Introduction:

TDM of psychotropic drugs has clinical utility for the following reasons:

- Excessively high drug levels may be associated with clinical deterioration of the patient because of drug toxicity.
- Plasma level monitoring may help assure compliance and may reduce medication defaulting because of ADR.
- Blood levels clearly correlate with therapeutic response for a minority of the psychotropic drugs, including the antipsychotics haloperidol, clozapine, olanzapine.

1. Selective Serotonin reuptake inhibitor antidepressants:

Fluoxetine: oral

- Depression: Adult 20-40 mg daily. Max: 80 mg daily
- Obsessive compulsive disorder
  Adult: Initially 20 mg daily increased up to 60 mg daily Max: 80 mg daily.
- Panic disorder: Adult initial dose 10 mg daily, may increase to 20 mg daily after a wk. May ↑ dose to 60 mg daily after a wk if needed.

Metabolism:

- It exhibits nonlinear pharmacokinetics.
- A period of 6-7 weeks may be required before steady-state serum concentrations are reached due to long half-life and the same period of time is required to wash out the drug in non-responding patients.
- Pharmacokinetics parameters of fluoxetine are not altered in patients with decreased renal function.
- The rate of elimination of fluoxetine is decreased in point with alcohol induced cirrhosis.

Therapeutic levels:

- Therapeutic levels have not been established.
- There may be a negative correlation bit nor-fluoxetine concentration and therapeutic response.

• Patient with high ratios of fluoxetine to norfluoxetine are more likely to respond than point with low ratios.

□ Selective serotonin reuptake inhibitors:

• Are used as antidepressants in the treatment of depression, anxiety disorders and some personality disorders, they are also typically effective and used in treating some cases of insomnia.

• SSRIS are believed to increase the extracellular levels of the neurotransmitter serotonin by inhibiting its reuptake into the presynaptic cell, increasing the level of serotonin.

□ Drug interaction:

• One major contraindication of SSRIS is the concomitant use of MAOIS. This is likely to

cause severe serotonin syndrome.

- With opoid analgesic tramadol hydrochloride can, in rare cases produce seizures.
- SSRVs may increase in blood levels and risk of toxicites of certain medication.
- Waratin and digoxin.

Pharmacokinetic parameters	Flouxetine exhibits non linear pharmacokinetics.
Absorption	Well absorb through the gut
Distribution	Bound to albumin and alpha 1 glycoprotein
Metabolism	Hepatic metabolism (N-demethylation and glucuronide)
Elimination	Urinary excretion, only 12% can see in feces. Elimination half-life: for chronic admin is 4-6 days and for acute admin is 1-3 days a mean elimination half-life is 3.6 days

Need for TDM:

- A clear relationship between clinical efficacy and plasma concentration has not

been found.

- Toxic concentration is not well defined.
- Therapeutic failure or toxic events are experienced at clinically relevant dosages.

□ Specimen collection and method of analysis:

- Several analytical methods have been described for all SSRIs. Most assays are based on separation by high-performance liquid chromatography or gas chromatography.
- Specimen: Plasma or urine

Antidepressants

Tricyclic antidepressants

Absorption:

- TCAs, are rapidly and completely absorbed from the small intestine following oral administration.

• Peak blood concentration are usually reached within 2 to 8 hrs.

• Food in the stomach does not delay absorption.

□ Distribution:

TCAs are highly lipophilic agent that distribute widely throughout the body.

• TCAs concentrate to the greatest extent in myocardial and cerebral tissues with <1% of the drug present in the plasma.

• TCAs are extensively but reversibly bound to α_1-acid glycoproteins (α-A6).

Antidepressant pharmacokinetic parameters:

Drug	Oral bioavailability	Plasma protein binding (%)	Clearance (ml/mg/kg)	Vol of D(L/Kg)	t½ (hr)
Anitriptyline	48±11	94.8	11.5±3.4	15±3	21±5
Moxapine	46-82	-	-	-	8.8-14
Bupropion	>90	84±2	35±9	7.2±1.6	12±4
Fluoxetine	>60	94	9.6±6.9	35±21	53±4
Inipraomme	39±7	90.1±1.4	15±4	18±3	12±5

Metabolisms:

- TCAs are metabolized primarily by the liver
- Dimethylated TCAs, imipramine, amitriptyline, doxepin are demethylated to monomethylated tricyclics by CYP 450 3A4, which are active metabolites.
- When interpreting a TCA plasma level for a dimethylated TCA, both the dimethylated and monomethylated metabolities are measured and their values summed to estimate the concentration of active drug.

Eg: for amitriptyline, the total plasma concentration equals amitriptyline and nortriptyline.

- No dose alterations are necessary in patients with decreased renal function.

□ Elimination:

Clomipramine: Depression: Adult: initially, 10 mg daily, may increase gradually to 30-150 mg daily

OCD, panic disorder: initially, 25 mg daily, gradually increased to 100-150 mg daily

- The elimination half-life to TCAs can vary from 6-198h.
- With the exception of protriptyline, the half-lives are approximately 24hr for the monomethylated TCAs allowing for single daily dosing, usually at bedtime.

Sampling:

- Sampling should be carried out approximately 12 hr after the last dose so that plasma concentration are estimated during the TCA elimination phase.

Therapeutic levels:

- A meta-analysis of the TCA blood level literature using ROC curves as the primary statistical tool determined. The recommended therapeutic thresholds or ranges for four TCAs: nortriptyline, desipramine, amitriptyline & imipramine

TCA response rates in and out of the suggested therapeutic concentrations:

Drug	Therapeutic range (ng/ml)	Response rate (in Vs out)
Nortriptyline	58-148	66% Vs 26%
Desipramine	>116	51% Vs 15%
Imipramine	175-350	67% Vs 39%
Amitriptyline	93-140	50% Vs 30%

□ Sample timing:(TCA)

- While the half-lives of amitriptyline and nortriptyline range from 9 to 56 hrs with a steady state attained within 4-11 days in most patients, the half lives of imipramine and desipramine range from 6-28 hrs with a steady state attained in 6 days. As a general rule, the clinician should wait at least a week before drain any blood samples for serum concentration monitors.
- Peak serum concentration within the dosing interval following oral administration of the TCAs occur b/w 2-8 hours.
- A standardized sampling is commonly used 12 to 14 hours after the bed time.
- If the TCA happens to be given in divided doses 4 to 5 hr post dose sample time is recommended.

- To minimize the chance of hemolysis, serum should be separated from the red blood cells within 1 hr of collection.
- Lithium in serum or plasma is stable at room temperature or refrigeration temperature for extended periods of time.
- Lithium erythrocyte concentration has been proposed to correlate better with response and toxicity since it represents intracellular lithium
- Saliva concentration of lithium have been proposed as noninvasive substitutes for serum or plasma lithium concentration.
- Flame emission photometry and atomic absorption spectroscopy are still the most commonly used methods for lithium quantization, accuracy and low interferences.
- Ion-Selective Electrode (ISE) methods are more rapid and less costly but may have problems with interference.