

Amitriptyline

Class: Antidepressant, Tricyclic (Tertiary Amine); Antimigraine Agent, Prophylaxis

Pharmacokinetics

Absorption

- i.) Non-genetic
 - a. Concomitant medications/substances: p-glycoprotein inhibitors
- ii.) Genetic
 - a. Genetic variation in p-glycoprotein gene

Distribution

- i.) Non-genetic
 - a. Altered serum or tissue protein (extensively bound to plasma and tissue protein)
 - b. Concomitant medications/substances: p-glycoprotein inhibitors or activators
- ii.) Genetic
 - a. Genetic variation in p-glycoprotein gene

Metabolism

- i.) Non-genetic
 - a. Concomitant medications: CYP1A2, CYP2C9, CYP2C19, **CYP2D6**, CYP3A4
 - b. inducers or inhibitors
 - c. Alcoholics demethylate less amitriptyline and hydroxylate and conjugate more (vs non-alcoholics)
 - d. Hepatic impairment: metabolism may be decreased
- ii.) Genetic
 - a. Genetic variation in drug metabolizing enzyme gene: CYP1A2, CYP2C9, CYP2C19, **CYP2D6**, CYP3A4

Excretion

- i.) Non-genetic
 - a. Renal impairment: clearance may be decreased
- ii.) Genetic
 - a. No clear genetic factors affecting excretion

Pharmacodynamics

Receptors

- i.) Non-genetic
 - a. Concomitant medications: serotonin or adrenergic receptor agonists/antagonists (may block or enhance effects of amitriptyline)
- ii.) Genetic
 - a. Genetic variation in alpha-1 adrenergic receptor gene
 - b. Genetic variation in cardiac potassium ion channel gene
 - c. Genetic variation in cardiac sodium channel gene
 - d. Genetic variation in G-protein beta-3 subunit gene
 - e. Genetic variation in Gs protein alpha subunit gene

Transporters

- i.) Non-genetic
 - a. Concomitant medications/substances:
 - i. Serotonin transporter or norepinephrine transporter inhibitors (additive effects)
 - ii. P-glycoprotein inhibitors or activators
- ii.) Genetic
 - a. Genetic variation in serotonin transporter
 - b. Genetic variation in norepinephrine transporter gene
 - c. Genetic variation in p-glycoprotein gene