

P76. MIRTAZAPINE: PHARMACOLOGY, INTER- AND INTRAINDIVIDUAL PHARMACOKINETIC VARIATIONS

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Mirtazapine is the first noradrenergic and specific serotonergic antidepressant. It is an antagonist of presynaptic alpha 2-adrenergic autoreceptors and heteroreceptors on both norepinephrine and serotonin (5-HT) presynaptic axons, plus is a potent antagonist of postsynaptic 5-HT₂ and 5-HT₃ receptors. The result is increased noradrenergic activity together with specific increased serotonergic activity, especially at 5-HT_{1A} receptors. This mechanism of action maintains equivalent antidepressant efficacy but minimizes many of the adverse effects. Mirtazapine is extensively metabolized in the liver to four metabolites via demethylation and hydroxylation, followed by glucuronide conjugation. Although mirtazapine is a substrate of P450 (CYP) isoenzymes 1A2, 2D6 and 3A4, in vitro studies show that it is not a potent inhibitor or inducer of any of these enzymes. Peak plasma concentration C_{max} is reached after about 2 hours. The absolute bioavailability at steady state is approximately 50%. Mirtazapine shows linear pharmacokinetics over a dose range of 15–75mg/d. Elimination half life of mirtazapine ranges from 20–40 h, and it is dependent on age and gender; females and the elderly show higher plasma concentrations than males and young adults. In a long term therapeutic drug monitoring study results show that, among patients with adverse events, lower desmethylmirtazapine concentrations were observed than in patients with no adverse events. Smoking patients' serum concentrations were lower than nonsmokers. Patients on multiple drug treatment had higher dose-corrected mirtazapine and demethylmirtazapine serum concentrations than patients taking only mirtazapine. Large inter-individual variations in plasma mirtazapine and desmethylmirtazapine concentrations have been observed in major depression patients receiving mirtazapine.