C (Ser486Thr)	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840
*CYP2D6*27*	3854G>A (Glu410Lys)	NM_000106.6:c.1228G>A	NP_000097.3:p.Glu410Lys	rs769157652
*CYP2D6*31*	2851C>T (Arg296Cys)	NM_000106.6:c.886C>T	NP_000097.3:p.Arg296Cys	rs16947
	4043G>A (Arg440His)	NM_000106.6:c.1319G>A	NP_000097.3:p.Arg440His	rs267608319
	4181G>C (Ser486Thr)	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840
*CYP2D6*36*[3]	100C>T (Pro34Ser)	NM_000106.6:c.100C>T	NP_000097.3:p.Pro34Ser	rs1065852
	4129C>G (Pro469Ala)	NM_000106.6:c.1405C>G	NP_000097.3:p.Pro469Ala	rs1135833
	4132A>G (Thr470Ala)	NM_000106.6:c.1408A>G	NP_000097.3:p.Thr470Ala	rs1135835
	4156C>T+4157A>C (His478Ser)	NM_000106.6:c.1432C>T + NM_000106.6:c.1433A>C	NP_000097.3:p.His47Ser	rs28371735 + rs766507177
	4159G>C (Gly479Arg)	NM_000106.6:c.1435G>C	NP_00097.3:p.Gly479Arg	
	4165T>G (Phe481Val)	NM_000106.6:c.1441T>G	NP_00097.3:p.Phe481Val	
	4168G>A+4169C>G (Ala482Ser)	NM_000106.6:c.1444G>A + NM_000106.6:c.1445C>G	NP_000097.3:p.Ala482Ser	rs74478221 + rs75467367
	4181G>C (Ser486Thr)	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840
*CYP2D6*41*	2851C>T[2] (Cys296Arg)	NM_000106.6:c.886T>C	NP_000097.3:p.Cys296Arg	rs16947
	2988G>A	NM_000106.6:c.985+39G>A	Variant occurs in a non-coding region (impacts slicing).	rs28371725
*CYP2D6*49*	100C>T (Pro34Ser)	NM_000106.6:c.100C>T	NP_000097.3:p.Pro34Ser	rs1065852
	1612T>A (Phe120Ile)	NM_00106.6:c.358T>A	NP_000097.3:p.Phe120Ile	rs1135822
	4181G>C (Ser486Thr)	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840

[1] In the literature, 1023C>T is also referred to as 1111C>T
[2] In the literature, 2851C>T is also referred to as 2938C>T
[3] *CYP2D6*36* is a gene conversion with *CYP2D7;* variants provided here are from the Pharmacogene Variation Consortium.
Alleles described in this table are selected based on discussion in the text above. This is not intended to be an exhaustive description of known alleles.
Pharmacogenetic Allele Nomenclature: International Workgroup Recommendations for Test Result Reporting (75).
Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS).
Nomenclature for Cytochrome P450 enzymes is available from the Pharmacogene Variation (PharmVar) Consortium.

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To view an earlier version of this summary from 10 September 2015, please click here.

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