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# PHARMACOGENETIC OF AMITRIPTYLINE - REVIEW ARTICLE

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## ABSTRACT

Amitriptyline is a tricyclic antidepressant (TCA) that used for the treatment of depression, postherpetic neuralgia, migraine prophylaxis and others. Many genetic variants have been shown to be associated with response to these drugs. The aimed of this research is to explore the impact genetic variants to amitriptyline responses. We reviewed the literature on pubmed and Science direct with keywords: pharmacogenetic and amitriptyline. We found 52 articles in Pubmed and 56 research articles with subject area pharmacology, Toxicology and pharmaceutical Science in science direct. Only 17 articles were reviewed due to suitability. We add 1 reference from https://go.drugbank.com/drugs/. We conclude that polymorphisme CYP2D6*3; CYP2D6*4; CYP2D6*5; CYP2D6*6; CYP2D6*7; CYP2D6*8; CYP2D6*11 ;CYP2D6*12; CYP2D6*13; CYP2D6*14A; CYP2D6*15; CYP2D6*19; CYP2D6*20; CYP2D6*31; CYP2D6*38; CYP2D6*40; CYP2D6*42; CYP2D6*44; CYP2D6*47; CYP2D6*51; CYP2D6*56; CYP2D6*57; CYP2D6*62; CYP2D6*68A; CYP2D6*92; CYP2D6*100; CYP2D6*101; CYP2C19*2; CYP2C19*3 ; CYP2C19*5 ; CYP2C19*6; CYP2C19*7; CYP2C19*22 ; CYP2C19*24 and CYP2C19*35 reduce metabolism of amitriptyline. Patients with polymorphism Multidrug resistance protein 1 (T > C (rs2032583) ABCB1 increase risk of adverse events with amitriptyline.

## Introduction

Amitriptyline is a tricyclic antidepressant that indicated in the treatment of depressive; anxiety-related depression; neuropathic pain (Lawson);[1] prophylactic of chronic tension-type headache (CTTH) in adults; prophylactic treatment of migraine in adults; treatment in children with nocturnal enuresis if there are no pathological abnormalities including spina bifida or others that do not respond to other drugs.[2]

## Chemical Formula and Structure

Chemical Formula of amitriptyline is $C_{20}H_{23}N$.[2]

Structure of Amitriptyline can be seen in figure 1

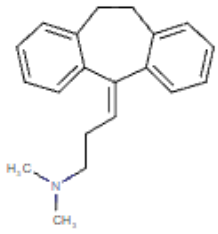

**Figure 1.** Structure of amitriptyline

## Pharmacologic properties

Amitriptyline (a tricyclic antidepressant) has anticholinergic and sedative properties. This medicine shown a good to moderate response in up to 2/3 of patients diagnostic with post-herpetic neuralgia and 3/4 of patients diagnosed with diabetic neuropathic pain, and a neurogenic pain syndrome that is often unresponsive to analgesics narcotics; patients with chronic non-malignant pain and some research showing efficacy in managing fibromyalgia (off-label use).[1]

Amitriptyline has strong anticholinergic properties. Amitriptyline can block ion channels, which are required for cardiac repolarization (hERG channels). Therefore, amitriptyline can increase the risk of cardiac arrhythmias, orthostatic hypotension and tachycardia. This drug can increase blood glucose levels.[3]

The volume of distribution (Vd) estimated after intravenous administration is 1221 L±280 L; range 769-1702 L (16±3 L/kg). It is found widely distributed throughout the body.[3] amitriptyline and the main metabolite *nortriptyline* pass across the placental barrier and small amounts are present in breast milk. This medicine has protein binding 95% in plasma and tissues. Amitriptyline is absorbed after oral administration completely. T max are usually reached within 4-8 hours. Amitriptyline undergoes hepatic presystemic elimination, and its systemic bioavailability ranges from 33%-62% after oral administration.[4] Amitriptyline is widely distributed throughout the body and this medicine bound to tissue and plasma proteins.[5] The plasma half-life ranges from 10-28 hours for amitriptyline and from 16-80 hours for its active metabolite, nortriptyline.[6,7]

Metabolism of amitriptyline are demethylation (CYP2C19, CYP3A4) and hydroxylation (CYP2D6). This step was followed by conjugation with glucuronic acid. CYP1A2 and CYP2C9 are minor involved in amitriptyline metabolism.[2]

Half-life (t1⁄2 ) amitriptyline is about 25 hours (24.65 ± 6.31 hours; range 16.49-40.36 hours) after po. administration; clearance (Cls) of amitriptyline is 39.24 ± 10.18 L/h (range: 24.53-53.73 L/h).[3]

The metabolism pathway can be seen in the figure 2.[2]

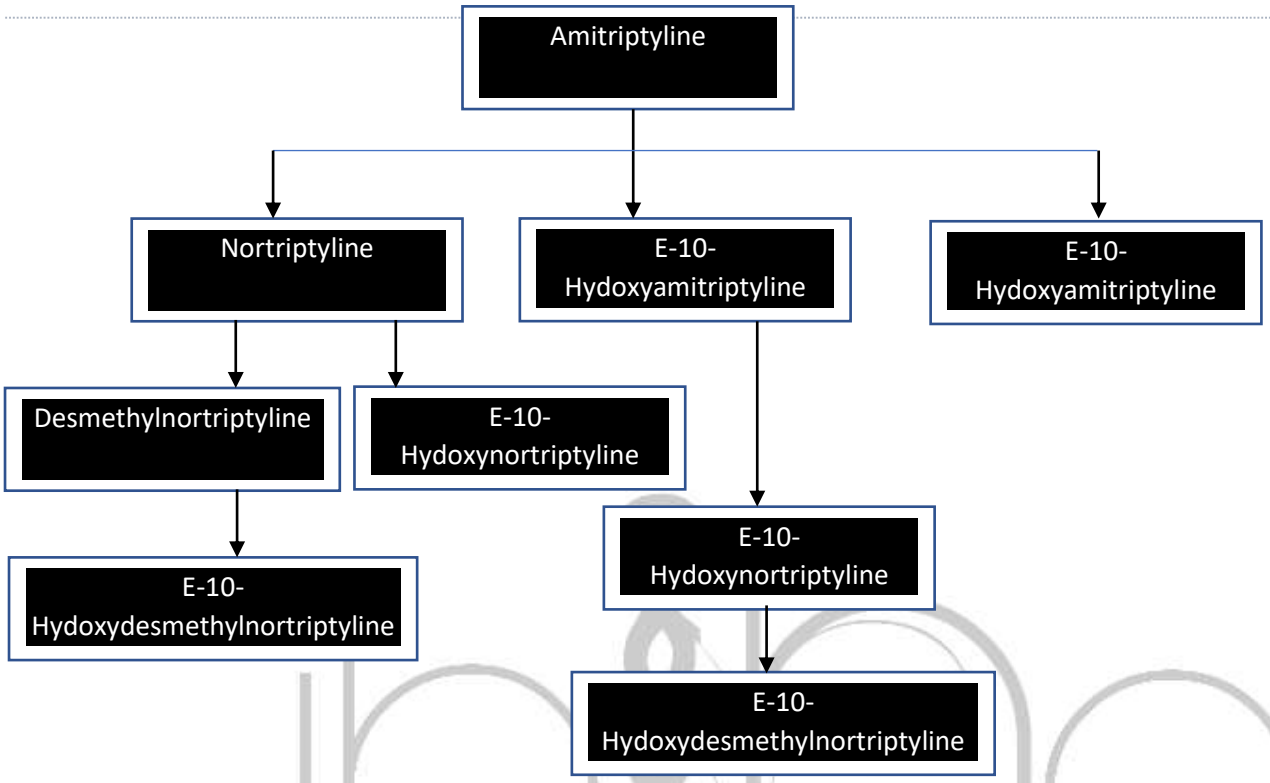


Figure 2. The metabolism pathway of amitriptyline (modification).[2]

**Mechanism of action**

The mechanism of action of this drug is not fully clear. The suspected mechanism of this medicine among others: block the reuptake of both serotonin and norepinephrine neurotransmitters; bind to alpha-adrenergic, histamine (H1), and muscarinic (M1) receptors;[8] increase noradrenergic or serotonergic neurotransmission by blocking the norepinephrine or serotonin transporter (NET or SERT) at presynaptic terminals.[9]

**Impact polymorphism on metabolism amitriptyline.**

The polymorphism of CYP2D6, CYP2C19 and Multidrug resistance protein 1 (ABCB1) impact metabolism and adverse effect of amitriptyline. The impact of this polymorphism can be seen in table 1

Table 1. Impact polymorphism CYP2D6, CYP2C19 and Multidrug resistance protein 1 (ABCB1) on metabolism of Amitriptyline

| Gene | Defining Change | Allele Name | Genotype(s) | Effect | Ref. |
|---|---|---|---|---|---|
| CYP2D6 | 1707delT rs5030655 | CYP2D6*6 | NA | poor metabolism of amitriptyline. | 10 |
| | Whole-gene deletion | CYP2D6*5 | Not Available | poor metabolism of amitriptyline | 10 |
| | 2549delA (rs35742686) | CYP2D6*3 | NA | poor metabolism of amitriptyline. | 10 |
| | A Allele (rs3892097) | CYP2D6*4 | (A;A) | reduced metabolism of amitriptyline | 10,11 |
| | 2935A>Crs5030867 | CYP2D6*7 | NA | poor metabolism of amitriptyline | 10 |
| | 1758G>Trs5030865 | CYP2D6*8 | NA | poor metabolism of amitriptyline | 10 |
| | 883G>Crs5030863 | CYP2D6*11 | NA | poor metabolism of amitriptyline | 10 |
| | 124G>Ars5030862 | CYP2D6*12 | NA | poor metabolism of amitriptyline | 10 |
| CYP2D6 | CYP2D7/2D6 hybrid gene structure | CYP2D6*13 | NA | poor metabolism of amitriptyline | 10 |
| | 1758G>Ars5030865 | CYP2D6*14A | NA | poor metaboli | 10 |

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|---|---|---|---|---|---|
| | | | | sm of amitriptyline | |
| | 137insT, 137_138insT | CYP2D6*15 | NA | poor metabolism of amitriptyline | 10 |
| | 2539_2542delAACT | CYP2D6*19 | NA | poor metabolism of amitriptyline | 10 |
| | 1973_1974insGrs72549354 2587_2590delGACTrs72549351 | CYP2D6*20 | NA | poor metabolism of amitriptyline | 10 |
| | 1770G>A; 1584C>G; 1235A>G; 740C>T; 678G>A; 310G>T; 746C>G; 843T>G; 1661G>C; 2850C>T; 3384A>C; 3584G>A; 3790C>T; 4042G>A; 4180G>C; 4481G>A; CYP2D7 gene conversion in intron 1 | CYP2D6*31 | NA | poor metabolism of amitriptyline | 10 |
| | 2587_2590delGACT | CYP2D6*38 | NA | poor metabolism of amitriptyline | 10 |
| | 1863_1864ins(TTT CGC CCC)2rs72549356 | CYP2D6*40 | NA | poor metabolism of amitriptyline | 10 |
| | 3259_3260insGT rs72549346 | CYP2D6*42 | NA | poor metabolism of amitriptyline | 10 |
| | 2950G>C | CYP2D6*44 | NA | poor metabolism of amitriptyline | 10 |
| | 100C>T; 1426C>T; 1235A>G; 1000G>A; 73C<T; 1039C>T; 1661G>C; 4180G>C | CYP2D6*47 | NA | poor metabolism of amitriptyline | 10 |
| | 1584C>G; 1235A>G; 740C>T; 678G>A; 1661G>C; 2850C>T; 3172A>C; 4180G>C; CYP2D7 gene conversion in intron 1 | CYP2D6*51 | NA | poor metabolism of amitriptyline | 10 |
| CYP2D6 | 3201C>Trs72549347 | CYP2D6*56 | NA | poor metabolism of amitriptyline | 10 |
| | 100C>T; 310G>T; 843T>G; 887C>T; | CYP2D6*57 | NA | poor | 10 |

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|---|---|---|---|---|---|
| | 1039C>T; 1661G>C; 3384A>C; 3582A>G; 4180G>C; gene conversion to CYP2D7 in exon 9 | | | metabolism of amitriptyline | |
| | 4044C>T | CYP2D6*62 | NA | poor metabolism of amitriptyline | 10 |
| | 1426C>T; 1235A>G; 1000G>A; 100C>T; 310G>T; CYP2D7 sequence from intron 1 onwards | CYP2D6*68A | NA | poor metabolism of amitriptyline | 10 |
| | 1995delC | CYP2D6*92 | NA | poor metabolism of amitriptyline | 10 |
| | 1426C>T;1235A>G;-1109C>T;1000G>A;100C>T;310G>T;843T>G;1039C>T;1661G>C;2097A>G;2828delC;3384A>C;3582A>G;4180G>C;4401C>T | CYP2D6*100 | NA | poor metabolism of amitriptyline | 10 |
| | 1426C>T; 1235A>G; 1000G>A; 1000G>A; 100C>T; 310G>T; 1661G>C; 2097A>G; 843T>G ; 1039C>T ;2927_2945delGATCCTACATCCGGATGTG | CYP2D6*101 | NA | poor metabolism of amitriptyline | 10 |
| CYP2C19 | G > A (rs4244285) | CYP2C19*2 | A;A) / (A;G | reduced metabolism of amitriptyline | 10 |
| | 636G>A (rs4986893) | CYP2C19*3 | NA | poor metabolism of amitriptyline | 10 |
| | 1297C>T rs56337013 | CYP2C19*5 | NA | poor metabolism of amitriptyline | 10 |
| | 395G>A rs72552267 | CYP2C19*6 | NA | poor metabolism of amitriptyline | 10 |
| | 19294T>A rs72558186 | CYP2C19*7 | NA | poor metabolism of amitriptyline | 10 |
| | 557G>C rs140278421; 991A>G | CYP2C19*22 | NA | poor metabolism of amitriptyline | 10 |

| | | | | | |
|---|---|---|---|---|---|
| | 99C>T rs17885098; 991A>Grs3758581; 1004G>Ars118203757; 1197A>G | CYP2C19*24 | NA | poor metabolism of amitriptyline | 10 |
| | 12662A>G rs12769205 | CYP2C19*35 | NA | poor metabolism of amitriptyline | 10 |
| Multidrug resistance protein 1 (ABCB1) | T > C (rs2032583) | - | (C;C) / (C;T) | increased risk of adverse events with amitriptyline | 12 |
| Multidrug resistance protein 1 Gene symbol: ABCB1 | C Allele (rs2032583) | - | (C;C) / (C;T) | increased likelihood of remission when using amitriptyline to treat major depressive disorder | 13 |

**Discussion**

Amitriptyline is metabolized primarily via the CYP2C19 and CYP2D6 pathways. Metabolism of this medicine is catalyzed by CYP2D6 resulting in the formation of the less active 10-hydroxy metabolites, whereas metabolism by CYP2C19 results in active metabolites, including nortriptyline. Individuals with CYP2D6 ultrarapid metabolizers have more than two alleles of normal function, meanwhile CYP2C19 ultrarapid metabolizers carry two alleles of increased function. Individuals whose CYP2D6 or CYP2C19 poor metabolizers carry two nonfunctional alleles for CYP2D6 or CYP2C19, respectively.[14]

Poor metabolism of amitriptyline (CYP2D6*3; CYP2D6*4; CYP2D6*5; CYP2D6*6; CYP2D6*7; CYP2D6*8; CYP2D6*11; CYP2D6*12; CYP2D6*13; CYP2D6*14A; CYP2D6*15; CYP2D6*19; CYP2D6*20; CYP2D6*31; CYP2D6*38; CYP2D6*40; CYP2D6*42; CYP2D6*44; CYP2D6*47; CYP2D6*51; CYP2D6*56; CYP2D6*57; CYP2D6*62; CYP2D6*68A; CYP2D6*92; CYP2D6*100; CYP2D6*101) that caused by Non-functional CYP2D6 result high level of amitriptyline in plasma.

CYP2C19*2; CYP2C19*3; CYP2C19*5; CYP2C19*6; CYP2C19*7; CYP2C19*22; CYP2C19*24 and CYP2C19*35 are nonfunctional CYP2C19. These genes reduce metabolism of amitriptyline resulting high level amitriptyline and low blood nortriptyline level.

Patients with multidrug resistance protein 1 (ABCB1) genotype (T > C (rs2032583) C;C)/(C;T) have high risk of

adverse events with amitriptyline.[12] The adverse effect of amitriptyline are orthostatic hypotension, dizziness, and sedation. It also can cause heart rate variability, slow intracardiac conduction, induce various arrhythmias, and cause QTc (corrected QT) prolongation (alpha-adrenergic receptor blockade) ; blurred vision, dry mouth, urinary retention, tachycardia, acute angle glaucoma, confusion, and delirium (anticholinergic effect );[15] increase the risk of bone fracture, bone marrow suppression (rare);[16] sedation, increased appetite, weight gain, confusion, and delirium;[17] abnormalities in liver function tests.[18]

**Conclusion**

Polymorphism of CYP2D6; CYP2C19 and MDR (ABCB1) change rate of metabolism of amitriptyline.

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