Depression

In the early part of the past century, depression was thought to be a long term illness, which required life long treatment **(Gerald et al.,1984).**

According to **Kraeplin et al., (1921)** the father of modern descriptive psychiatry, the duration of melancholia generally extends over a large number of months and even years. Most recovered cases lasted about 9 months to 1 year; however, almost one third of them lasted over a year.

During the 1960s and 1970s came the psychopharmacologic revolution, in which medications for depression caused dramatic improvement of symptoms in a matter of weeks. Concomitant with the pharmacotherapeutic advances came new psychotherapeutic strategies. These contrasted with traditional approaches, which were long term and intensive **(Beck et al., 1979).**

The newer psychotherapies were highly focused, short term, time limited, and highly interactive. Examples include cognitive behavioral therapy, developed by **Beck et al., (1979)** and interpersonal therapy, developed by **Gerald et al., (1984).** These psychopharmacologic and psychotherapeutic contributions gave rise to the notion that depression should be considered similar to a bacterial pharyngitis, where an appropriate, short term treatment "cures" the illness. But, depression proved to be inaccurate when studied carefully, and the evidence turned out to support the **Kraeplin et al., (1921)** notions of a long term disorder that was harder to manage.

Epidemiology and clinical course of depression:

House to house surveys of general population in the United States and Europe have demonstrated that depression is a very prevalent disorder. In the United States, one in ten people will suffer from an episode of major depressive disorder over the course of 1 year **(Kessler et al., 1994).**

A study of six countries in Europe reported a prevalence of major depressive disorder of nearly 7% over a 6 month period and70% of the population of these six countries will suffer from major or minor depression or depressive symptoms over a 6 month period. Depression occurs twice as frequently among women as among men **(Lepine et al., 1997).**

Recurrence and chronicity mark the clinical course of depression. Although the majority of patients treated for depression will recover from their presenting episodes, they are likely to experience further episodes over time **(Keller et al., 1992).**

Acute, continuation, and maintenance treatment:

Treatment of depression may be divided into three phases, acute, continuation, and maintenance **(Kupfer. 1991).**

Acute treatment:

The efficacy of pharmacotherapy for the acute treatment of depression is well established. The acute phase includes the stablization of the acute symptoms, which can generally be accomlished in 3 months or less **(Mac Gillivary et al., 2003).**

Tianeptine appears to be an effective antidepressant agent in patients with major depression without melancholia or psychotic features, or dysthymic disorder (n= 1858) **(Guelfi et al., 1990)** and in patients with endogenous depression (n=17) **(Bourgeoies et al., 1991)** significant improvement was observed after 14 days in patients with major depression and dysthymic disorder and after 7 days in patients with endogenous depression.

In a European multicenter double blind randomized study, the efficacy of tianeptine 25 to 50 mg/ day was greater than that of placebo and similar to that of imipramine 100 to 200 mg/ day in 186 in patients with moderate to sever major depression or depressed bipolar disorder **(Staner et al., 1994).**

Guelfi et al., (1992) overviewed the results of 5 double blind studies including a trial by **Bersani et al., (1989)** in which tianeptine 12.5mg 2 to 4 times daily was compared with amitriptyline 25mg 3 times daily (submaximal dosage). Imipramine 25mg 3 times daily (submaximal dosage). These agents were administrated for 30 to 56 days to a total of 781 outpatients with dythmic disorder, bipolar disorder or major depression without melancholia and psychotic features, with or without melancholia and psychotic features, with or without anxiety or alcoholism. The overall antidepressant efficacy of tianeptine as assessed by the Hamilton disorder rating scale (HDRS), Montgomery-Asberg depression rating scale (MADRS) or Hopkin's symptom checklist (HSCL) scales was similar to that of the other antidepressant agents.

The antidepressant efficacy of tianeptine in outpatients with major depression or dythymia and somatic complaints was similar to that of fluoxetine. The Hamilton anxiety rating scale (HARD) score was reduced by 62% with tianeptine and by 63% with fluoxetine; this reduction occurred after 15 days with both treatments **(Alby et al., 1993).**

Continuation therapy:

The purpose of continuation treatment is to prevent a recurrence of symptoms following withdrawal of medication too quickly after acute stablization of symptoms (i.e. a relapse) **(Mac Gillivary et al., 2003).**

Relapse is defined as the early reappearance of original symptoms, and recurrence is defined as a new episode of depression in a patient who shown evidence of a stable recovery. Following antidepressant withdrawal, up to 65% of patients with a satisfactory response my have another depressive episode within 1 year **(Bjork, 1983).**

Loo et al., (1991) had specifically addressed the effects of tianeptine on relapse and recurrence of depression. In this multicenter trial, 783 patients with major depression or dysthymic disorder without melancholia or psychotic features who initially responded to tianeptine therapy (25 to 50 mg/day for up 1 year); concomitant hypnotics and anxiolytics, were allowed as were low dosage of neuroleptics for sedation. 22% of patients withdrew beacause of relapse during the first 6 months. 7% of patients withdrew because of recurrence at 12 months. In patients who received tianeptine alone, relapse occurred in 4.7% and recurrence was not seen. Relapse and recurrence rates were lower in patients with a single episode of major depression (6.7 and 2.9% respectively) or dysthymic disorder (17.8 and 9.4 respectively). However,

the results of this trial are limited by its nonblind and noncomparative study design.

There are no trials directly comparing relapse or recurrence rates with tianeptine and those of other antidepressant agents. Relapse rates of 22 and 28% with amitriptyline **(Stein et al., 1980)** at 6 months and recurrence rates of 26% with fluoxetine at 12 months (Montgomery et al., 1988) and 9% with imipramine at 2 years **(Kupfer et al., 1992)** have been reported.

Thus, progressive therapeutic improvements are observed with long term (1 year) tianeptine therapy, supporting the continued use of tianeptine therapy after resolution of the depressive episode. Furthermore, long term tianeptine treatment may reduced the incidence of relapse and recurrence of depression.

Maintenance therapy:

The rational behind long term antidepressant therapy is to maintain or further increase therapeutic improvements, and to prevent relapse and recurrence of depressive symptoms **(Loo et al., 1992).**

Several non comparative trials assessing the efficacy of tianeotine 25 to 50 mg/ day over 1 year periods in patients with major depression without melancholia or psychotic features or dysthymic disorder. Results from the largest (380 valuable patients) most recent multicentre trial showed significant improvements in Globel Impression (CGI), Montgomery Asberg depression rating scale (MADRS), Hamilton anxiety ratingscale (HARS) and Hopkin' s symptom checklist (HSCL) were seen after 14 days. Thereafter,progressive improvements in all measures of

efficacy over the 1 year treatment period were observed **(Loo et al., 1992).**

Sarteschi et al., (1993), have also reported progressive improvements in depression scale scores over a 1 year period in patients with dysthymic disorder or major depression without psychotic features who received tianeptine 37.5 mg/ day (n=111).

In general, maintenance therapy should be continued for several years, and indefinitely in patients who have had multiple or more sever episodes in the past. Psychotherapy plays a critical function in the lond term treatment of depression **(Buhl et al., 2003).**

Patients with depression, especially long standing recurrent depression, often have serious marital, familial, social, and occupational problems that have been exacerbated by their illness. In addition, psychotherapy may help to improve compliance, which helps to prevent relapse **(Thase and Ninan, 2002).**

Individuals at risk for recurrence include those who have had 3 or more episodes of major depression in the past, those who were older at onset od depression (i.e., over 60 years of age), those who have had more sever episodes of depression, and those with family history of mood disorder. Patients who had incomplete recovery between episodes are also likely candidates for recurrence **(Thase and Ninan, 2002).**

Antidepressant drugs:

Up to 70% of people with depression respond to antidepressant drugs. These medications appear to work by altering the levels of

serotoinin, norepinephrine and other neurotransmitters in the brain. To avoid relapse, people usually must continue taking the medication for several months after their symptoms improve **(Yonkers et al., 2003).**

Antidepressant drugs fall into nine classes:

1-Monoamine oxidase inhibitors (MAOIs):

MAOIs work by inhibiting the enzyme (monoamine oxidase) that breaks serotonin, norepinephrine and dopamine in the synaptic cleft. Thus they increase the levels of all three neurotransmitters without working at any specific receptors. The original MAOIs were irreversible inhibitors of both A and B enzyme sub- types; these include:

- phenelzine
- tranylcypromine
- isocarboxazid.

The newer MAOIs are reversible and selective for either A (e.g moclobemide), or B (e.g deprenyl). Moclobemide is an effective antidepressant. Deprenyl is most useful in neurodegenrative diseases such as Parkinson's or Alzheimer's disease **(Knoll, 1989).**

2-Tricyclic antidepressants (TCAs):

TCAs work by bloking the reuptake pumps for both serotonin and noreoinephrine and to a lesser extent, dopamine. Some tricyclics are more potent SSRIs (e.g. clomipramine) and others are more potent norepinephrine reuptake inhibitors (NRIs) (e.g desipramine, maprotiline, nortriptyline) but most block both . in addition, TCAs act at several other types of receptors, including histamine-1, muscarinic cholinergic, and alpha-1 adrenergic receptors, as well as at sodium channels in the heart and brain. These actions are largely responsible for unwanted side effects such as orthostatic hypotension, and dizziness (alpha-1); confusion, blurred vision and dry mouth (M1); weight gain and sedation (H1); and cardiac arrhythmia and seizures in over dose (sodium channels). The

adrenergic and cholinergic blockade may also responsible for symptoms of sexual dysfunction.

3-Selective serotonin reuptake inhibitors (SSRIs):

SSRIs are more potent and more selective inhibitors of serotonin reuptake than most of the TCAs. They act by increasing the levels of serotonin both in the synaptic cleft and around the somatodendritic 5HT2A receptors of the cell body itself. This increase in serotonin results in down regulation and desensitization of both pre synaptic and post synaptic 5HT receptors of all sub- types through altered gene expression **(Stahl, 2000).** SSRIs include:

- fluoxetine (prozac) . Is an agonist at the 5HT2C receptor and a mild NRI.
- Paroxetin (paxil) has anticholinergic properties, is a mild NRI and as an inhibitor of nitric oxide synthase.
- Sertraline (zoloft) is a mild dopamine reuptake inhibitor (DRI).
- Citalopram (cipram) are relatively pure SRI.

These drugs generally produced fewer and milder side effects than done other types of antidepressants, although SSRIS may cause anxiety, insomnia, drowsiness, headaches and sexual dysfunction due to stimulation of 5HT2A receptors reduced dopamine activity in mesolimbic pleasure centers, which may reduce sexual desire. Serotonin also stimulates the secretion of prolactin often associated with sexual dysfunction **(Rosen et al., 1999).**

4-Serotonin and norepinephrine reuptake inhibitors (SNRIs):

venlafaxine is the only specific SNRI on the market and its frequent side effect of sexual dysfunction, nausea and vomiting **(PDR, 2001).**

5-Dual serotonin 2 antagonists/ serotonin reuptake inhibitors (SARI):

SARIs such as nefazodone and trazodone are powerful 5HT2A antagonists and to a lesser extent 5HT reuptake inhibitors. Nefazodone is

also a blocker of alpha –1 receptors, but this is probably offset by its mild inhibition of NE reuptake. Trazodone is also an alpha-1 and H1 blocker, which may account for its usefulness as a hypnotic. The combination of serotonin reuptake with antagonism at 5HT2A receptors leads to corresponding activation at 5HT1A receptors, and greater changes in gene expression than either action alone **(Stahl 2000).** This may account for its efficacy as an antidepressant.

6-Noradrenergic reuptake inhibitors (NRIs):

NRIs work by inhibiting the reuptake of norepinephrine in the synaptic cleft and indeed anywhere NE is released. There is only one NRI, reboxetine, on the market, although more NRIs are in clinical trials. They are thought to work as antidepressants by stimulating B-1 receptors in the frontal cortex. Side effects include tremor, agitation, hypertension, tachycardia and urine retention **(Stahl, 2000).**

7-Alpha- 2 adrenergic blocking pluse 5HT antagonism (also called noradrenergic and specific serotonergic antidepressant NaSSA) activity:

mirtazapine boots both serotonin and norepinephrine levels through antagonism of the alpha- 2 autoreceptor involved in the inhibition of both 5HT and NR release. In addition, mirtazapine is an antagonist at 5HT2A, 5HT2C, 5HT3 and H1 receptors.

8- Norepinephrine and dopamine reuptake inhibitors (NDRIs):

Include:

- bupropion.

It does have weak DRI properties and even weaker NRI actions, but it is the NRI activity of its metabolite that is most powerful which appears to be concentrated in the brain **(Stahl, 2000).**

9- Serotonin reuptake enhancers:

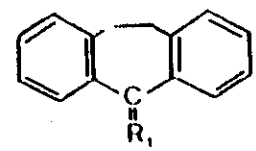
tianeptine is the only medication in this noval class of antidepressants. It acts counter intuitively by enhancing the reuptake of 5HT at the synapse. The mechanism of antidepressant efficacy is unclear, although one might hypothesise that tianeptine targets the pre- synaptic neuron by restoring depleted reserves of serotonin, but without activating post-synaptic $5HT_{2A}$ receptors responsible for sexual dysfunction. There are also some data to suggest that tianeptine enhances dopaminergic tone, but not through inhibition of dopamine reuptake **(Vaugeois et al., 1999).**

Amitriptyline

Chemical structure:

Amitriptyline is chemically described as:

3(10,11Dihydro5H_dibenzo(a,d)cycloheptен5ylidene)propyldimethylamine;10,11-dihydroN,Ndimethyl5H_dibenzo(a,b)cycloheptenepropylamine. Its emprical formula is C20 H23 N, and its molecular weight is 277.4. **(Enever et al., 1986)** (Fig. 1).



R_1:=$CH(CH_2)_2N(CH_3)_2$

Amitriptyline

Fig.(1): Chemical structure of amitriptyline **(Buckles and Walters ,1987)**

Pharmacokinetics properties:

Glassman and Perel, (1987) reported that amitriptyline is readily absorbed from the gastrointestinal tract, and peak plasma concentrations occuring within about 6 hours of oral administration. Amitriptyline slows gastrointestinal transit time so, absorption can be delayed, particularly in overdosage **(Baldessarini, 1984).**

Kutcher et al., (1986) found that amitriptyline is extensively demethylated in the liver to its primary active metabolite, nortriptyline. The metabolism of both amitriptyline and nortriptyline include hydroxylation (to active metabolite), N – oxidation, and conjugation with glucuronic acid **(Baldessarini, 1983).** Amitriptylin and nortriptyline are

widely distributed throughout the body and extensively bound to plasma and tissue protein **(Schulz et al., 1985).**

Simon, (2002) noted that amitriptyline has been estimated to have a half life ranging from 9 to 25 hours, which considerably extended in over dosage.

Amsterdam et al., (1980) demonstrated that amitriptyline is excreted in urine, mainly in the form of its metaholites, either free or in conjugated form .

Balder and Newman, (1980) added that amitriptyline and nortriptyline cross the placental barrier and excreted in milk.

Pharmacodynamic properties of TCAs:

Amitriptyline inhibit the uptake of 5HT and norepinephrine equally well, it is about 20 fold less potent than desipramine in blocking norepinephrine transport **(Hollister et al., 1987).**

Nieforth et al., (1989) found that the administration of therapeutic doses of amitriptyline to normal subjects produces sleepiness, a slight fall in blood pressure and anticholinergic effects **(Baldessarini, 1984).** Gait may become unsteady **(Amesterdam et al., 1980)** subjects feels tired and have difficulty in concentrating and thinking **(Hollister et al., 1987).**

Kupfer et al., (1981) reported that if the drug is given over a period of time to depressed patients, an elevation of mood occurs. About 2 to 3 weeks must pass before the therapeutic effects of the drug are

evident for this reason, the tricyclic antidepressants cannot be prescribed on An "as-needed " basis.

Baldessarini, (1984) found that all tricyclic antidepressants potientiate the actions of biogenic amines in the CNS by blockage of their major means of physiological inactivation reuptake at nerve terminals.

MaxWell, (1983) added that non of these agents is very effective as an inhibitor of dopamine transport. Blockage of dopamine transport seems to be associated with stimulant rather than antidepressant activity. While, inhibition of 5-HT uptake and inhibitory actions on the uptake of norepinephrine seems to be correspond with antidepressant activity.

Menkes et al., (1983) demonstrated that the administration of a tricyclic antidepressant produces an immediate reduction in the firing rate of neurons containing norepinephrine, with decrease in the turnover of the amines. These changes are thought to be a consequence of blockade of the uptake of monoamines by neurons, with a resultant increase in their action upon presynaptic alpha 2-adrenergic that serve to regulate the excitability of and transmitter release from monoaminergic neurons (**U' Prichard et al., 1987).**

Menkes et al., (1983) added that with continued treatment for 1 to 3 weeks, neuronal firing and monoamine turnover return to and even exceed pretreatment values, despite persistent blockade of uptake. These adaptive changes may involve in part a desensitization of presynaptic alpha2-adrenergic receptors.

DeMontigny and Aghajanian, (1987) demonstrated that repeated administration of tricyclic antidepressants increase neuronal sensitivity to 5-HT but reduce number of 5-HT receptors **(Peroutka and Synder, 1980).**

Prolonged administration of tricyclic antidepressants results in a sustained or even an increased neuronal responsiveness to alpha 1-adrenergic agonists, with increase potency of such agonists in inhibiting the binding of prazosin, a specific alpha 1 –adrenergic antagonist **(Menkes et al., 1983).**

Sulser and Mobley, (1980) added that TCAs reduces the number of B-adrenergic binding sites and responsiveness of brain tissue to B-adrenergic agonist.

Tricyclic antidepressants also act as antagonists at receptors for various neurohormones; these include moderate to high affinity at muscarinic cholinergic **(Yamamura, 1980),** alpha 1 –adrenergic **(U'Prichard et al., 1987),** and both H1 and H2- histaminergic receptors **(Richelson, 1997).**

Amitriptylin is one of the most potent of the group in blocking muscarinic cholinergic, H1- histaminergic, and alpha1- adrenergic receptors, while despramine is 10 to 100 fold less potent than amitriptyline **(Amesterdam et al., 1980).** These actions do not correlate with antidepressant potency, but they are related to side effects, such as confusion, sedation and postural hypotension **(Ray et al., 1987).**

Uses:

Nutt, (1997) noted that amitriptyline and other tricyclic antidepressants are used in the treatment of depression, particularly endogenous depression; they are less effective in reactive depression, associated anxiety may respond to the sedative action of tricyclices, but concomitant administration of anxiolytic, such as benzodiazepine may also be necessary.

Amitriptyline is usually given as hydrochloride, by mouth, in doses of 75 mg daily initially, gradually increased, to 150 mg daily,the additional doses being given in late afternoon or evening . Maintenance doses are usually 50 to 100 mg daily and therapy should be continued for at least several months before being gradually withdrawn **(Bech et al., 1993).**

Williamson et al., (1992) added that adolescent or elderly patients often have reduced tolerance to tricyclic antidepressants and amitriptyline hydrochloride 50 mg daily may be adequate, given either as divided doses or as single dose, preferably at night.

Amitriptyline is given also for the treatment of nocturnal enuresis in children aged 5 to 10 years, and 25 mg to 50 mg at bed time for children over 11 years of age **(Glazener and Evans, 2000).**

Amitriptylines alone or with fluphenazines have beneficial results in diabetic neuropathy **(Max, 1987).** Some cases of chronic pain, neuralgias, migraine, sleep apnea, fibromyalgia **(Reisner, 2003)** and irritable bowel syndrome may respond to an antidepressant agent **(Orsulake and Walter, 1989).**

Amitriptyline may be benefit in the treatment of patients with peptic ulcer **(Gobel et al., 1993).**It is not certain whether the blockage of muscarinic and H2 – Histaminergic receptors by these agents can account completely for these effects **(Sen et al., 2002).**

Drug Interactions:

The TCAs are involved in several clinically important drug interactions **(Anonymous et al., 1993).**

Katz, (1991) noted that antiarrythmic agents which prolong the QT interval may increase the likelihood of ventricular arrhythmias when given concomitant with TCAs. Reviewing interactions between tricyclic antidepressants and antipsychotics **Lott, (1985)** has commented that the interactions may be generally of two forms; additive pharmacological effects such as antimuscarinic effects and hypotension or secondly alteration of the pharmacokinetic properties of one drug by the other.

Miller et al., (1983) demonstrated that cimetidine is a known inhibitor of hepatic metabolism of drugs and symptoms of tricyclic toxicity have been reported in patients receiving cimetidine concurrently with desipramine and imipramine, and there has been a report of psychosis developing in patient given imipramine in addition to cimetidine treatment **(Miller et al., 1987).**

Combined antidepressant therapy utilizing tricyclic antidepressants and monoamine oxidase inhibitors should be used with extreme care **(Kline et al., 1982).** MAO inhibitors , by increasing stores of catecholamines , sensitize the patient to indirectly acting sympathomimetics such as tyramine, which is found in many fermented

foods and beverages,and to sympathomimitic drugs that may be administrated therapeutically , such as diethyl propion or phenyl propanolamine **(Kline et al., 1982).**

Bayce and Judd (1999) added that side effects may be enhanced by the concurrent administration of CNS depressants, including alcohol and antimuscarinic agents .

Pfister,(1987) reported that barbiturates and other enzyme inducers such as rifampicin and some antidepressants may result in lowered plasma concentrations and reduced antidepressant response.

Adverse reactions:

Bryant et al., (1987) found that side effects of amitriptyline and the other tricyclic antidepressants are caused by their marked anticholinergic actions. These include dry mouth, metallic taste, and constipation occasionally leading to paralytic ileus, urinary retention, blurred vision and changes in accommodation. Palpitation, tachycardia, and orthostatic hypotension were recognized early as unwanted effects of these drugs. Later, arrhythmias and electrocardiographic abnormalities were found. Congestive heart failure and sudden death are rare complication **(Veith et al., 1982).** These effects can in part be explained by the pharmacology of the TCAs which, inhibit the neuronal reuptake of noradrenaline and thus, facilitate sympathetic transmission, and their atropine –like action which increases the speed of diastolic depolarization of the sinoatrial node, hence the frequency of discharge, and it encourages ectopic impulse formation **(Slavicek et al., 1998).** Impaired conduction in the specialised conducting system of the ventricles is probably caused by a direct effect on the conducting cell membrane.

Lane and Routledge, (1983) demonstrated that, tremor is common, drowsiness, dizziness, weakness and fatigue, ataxia,epileptiform seizures, occasionally extrapyramidal symptoms and gastric irritation with nausea and vomiting may occur.

Weight gain is frequent with these drugs. It may be due in part to increased appetite with remission of depression action but may be due to central effect **(Kulkami and Kaur, 2001).**

Montogomery et al., (2002) reported that endocrinal effects associated with TCAs therapy include changes in libido, impotence, gynaecomastia and breast enlargement and galactorrhea. Also, changes in blood sugar concentration may occur and very rare, inappropriate secretion of antidiuretic hormone.

Kulkami and Kaur, (2001) demonstrated that symptoms of overdosage may include excitement and restlessness with marked antimuscarinic effects, sever symptoms include unconsciousness, acidosis, and respiratory and cardiac arrhythmias that may recure some days after apparent recovery. Cardiac toxicity and hypotension in such poisonings can be especially difficult to manage. The heart is usually hyperactive, with supraventricular tachycardia and a high cardiac output. The effects of the drugs on the Hiss purkinje conduction system are mainfest by a prolonged duration of the QRS complex. Cardiac glucosides and antiarrythmic drugs such as quinidine or procainamide are contraindicated, but phenytoin has been given safely and may simultaneously be useful to suppress the convulsive seizures that are often present **(Curtis et al., 2003).**

Baldessrini,(1984) added that B adrenergic antagonists and lidocaine have been recommended. Diazepam has been used to control seizures and myoclonic and dystonic features of tricyclic antidepressant poisoning.

Contraindications:

Amitriptyline and other tricyclic antidepressants should be used with caution in-patients with cardiovascular disease and should be avoided in the immediate recovery phase after myocardial infarction **(Glassman , 1989)**.

Tricyclic antidepressants should also be used with caution in patients with hyperthyroidism or with impaired liver function and in those with a history of epilepsy, glaucoma, urinary retention, prostatic hypertrophy, or constipation **(Baldessrini, 1984).**

Psychosis may be activated in schizophrenic patients and manic depressive patients may switch to a manic phase; patients with suicidal tendencies should be carefully supervised during treatment **(Peet , 1994).**

Elderly patients and children under 5 years of age are sensitive to the side effects of the tricyclic antidepressants reduced dosage should be used **(Williamson et al., 1992).**

Tianeptin

Tianeptine is a noval antidepressant agent, both structurally (Modified tricyclic) and in terms of its Pharmacodynamic Profile **(Mennini et al., 1987).**

Chemical structure:

Tianeptine is chemically described as:

7 ((3- chloro- 6, 11- dihrdro- 6- methyldibenzo(c,f)(1,2) thiazepin-11-yl) amino)heptanoic acid S,s-dioxide. C21H25clN2O4S; and its molecular weight 436.96. **(Malen et al., 1972)** (Fig.2).

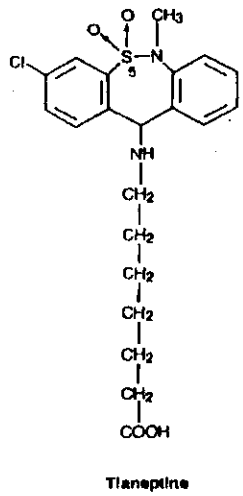


Fig (2): structural formulae of tianeptine **(Mennini et al., 1987)**

Pharmacokinetic properties:

Tianeptine is rapidly and completely absorbed after a single oral dose of 12.5 mg in healthy volunteers.It has a high bioavailability and is not subjected to hepatic first pass metabolism **(Salvadori et al., 1990)** .

Concomitant food intake slightly delays tianeptine absorption (maximum plasma concentration (Cmax) decreased by 25% and time to Cmax (tmax) increased by 0.5 h) but does not affect the extent of absorption (area under the plasma concentration – time curve (AUC) was unchanged) **(Dresse et al., 1988).**

The distribution of tianeptine is rapid (distribution half – life (t1/2 a) 0.7h). However, the apparent volume of distribution (VD) is low and protein binding is high; serum albumin accounts for the majority of protein binding (95%) **(Salvadori et al., 1990).**

Tianeptine is extensively metabolized predominantly by extra renal routes (The percentage of unchanged drug excreted via the kidney is low) and has a short elimination half – time (t½B) **(Roger et al., 1988).**

The major metabolic pathway of tianeptine is Beta - oxidation of the heptanoic acid side chain to form the shorter chain derivatives MC5 (Pentatonic acid) and MC3 (Propionic acid) **(Grislain et al., 1990).**

MC5 is the major metabolite of tianeptine in plasma and MC3 is the major metabolite in urine. The presence of a third metabolite LMC5, a lactam metabolite formed from MC5 has also been reported. MC5 possesses antidepressant activity **(Grislain et al., 1990).**

The pharmacokinetics of tianeptine and its MC5 metabolite were linearly related to dose in a study in 8 healthy male volunteers who received gradually increasing single oral tianeptine doses of 4.2 to

337.5mg (**Ansseau, 1993**). This suggests a lake of saturation in the absorption and elimination of tianeptine over a wide dose range.

Salvadori et al., (1990) reported that following intravenous administration of a single dose of tianeptine 12.5 mg to healthy volunteers, the AUC, T1/2B, VD, total clearance (CLR) (13.8 L/h) and renal clearance (CLR)(0.024L/h) were similar to these with oral administration (**Ansseau, 1993).** On the other hand, clearance of tianeptine and the MC5 metabolite by haemodialysis is low (0.2 and 1.1 L/h, respectively) **(Salvadori et al., 1990).** Also, because tianeptine is not subject to hepatic first pass metabolism, The risk of an increase in the total amount of tianeptine absorbed in patients with liver impairment or gastrointestinal disease are minimal.

Royer et al., (1989) added that, the overall pharmacokinetic profile of oral tianeptine (12.5mg) was not significantly altered in-patients with compensated cirrhosis. Dosage adjustments in these patients are not likely to be necessary. Also, it has been recommended that the dosage of tianeptine should be reduced to two 12.5mg tablets per day in patients aged >70 years **(Demotes- Mainardet et al., 1991).**

Pharmacodynamic properties:

Tianeptine is a noval antidepressant agent that, unlike other antidepressant agents, increase pre-synaptic reuptake of seretonin (5-hydroxytryptamine; 5-HT) **(Ansseau, 1993).** The long aminoheptanoic acid side chain with a terminal acidic group and the dibenzothiazepine nucleus containing 2 heteroatoms distinguishes tianeptine from the classical tricyclic antidepressant agents **(Ansseau, 1993).**

Tianeptine and its metabolites have no effect on serotonin uptake in Vitro following incubation with synaptosomal preparations **(Mennini et al., 1987)** Suggests that the drug acts on allosteric sites of the serotonin reuptake system that are not functional in synaptosomal preparations **(Mennini et al., 1987).** But, stimulation of serotonin uptake in vivo has been observed in rat cortical and hippocampal (but not mesencephalic) synaptosomes following both short (by 21 to 28% and 33%, respectively) and long term (by 30 to 71% and 24 to 55%, respectively) in vivo administration of tianeptine **(Mocaer et al., 1988)**.

Tianeptin enhances the depletion of serotonin caused by H75/12 (the H75/12 test is an indicator of reuptake inhibition in vivo) **(Fattaccini et al., 1990)**.

Tianeptine opposes the increase in extracellular serotonin levels in the frontal cortex of rats after administration of 5 hydroxytryptophan (5-HT; a precursor of serotonin), **(Datla and Curzon, 1993)** and attenuates potassium-evoked release of serotonin in rat hippocampal dialysates **(Whitton et al., 1991)** and in rat cortex and hippocampal slices **(Mocaer et al., 1988)**. The increase in serotonin uptake observed with tianeptine is due to a significant increase in Vmax (Maximal velocity) of the reuptake carrier for serotonin with no significant change in Km values (affinity for the reuptake site) **(Mennini et al., 1987).**

Tianeptine induced increases in serotonin uptake have been observed in rat platelets after short and long term administration **(Kato and weitsch, 1988)** . In an ex vivo study, tianeptine administered for 15 days increased serotonin uptake in rat platelets by approximately 30%,

whereas clomipramine inhibited uptake by 40%**(Datla and Curzon, 1993).**

In patients with depression, tianeptine significantly increased platelet serotonin uptake by 13% after single and multiple dose administration and increased platelet serotonin content by 32**% (Chamba et al., 1991).**

The activity of tianeptine appears to be selective for serotonergic mechanisms and essentially presynaptic although, most investigations have reported that tianeptine does not bind to serotonin receptor subtypes in vitro **(Mennini et al., 1987).**

Tianeptine either does not bind to or has low affinity for alpha1, alpha2 and B-adrenoceptors, gamma-aminobutyric acid (GABA), glutamate, dopamine D2, benzodiazepine, muscarinic, nicotinic, histamine, adenosine 1, adenosine 2 receptors or calcium channels **(Kato and Weitsch 1988)**. The lack of affinity of tianeptine for alpha-adrenergic and histaminic receptor is likely to account for the observed lack of sedation with this drug.

Sacchetti et al., (1993) reported that, tianeptine does not directly affect the uptake or release of dopamine in rat striatum or cortex, or interfere with monoamine oxidize activity or monoamine uptake into synaptosome **(Mennini et al.,1987).** While, levels of the dopamine metabolite dihydroxyphenylacetic acid (DOPAC) were increased in rat cerebral cortex, striatum and nucleus accumbens **(Sacchetti et al., 1993),** and extracellular concentrations of dopamine were increased in the nucleus accumbens of the rat after a single dose of tianeptine **(Invernizzi et al., 1992)** . Increases in extracellular concentrations of dopamine were

also observed in the striatum although these were less marked and shorter lasting, and occurred only at high doses (10 mg/day Vs 2.5 and 5 mg/kg)**(Sacchetti et al., 1993).**Fluoxetine and tricyclic antidepressants are also known to increase extracellular dopamine levels. The effect of tianeptine on extracellular dopamine concentrations may be mediated by indirect mechanism **(Sacchetti et al., 1993).**

On the other hand, tianeptine decreases acetylcholine release in rat dorsal hippocampus and frontal cortex,but does not influence noradrenaline uptake **(Bertorelli et al., 1992).**

The antidepressant tianeptine has been shown to decrease the response of the hypothalamic pitutary adrenal (HPA) axis to stress **(Castanon et al., 2003).**

Tianeptine counteracted the anoxiogenic effects of benzodiazepin withdrawal and ethanol withdrawal in the rat, as assessed by the social interaction test of anxiety **(File et al., 1993)**. These effects are consistent with reduced serotonergic function. Tianeptine antagonises stress induced behavioral deficits in animal model of depression. When administered 1 hour before, 15days before or 2 hours after immobilisation stress in rats **(Curzon et al., 1992).**

Tianeptine opposed the reductions in the exploratory activity when the animals were placed in an open field. Moreover, tianeptine reduced emotional stress induced increases in the colonic motility in the rat **(Bueno et al., 1993)** and prevents stress induced changes in cerebral morphology such as the retraction of apical dendrites of hippocampal CA3 pyramidal neurons **(Magarinos et al., 1999).** Although the exact

mechanism of these effects is unknown, evidence suggests that the effects of tianeptine on serotonin reuptake account for these observations.

Tianeptine had no significant effects on memory or vigilance in healthy volunteers **(Guillaume et al., 1993),** single doses had activating effects followed by sedation according to electroencephalograph (EEG) mapping **(Poirier et al., 1993)**. Tianeptine dose not significantly affect sleep EEG parameters including sleep onset latency, total sleep time, number of awakenings, slow wave sleep, rapid eye movement (REM) duration and REM sleep latency; there was a trend towards an increase in sleep period time and duration of stage 4 sleep with tianeptine in healthy Volunteers **(Mendlewiez, 1994).**

Drug Interactions:

Because tianeptine is highly protien bound, there is potential for interactions with other highly protein bound agents, especially those that bind to human serum albumin. High plasma concentrations of salicylic acid (>500umol/L), an agent that is extensively bound to human serum albumin, significantly impaired tianeptine binding Thus, it has been recommended that the dosage of tianeptine should be decreased when it is administered with high dosage of salicylic acid. **(Zini et al., 1991, Poirier et al., 1993).**

Interestingly, diclofenac did not impair the protein binding of tianeptine despite being highly bound to serum albumin**(Zini et al.,. 1991). et al., 1991).**

The lake of interaction between tianeptine and oxazepam is supported by a further study in healthy volunteers. There were no significant changes in the pharmacokinetics or psychomotor effects of tianeptine or oxazepam when the two agents were administered concomitantly(**Toon et al., 1990).** while the neuroleptic agents as levomepromazine and the anxiolytic agents flunitrazepam had no effect.

Tianeptine is activated and transformed by the human liver cytochrome P450 system into a active metabolite (MC3) which binds to liver microsomal proteins **(Larrey et al., 1990).** This activation has been shown to be mediated by the glucocorticoid inducible cytochrome P450 IIIA3 but not by cytochrome P450 IID6 (Which oxidizes debrisoquine) or cytochrome P450 IA1 (which is inducible by polycyclic aromatic compounds). On the other hand, most tricyclic antidepressants are partly oxidized by cytochrome P450 IID6.The value of these findings in predicting potential drug interaction remains to be determined.

Clinical adverse events :

Tianeptine has been well tolerated in both the shorts (up to 3 months) and long term treatment (up to 1 year), and has a low propensity to cause many of the adverse events (particularly anticholinergic, sedative and cardiovascular) associated with classical tricyclic antidepressant agents (**Guelfi et al., 1992**).

Guelfi et al., (1992) found in non comparative study of patients with major depression or dysthmic disorder (n= 1858) treated with tianeptine 25 to 37.5mg/day for 3 months, the most common adverse events were dry mouth (12% of patients), constipation (4%), change in dreaming (4%), weight gain (3%), agitation/tension (3%) and nausea (3 %) .These

adverse events were moderate in severity. Only 4.8%of patients withdrew because of an adverse event; these included nausea (0.9%), sleep disturbance (0.9%), anxiety /irritability (0.8%), vertigo (0.8%), fatigue/dizziness (0.6%), headache (0.6%), gastric disturbance (0.6%), dry mouth (0.5%), skin allergy (0.5%), palpitations (0.4%) and constipation (0.3%). Minor ECG changes and the rare occurrence of postural hypertension (0.01%) were not clinically significant **(Guelfi et al., 1992).**

Delalleau et al., (1988) stated that tianeptine appears to have a more favorable tolerability profile than classical tricyclic antidepressants, having a lower propensity to cause sedative, anticholinergic and cardiovascular (tachycardia, postural hypertension and ECG changes including conduction disorders) adverse effects than reference tricyclic antidepressants **(Guelfi et al., 1992).** The favorable tolerability profile of tianeptine in the short term has been confirmed in long term trials. In a review of 3 non comparative, non blind, long term (up to 1 year) trials of tianeptine in more than 3300 patients with depression, the drug was well tolerated and did not modify heart rate, blood pressure, cardiac conduction or ventricular function **(Delalleau et al., 1988).**

Droupout rate because of adverse effects, which included gastro-intestinal disturbance (1.3%), anxiety (0.7%), insomnia (0.5%), headache (0.4%), dry mouth (0.3%), and palpation's (0.3%) **(Delalleau et al., 1988).** The low incidences of anticholinergic effects, sedation, postural hypertension and cardiotoxicity make tianeptine particularly useful in elderly patients, who are known to have increased sensitivity to the adverse effects of antidepressant drugs and a high rate of coexisting disease (predominantly cardiovascular diseases) **(Wilde and Benfield,**

1995). The low incidence of anticholinergic effects with tianeptine enables this drug to be administered to elderly patients with coexisting benign prostetic hypertrophy **(Wilde and Benfield, 1995).**

Guelfi et al., (1992) reported that, tianeptine has not significantly affected hematological, metabolic, biochemical, renal or hepatic parameters in-patients with depression, including the elderly and those having undergone alcohol detoxification.

Dosage and Administration:

The recommended dosage of oral tianeptine in-patients with depression is 12.5 mg 3 times daily. Some patients may benefit from 50m/day, while dosage reductions (12.5mg twice daily) are recommended in the elderly (>70 years) and in-patients with sever renal impairment Although improvements are seen after approximately 2 weeks tianeptine treatment and most patients with depression receive tianeptine for 6 weeks to 3 months, progressive therapeutic improvments have been observed over a 1 – year treatment period. Long term treatment may reduce the incidence of relapse and recurrence of depression **(Guelfi et al., 1990).**

Discontinuation of tianeptine treatment in patients with depression or in those with coexisting alcoholism has not been associated with a withdrawal syndrome **(Delalleau et al., 1988).** There have been no reported signs of physical or psychological dependance following tianeptine withdrawal. Furthermore, there was no spontaneous increase in the dosage of tianeptine when it was administereted for 1 to 2 months to patients perviously addicted to opiates **(Costa et al., 1994).**

Tianeptine has a wide therapeutic margin; only minor and transient adverse effects (nausea, vomiting and sedation) occurred after a single of 337.5mg in healthy volunteers **(Ansseau et al., 1992).** No sever toxic effects were observed in 3 patients after massive ingestion of tianeptine (dose not stated) alone or with other drugs .**(Guelfi et al., 1992).**

Seven patients who attempted suicide by tianeptine overdosage had a favourable outcome despite concomitantly taking other psychotropic drugs or alcohol ;slight transient drowsiness was the most common adverse event **(Loo et al., 1992).**No deaths from tianeptine overdosage have been reported.

Tianeptine provides major antidepressant efficacy without or with minimal anticholinergic effects **(Mennini et al., 1987).**