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Dronabinol Therapy and *CYP2C9* Genotype

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Introduction

Dronabinol (brand names Marinol, Syndros) is the main psychoactive component in marijuana. Dronabinol is used in the treatment of chemotherapy-induced nausea and vomiting (CINV) among individuals who have not responded to conventional antiemetic therapy, and to treat anorexia associated with weight loss in individuals with acquired immunodeficiency syndrome (AIDS).

Dronabinol is primarily metabolized by CYP2C9, which is responsible for the formation of the major active metabolite (11-hydroxy-delta-9-THC). Individuals who lack CYP2C9 activity ("CYP2C9 poor metabolizers") have an increased exposure to dronabinol and an increased risk of side effects. Adverse events associated with dronabinol therapy include sedation, physical weakness, facial flushing, and palpitations.

The FDA-approved drug label for dronabinol recommends monitoring for the increased adverse reactions that could potentially occur in individuals who are known to have genetic variants associated with diminished CYP2C9 function (Table 1). The label states that published data indicates these individuals may have a 2- to 3-fold higher exposure to dronabinol (1).

Table 1. The FDA Drug Label for Dronabinol. Effect of *CYP2C9* Polymorphism (2020)

Phenotype	Recommendations
CYP2C9 poor metabolizer	Published data suggest that systemic clearance of dronabinol may be reduced and concentrations may be increased in the presence of *CYP2C9* genetic polymorphism. Monitoring for potentially increased adverse reactions is recommended in individuals known to have genetic variants associated with diminished CYP2C9 function.

This table is adapted from (1).

Drug: Dronabinol

Dronabinol is used to stimulate appetite in individuals with AIDS-related anorexia associated with weight loss, and to treat CINV in individuals who have failed to respond adequately to conventional antiemetic treatments (1).

Dronabinol is taken orally, as capsules or a solution, and the recommended dose varies depending on the indication. Dronabinol is a cannabinoid and is also known as delta-9-tetrahydrocannabinol (delta-9-THC, or "THC").

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Cannabinoids are lipids derived from the cannabis (marijuana) plant. The plant contains more than 100 cannabinoids and dronabinol is a synthetic form of the primary psychoactive cannabinoid THC (2). Psychoactive agents affect brain function, and can cause a change in perception, mood, behavior, and level of consciousness.

Dronabinol is a Schedule III controlled substance. This means it is a drug that has a potential for abuse, but this is less of a risk than for Schedule I or II drugs. Abuse of dronabinol (taking high doses) will increase the risk of adverse psychiatric reactions such as psychosis, hallucinations, mood alteration, and paranoia. Continued abuse can lead to addiction (1).Two drugs that contain dronabinol as their active ingredient are Marinol, also Schedule III, and Syndros, which is a Schedule II substance (3).

In individuals with AIDS, to stimulate appetite, the recommended starting dose of dronabinol is 2.5 mg orally, twice daily, one hour before lunch and dinner (1). Weight loss associated with human immunodeficiency virus (HIV) and AIDS is common. Despite treatment with antiretroviral therapy, it is thought that the prevalence of HIV wasting syndrome is between 14 38%. Dronabinol appears to be well tolerated, improves appetite and may stop weight loss, but has variable results in terms of weight gain (4, 5, 6, 7).

In individuals undergoing chemotherapy, to treat CINV, the typical dose of dronabinol is 5 mg/m^2, 3–4 times a day. According to the drug label, the first dose of 5 mg/m^2 should be taken 1–3 hours before chemotherapy and at least 30 minutes before eating. This dose can be repeated every 2–4 hours after chemotherapy (without regard to meals) for a total of 4–6 doses per day (1).

Nausea and vomiting are common symptoms of chemotherapy and can have a significant detrimental impact on an individual's quality of life. Several types of antiemetics are commonly used to prevent and treat CINV before cannabinoids such as dronabinol are considered. These include corticosteroids (for example, dexamethasone), serotonin receptor antagonists (for example, ondansetron), and neurokinin receptor antagonists (for example, aprepitant).

There are many other medicines that can be used for CINV, but they tend to have more adverse effects. These medicines include antihistamines (for example, cyclizine), dopamine antagonists (for example, metoclopramide, olanzapine), benzodiazepines (for example, lorazepam), and anticonvulsants (for example, levetiracetam) (8).

Data on the efficacy of dronabinol is conflicting and limited to small trials (9). As an antiemetic, dronabinol has been reported to be superior to placebo in one trial, and inferior to metoclopramide in another (10, 11, 12). Dronabinol is only indicated for CINV in adults, although some data suggests adjunct dronabinol may be helpful in children (13). One review found no evidence to suggest that cannabinoids such as dronabinol were of value for anorexia or cachexia (extreme weight loss and wasting due to illness) in individuals with cancer or HIV (14). Because of the potential risk to the fetus, dronabinol should not be taken during pregnancy (1).

The mechanism of action of dronabinol is not clear –– it has complex effects on the central nervous system, including impairment of higher order processing, short term memory loss, and enhanced sensation. Central sympathomimetic activity can cause tachycardia (experienced as palpitations) and redness of the eyes (conjunctival injection).

Two cannabinoid receptors have been identified so far, CB1 –– which is located in the brain and some peripheral tissues also and may account for behavioral effects of cannabinoids; and CB2 –– mainly found peripherally and may affect immune function (15). Appetite stimulation is thought to be mediated at the lateral hypothalamus, antiemetic actions may be mediated by the vomiting center in the medulla, and the area subpostrema of the nucleus tractus solitarii may be involved in both appetite stimulation and antiemesis.

Outside of the US, synthetic cannabinoids such as dronabinol have been licensed to treat spasticity associated with multiple sclerosis (MS) and licensed as an adjunctive treatment of moderate to severe cancer pain. In the US, state medical marijuana programs may authorize eligible individuals to legally use marijuana for these

conditions. However, there are many medical and legal differences between dronabinol and medical marijuana. Marijuana contains over 400 compounds, it does not have FDA approval, it is a schedule I controlled substance, and is illegal at the federal level (16).

The importance of dronabinol in the management of chronic pain is unclear –– studies give a mixed picture, but dronabinol as an adjunct treatment may be more beneficial in neuropathic pain (for example, MS) than cancer pain (17, 18).

CYP2C9 is the main enzyme involved in the metabolism of dronabinol to its major active metabolite, 11-hydroxy-delta-9-THC. Individuals who have low CYP2C9 activity ("CYP2C9 poor metabolizers") have a higher exposure to dronabinol (19). Data suggest that the route of THC administration affects the rate of metabolism, with oral administration—as in the case of dronabinol—showing significant inter-individual variation not only due to CYP2C9 activity, but also fed versus fasted states (1, 20, 21). Total exposure to dronabinol was increased in the fed state, particularly following a high-fat content, high calorie meal (1, 20). Of note, CYP2C9 activity can be altered by co-medication, infection, and other disease processes, resulting in phenoconversion from normal metabolizer to poor metabolizer phenotypes (22, 23, 24).

While the FDA-approved label for dronabinol states that both CYP2C9 and CYP3A4 contribute to the metabolism of dronabinol, it is important to note that CYP3A4 is not involved in the formation of the primary active metabolite (11-hydroxy-delta-9-THC) (1). As such, adverse reactions due to coadministration with CYP2C9 inhibitors may differ compared with reactions due to CYP3A4 inhibitors.

The FDA states that "Dronabinol, a synthetic cannabinoid, may cause fetal harm. Avoid use of dronabinol capsules in pregnant women. Although there is little published data on the use of synthetic cannabinoids during pregnancy, use of cannabis (for example, marijuana) during pregnancy has been associated with adverse fetal/neonatal outcomes" (1). Similarly, dronabinol is not advised for nursing mothers, either because of HIV positive status or due to possible adverse effects on the nursing infant in individuals with CINV (1).

Gene: CYP2C9

The cytochrome P450 (CYP450) superfamily 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 polymorphic and can result in reduced, absent, or increased enzyme activity.

The *CYP2C9* gene is highly polymorphic, with more than 50 known star (*) alleles, which are catalogued by the Pharmacogene Variation (PharmVar) consortium (25). The *CYP2C9*1* is considered the wild-type allele when no variants are detected and is associated with normal enzyme activity and the "normal metabolizer" phenotype (26). Individuals who have 2 normal function alleles (for example, *CYP2C9 *1/*1*) are classified as "normal metabolizers" (Table 2).

Table 2. The CPIC Assignment of likely *CYP2C9* Phenotype based on Genotype (2020)

Likely phenotype[a,b]	Activity score	Genotype	Examples of diplotype
Normal metabolizer	2	An individual with 2 normal function alleles	*1/*1
Intermediate metabolizer	1.5 1	An individual with one normal function allele plus one decreased function allele; OR one normal function allele plus one no function allele OR 2 decreased function alleles	*1/*2 *1/*3 *2/*2
Poor metabolizer	0.5 0	An individual with one no function allele plus one decreased function allele; OR 2 no function alleles	*2/*3 *3/*3

Table 2. continued from previous page.

Likely phenotype[a,b]	Activity score	Genotype	Examples of diplotype
Indeterminate	n/a	An individual with allele combinations with uncertain or unknown function alleles	*1/*7 *1/*10 *7/*10 *1/*58

This CPIC table has been adapted from (27). Additional information on allele function is available from PharmVar and CPIC.

Multiple allelic variants associated with reduced enzyme activity (with definitive or moderate evidence), these include *CYP2C9*2*, **5*, **8, *11, *14* and others (28, 29). The **2* allele is more common in Caucasian (10–20%) than Asian (1–3%) or African (0–6%) populations. Alleles assigned an activity score of zero include *CYP2C9*3* and **13.* The **3* allele has a frequency of <10% in most populations and is extremely rare in African populations. Of note, among African-Americans, the *CYP2C9*5*, **6*, **8* and **11* variants are more common (30, 31, 32).

Linking Gene Variation with Treatment Response

One small study (43 healthy volunteers) reported that while orally administered THC pharmacokinetics did not differ by *CYP2C9*2* allele status, the *CYP2C9*3* allele did influence pharmacokinetics, therapeutics, and adverse effects. On average, individuals who were *CYP2C9*3/*3* homozygotes had a greater exposure to THC (the median area under the curve of THC was 3-fold higher than in than in *CYP2C9*1/*1* homozygotes), and these individuals showed a trend toward increased sedation following administration of THC (19). However, it is not possible to draw conclusions for the influence of the *CYP2C9*3/*3* genotype on dronabinol response, due to the small sample size (n=43) and nonblinded study design (19). Another study examined the pharmacokinetics of intravenously- and orally-administered THC and observed there was a significant contribution from the *CYP2C9*3* allele to individual dose exposure following oral ingestion, contributing to adverse effects in these individuals (21).

Genetic Testing

Clinical genotyping tests are available for several *CYP2C9* alleles. The NIH Genetic Testing Registry (GTR) provides examples of the genetic tests that are available for the *CYP2C9* gene and the dronabinol response. In addition, variant *CYP2C9* alleles to be included in clinical genotyping assays have been recommended by the Association for Molecular Pathology (AMP) (33).

The *CYP2C9* variants are usually reported as a diplotype, such as *CYP2C9 *1/*1*, and may also include an interpretation of the individual's predicted metabolizer phenotype (normal, intermediate, or poor) (Table 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.

2020 Statement from the US Food and Drug Administration (FDA)

Dronabinol is primarily metabolized by CYP2C9 and CYP3A4 enzymes based on published in vitro studies. Inhibitors of these enzymes may increase, while inducers may decrease, the systemic exposure of dronabinol and/or its active metabolite resulting in an increase in dronabinol-related adverse reactions or loss of efficacy of dronabinol capsules.

[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.

Monitor for potentially increased dronabinol-related adverse reactions when dronabinol capsules is coadministered with inhibitors of CYP2C9 (e.g., amiodarone, fluconazole) and inhibitors of CYP3A4 enzymes (e.g., ketoconazole, itraconazole, clarithromycin, ritonavir, erythromycin, grapefruit juice).

[…]

Published data suggest that systemic clearance of dronabinol may be reduced and concentrations may be increased in the presence of CYP2C9 genetic polymorphism. Monitoring for potentially increased adverse reactions is recommended in patients known to carry genetic variants associated with diminished CYP2C9 function.

[…]

Published data indicate a potentially 2-to 3-fold higher dronabinol exposure in individuals carrying genetic variants associated with diminished CYP2C9 function.

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

Nomenclature for Selected *CYP2C9* Alleles

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2C9*2*	430C>T Arg144Cys	NM_000771.4:c.430C>T	NP_000762.2:p.Arg144Cys	rs1799853
*CYP2C9*3*	1075A>C Ile359Leu	NM_000771.4:c.1075A>C	NP_000762.2:p.Ile359Leu	rs1057910
*CYP2C9*5*	1080C>G Asp360Glu	NM_000771.4:c.1080C>G	NP_000762.2:p.Asp360Glu	rs28371686
*CYP2C9*6*	817delA Lys273Argfs	NM_000771.4:c.817delA	NP_000762.2:p.Lys273Argfs	rs9332131
*CYP2C9*7*	55C>A Leu19Ile	NM_000771.4:c.55C>A	NP_000762.2:p.Leu19Ile	rs67807361
*CYP2C9*8*	449G>A Arg150His	NM_000771.4:c.449G>A	NP_000762.2:p.Arg150His	rs7900194
*CYP2C9*10*	10598A>G Glu272Gly	NM_000771.4:c.815A>G	NP_000762.2:p.Glu272Gly	rs9332130
*CYP2C9*11*	1003C>T Arg335Trp	NM_000771.4:c.1003C>T	NP_000762.2:p.Arg335Trp	rs28371685
*CYP2C9*13*	3276T>C Leu90Pro	NM_000771.4:c.269T>C	NP_000762.2:p.Leu90Pro	rs72558187
*CYP2C9*14*	3552G>A Arg125His	NM_000771.4:c.374G>A	NP_000762.2:p.Arg125His	rs72558189
*CYP2C9*58*	1009C>A Pro337Thr	NM_000771.4:c.1009C>A	NP_000762.2:p.Pro337Thr	rs1274535931

Note: the normal "wild type" allele is *CYP2C9*1* and is reported when no variant is detected.
Pharmacogenetic Allele Nomenclature: International Workgroup Recommendations for Test Result Reporting (34).
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 Pharmacogene Variation (PharmVar) Consortium.

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