21 - B. SSRIs

B. SSRIs

 The SSRIs are rapidly absorbed. Sertraline availability may be increased by the presence of food. Most are highly protein bound except escitalopram which is 56% bound. Fluoxetine is metabolized to norfluoxetine, which has similar activity on 5-HT reuptake as fluoxetine. The half-life of norfluoxetine is 4–16 days while t1/2 of fluoxetine itself is 4–6 days. Similarly, sertraline metabolite has longer half-life but unlike norfluoxetine it is not a potent reuptake inhibitor. Desmethylcitalopram is a potent noradrenaline uptake inhibitor but not produced sufficiently and weakly crosses the blood–brain barrier. Fluvoxamine and paroxetine do not have active metabolites. Both fluoxetine and paroxetine are capable of inhibiting their own clearance at clinically relevant doses. As such, they have nonlinear pharmacokinetics: changes in dose can produce proportionately large plasma levels. The half-life is not related to time to onset of action, but it is relevant for discontinuation reactions. Fluvoxamine Sertraline Escitalopram Citalopram Fluoxetine Paroxetine Lower end: Greatest nonlinearity of kinetics Unpredictable side effects

  Selectivity: Citalopram is the most selective (and escitalopram) while paroxetine is the most potent. Fluoxetine weakly inhibits noradrenaline reuptake and binds to 5-HT2C receptors; sertraline weakly inhibits noradrenaline and dopamine reuptake. Paroxetine has significant anticholinergic activity at higher dosages and binds to nitric oxide synthase. Fluoxetine & olanzapine when taken together increase brain concentrations of noradrenaline. Dosing: Apart from depression and GAD, panic disorder, OCD, OCD spectrum disorders and bulimia respond to SSRIs. OCD may need a higher dose for several months for the effects to become evident. Fluoxetine treatment of bulimia is best given together with psychotherapy. Again higher dosages are required. SSRIs are useful in premenstrual dysphoria (PMDD) where sertraline or paroxetine used either daily or only during luteal phase produces a positive effect. Intermittent dosing is usually as effective as continuous administration. Beneficial effects are seen very quickly in one to two days, but proof of efficacy is lacking. Fluvoxamine reduces the clearance of both diazepam and its active metabolite, Ndesmethyldiazepam, there is a strong likelihood of substantial accumulation of both. Accordingly, diazepam and fluvoxamine should not ordinarily be co-administered. Citalopram is metabolized by CYP2C19 initially and then by CYP2D6. CYP3A3 and CYP3A4 are responsible for demethylation of sertraline. Drug CYP450 Profile Interacting psychotropic drug Effect Clinical notes Fluoxetine Inhibits 2C19, 2D6. Partially metabolized by 2D6.

All TCAs especially Clomipramine Imipramine (both 2C19 & 2D6), Citalopram, Sertraline, Moclobemide, Duloxetine, Mirtazapine Venlafaxine. Levels of these drugs increase in plasma.

Potential TCA toxicity. Associated with therapeutic benefit? Effect may last up to 2 weeks after stopping fluoxetine. Paroxetine Predominantly metabolized by 2D6. Inhibits 2D6 All TCAs Citalopram, Fluoxetine, Fluvoxamine, Duloxetine, Mirtazapine, Venlafaxine. Levels of these drugs increase in plasma. Potential TCA toxicity, may be associated with therapeutic benefit when combined. May have non-competitive inhibition resulting in unpredictable effect in combinations.

© SPMM Course The autoinhibition of CYP2D6 is responsible for nonlinear pharmacokinetics of paroxetine and at least partially for the nonlinear pharmacokinetics of fluoxetine. Fluvoxamine reduces the clearance of theophylline approximately 3-fold via CYP1A2 inhibition. Therefore, if theophylline is co-administered with fluvoxamine, its dose should be reduced to one-third of the usual daily maintenance dose and plasma concentrations of theophylline should be monitored. No dosage adjustment is required for fluvoxamine. When fluvoxamine is administered with warfarin, warfarin plasma concentrations increases by 98% and prothrombin times are prolonged. Hence, anticoagulant dose must be adjusted accordingly. Fluvoxamine Inhibits 1A2, 2C19, 3A4 Clomipramine, Doxepine, Trimipramine Duloxetine, Mirtazapine Citalopram, Escitalopram, Sertraline Trazodone. Levels of these drugs increase in plasma. Potential TCA toxicity. Duloxetine

Inhibits 2D6, similar to SSRIs. All TCAs Citalopram, Fluoxetine, Paroxetine, Fluvoxamine, Mirtazapine, Venlafaxine. Levels of these drugs increase in plasma. Potential TCA toxicity especially at higher dose - may not be clinically meaningful at lower doses. Desipramine, Clomipramine Inhibits 2D6 All TCAs Citalopram, Fluoxetine Fluvoxamine, Duloxetine, Mirtazapine Venlafaxine. Can increase levels of these drugs Potential serotonin toxicity. SSRI Plasma elimination half-life Linearity of pharmacokinetics

Single dose Multiple dose [active metabolite]

Paroxetine 10h. 21h. Nonlinear Fluvoxamine 11h. 14h. Nonlinear Sertraline 26h. 26h. [36h.] Linear Citalopram 33h. 33h. Linear Fluoxetine 1.9 days 5.6 days [7-15 days] Nonlinear

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