Chapter 33 Drugs Used in Mental Illness: Antidepressant and Antianxiety Drugs

Major depression and mania are two extremes of *affective disorders* which refer to a pathological change in mood state. *Major depression* is characterized by symptoms like sad mood, loss of interest and pleasure, low energy, worthlessness, guilt, psychomotor retardation or agitation, change in appetite and/or sleep, melancholia, suicidal thoughts, etc. It may be a *unipolar* or a *bipolar disorder* in which cycles of mood swings from mania to depression occur over time. The mood change may have a psychotic basis with delusional thinking or occur in isolation and induce anxiety. On the other hand, pathological anxiety may lead to depression. Anxiety and depression are the leading psychiatric disorders now.

ANTIDEPRESSANTS

These are drugs which can elevate mood in depressive illness. Practically all antidepressants affect monoaminergic transmission in the brain in one way or the other, and many of them have other associated properties. Over the past three decades, a large number of antidepressants with an assortment of effects on reuptake/metabolism of biogenic amines, and on pre/post-junctional aminergic/cholinergic receptors have become available so that a cogent classification is difficult. The following working classification may be adopted.

CLASSIFICATION

I. *Reversible inhibitors of MAO-A (RIMAs)*
Moclobemide, Clorgyline

II. *Tricyclic antidepressants (TCAs)*
A. *NA + 5-HT reuptake inhibitors*
Imipramine, Amitriptyline, Trimipramine, Doxepin, Dothiepin, Clomipramine
B. *Predominantly NA reuptake inhibitors*
Desipramine, Nortriptyline, Amoxapine, Reboxetine

III. *Selective serotonin reuptake inhibitors (SSRIs)*
Fluoxetine, Fluvoxamine, Paroxetine, Sertraline, Citalopram, Escitalopram, Dapoxetine

IV. *Serotonin and noradrenaline reuptake inhibitors (SNRIs)*
Venlafaxine, Duloxetine

V. *Atypical antidepressants*
Trazodone, Mianserin, Mirtazapine, Bupropion, Tianeptine, Amineptine, Atomoxetine

Many other drugs like Protriptyline, Maprotiline, Nafazodone, etc. are marketed in other countries.

MAO INHIBITORS

MAO is a mitochondrial enzyme involved in the oxidative deamination of biogenic amines (Adr, NA, DA, 5-HT). Two isoenzyme forms of MAO have been identified.

MAO-A: Preferentially deaminates 5-HT and NA, and is inhibited by clorgyline, moclobemide.

MAO-B: Preferentially deaminates phenylethylamine and is inhibited by selegiline.

Dopamine is degraded equally by both isoenzymes.

Their distribution also differs. Peripheral adrenergic nerve endings, intestinal mucosa and human placenta contain predominantly MAO-A, while MAO-B predominates in certain areas (mainly serotonergic) of brain and in platelets. Liver contains both isoenzymes.

Two hydrazine drugs—*isoniazid* and *iproniazid* were used for tuberculosis in 1951; the latter was especially found to cause disproportionate elevation of mood. Its capacity to inhibit degradation of biogenic amines was soon discovered and was believed to be responsible for the mood elevating action. Its less hepatotoxic congeners like *phenelzine* and

isocarboxazid and some nonhydrazine MAO inhibitors (related to amphetamine) like *tranylcypromine* were used as antidepressants in the 1960s. They inhibited MAO irreversibly and were nonselective for the two isoforms. Because of high toxicity and interactions with foods and other drugs, they have become obsolete.

The selective MAO-A inhibitors possess antidepressant property. Selegiline selectively inhibits MAO-B at lower doses (5–10 mg/day), but these are not effective in depression. It is metabolized to amphetamine and at higher doses it becomes nonselective MAO inhibitor—exhibits antidepressant and excitant properties.

Nonselective MAO Inhibitors

The nonselective MAO inhibitors elevate the mood of depressed patients; in some cases it may progress to hypomania and mania. Excitement and hypomania may be produced even in nondepressed individuals.

The active metabolites of nonselective MAO inhibitors inactivate the enzyme irreversibly. The drugs themselves stay in the body for relatively short periods, but their effects last for 2–3 weeks after discontinuation: they are 'hit and run' drugs. Return of MAO activity depends on synthesis of fresh enzyme; tissue monoamine levels remain elevated long after the drug has been largely eliminated.

Interactions These drugs inhibit a number of other enzymes as well, and interact with many food constituents and drugs.

(i) *Cheese reaction* Certain varieties of cheese, beer, wines, pickled meat and fish, yeast extract contain large quantities of tyramine, dopa, etc. In MAO inhibited patients these indirectly acting sympathomimetic amines escape degradation in the intestinal wall and liver → reaching into systemic circulation they displace and release large amounts of NA from transmitter loaded adrenergic nerve endings → *hypertensive crisis*, cerebrovascular accidents. When such a reaction occurs, it can be treated by i.v. injection of a rapidly acting α blocker, e.g. phentolamine. Prazosin or chlorpromazine are alternatives.

(ii) *Cold and cough remedies* They contain ephedrine or other sympathomimetics—hypertensive reaction can occur.

(iii) *Reserpine, guanethidine, tricyclic antidepressants* Excitement, rise in BP and body temperature can occur when these drugs are given to a patient on MAO inhibitors. This is due to their initial NA releasing or uptake blocking action.

(iv) *Levodopa* Excitement and hypertension occur due to increase in biological t½ of DA and NA that are produced from levodopa.

(v) *Antiparkinsonian anticholinergics* Hallucinations and symptoms similar to those of atropine poisoning occur.

(vi) *Barbiturates, alcohol, opioids, antihistamines* Action of these drugs is intensified and prolonged. Respiration may fail.

(vii) *Pethidine* High fever, sweating, excitation, delirium, convulsions and severe respiratory depression have occurred. The most accepted explanation is—
MAO inhibitors retard hydrolysis of pethidine but not its demethylation. Thus, excess of *norpethidine* (normally a minor metabolite—*see* p. 475) is produced which has excitatory actions.

Reversible inhibitors of MAO-A (RIMAs)

Moclobemide It is a reversible and selective MAO-A inhibitor with short duration of action; full MAO activity is restored within 1–2 days of stopping the drug. Because of competitive enzyme inhibition, tyramine is able to displace it from the enzyme, so that potentiation of pressor response to ingested amines is minor, and dietary restrictions are not required. Clinical trials have shown moclobemide to be an efficacious antidepressant, comparable to TCAs, except in severe cases. It lacks the anticholinergic, sedative, cognitive, psychomotor and cardiovascular adverse effects of typical TCAs and is safer in overdose. This makes it a particularly good option in elderly patients and in those with heart disease.

Dose: 150 mg BD–TDS (max 600 mg/day)
RIMAREX, TRIMA 150, 300 mg tabs.

Adverse effects are nausea, dizziness, headache, insomnia, rarely excitement and liver damage. Chances of interaction with other drugs and alcohol are remote, but caution is advised while coprescribing pethidine, SSRIs and TCAs.

Moclobemide has emerged as a well tolerated alternative to TCAs for mild to moderate depression and for social phobia.

TRICYCLIC ANTIDEPRESSANTS (TCAs)

Imipramine, an analogue of CPZ was found during clinical trials (1958) to selectively benefit depressed but not agitated psychotics. In contrast to CPZ, it inhibited NA and 5-HT

IMIPRAMINE

reuptake into neurones. A large number of congeners were soon added and are called *tricyclic antidepressants (TCAs)*.

These older compounds, in addition to uptake blockade have direct effects on adrenergic, cholinergic and histaminergic receptors, and are referred to as '*first generation antidepressants*,' a group which also includes MAOIs.

The subsequently produced *second generation antidepressants* have more selective action on amine uptake; are either *Selective serotonin reuptake inhibitors (SSRIs)*, or *Serotonin and noradrenaline reuptake inhibitors (SNRIs)*, with no direct action on cholinergic/adrenergic/histaminergic receptors, or have some *atypical features*. They have a limited spectrum of action resulting in fewer side effects.

PHARMACOLOGICAL ACTIONS

The most prominent action of TCAs is their ability to inhibit norepinephrine transporter (NET) and serotonin transporter (SERT) located at neuronal/platelet membrane at low and therapeutically attained concentrations.

The TCAs inhibit monoamine reuptake and interact with a variety of receptors *viz.* muscarinic, α adrenergic, histamine H_1, 5-HT_1, 5-HT_2 and occasionally dopamine D2. However, relative potencies at these sites differ among different compounds. The actions of imipramine are described as prototype.

1. CNS Effects differ in normal individuals and in the depressed.

In normal individuals It induces a peculiar clumsy feeling, tiredness, light-headedness, sleepiness, difficulty in concentrating and thinking, unsteady gait. These effects tend to provoke anxiety. There is no mood elevation or euphoria; effects are rather unpleasant and may become more so on repeated administration.

In depressed patients Little acute effects are produced, except sedation (in the case of drugs which have sedative property). After 2–3 weeks of continuous treatment, the mood is gradually elevated, patients become more communicative and start taking interest in self and surroundings. Thus, TCAs are not euphorients but only antidepressants. In depressed patients who have preponderance of REM sleep, this phase is suppressed and awakenings during night are reduced. The EEG effects of low doses are similar to hypnotics but high doses cause desynchronization. Sedative property varies among different compounds (*see* Table 33.1). The more sedative ones are suitable for depressed patients showing anxiety and agitation. The less sedative or stimulant ones are better for withdrawn and retarded patients.

The TCAs lower seizure threshold and produce convulsions in overdose. Clomipramine and bupropion have the highest seizure precipitating potential. Amitriptyline and imipramine depress respiration in overdose only.

Mechanism of action The TCAs and related drugs inhibit NET and SERT which mediate active reuptake of biogenic amines NA and 5-HT into their respective neurones and thus potentiate them. They, however, differ markedly in their selectivity and potency for different amines (*see* classification above).

Most of the compounds do not inhibit DA uptake, except bupropion. Moreover, amphetamine and cocaine (which are not antidepressants but CNS stimulants) are strong inhibitors of DA uptake. However, it has been proposed that TCAs indirectly facilitate dopaminergic transmission in forebrain that may add to the mood elevating action.

Reuptake inhibition results in increased concentration of the amines in the synaptic cleft in both CNS and periphery. Tentative conclusions drawn are:

- Inhibition of DA uptake correlates with stimulant action; but is not primarily involved in antidepressant action.
- Inhibition of NA and 5-HT uptake is associated with antidepressant action.

Certain findings indicate that uptake blockade is not directly responsible for the antidepressant action, e.g.

- Uptake blockade occurs quickly but antidepressant action develops after weeks
- Mianserin is antidepressant but has no uptake blocking action.

Initially the presynaptic α_2 and 5-HT_1 autoreceptors are activated by the increased amount of NA/5-HT in the synaptic cleft resulting in decreased firing of locus coeruleus (noradrenergic) and raphe (serotonergic) neurones. After, long-term administration, antidepressants desensitise the presynaptic α_2, 5-HT_{1A}, 5-HT_{1D} autoreceptors and induce other adaptive changes in the number and sensitivity of pre and post synaptic NA and/or 5-HT receptors as well as in amine turnover of brain, the net effect of which is enhanced nor-adrenergic and serotonergic transmission. Thus, uptake blockade appears to initiate a series of time-dependent changes that culminate in antidepressant effect.

None of the TCAs, except amoxapine, block DA receptors or possess antipsychotic activity.

2. ANS Most TCAs are potent anticholinergics—cause dry mouth, blurring of vision, constipation and urinary hesitancy as side effect. The anticholinergic potency is graded in Table 33.1.

They potentiate exogenous and endogenous NA by blocking uptake, but also have weak α_1 adrenergic blocking action. Some, e.g. amitriptyline, doxepin, trimipramine have slight H_1 antihistaminic action as well.

3. CVS Effects on cardiovascular function are prominent, occur at therapeutic concentrations and may be dangerous in overdose.

Tachycardia: due to anticholinergic and NA potentiating actions.

Postural hypotension: due to inhibition of cardiovascular reflexes and α_1 blockade.

ECG changes and cardiac arrhythmias: T wave suppression or inversion is the most consistent change. Arrhythmias occur in overdose mainly due to interference with intraventricular conduction. The NA potentiating + ACh blocking actions along with direct myocardial depression compound the proarrhythmic potential. Older patients are more susceptible. The SSRIs, SNRIs and atypical antidepressants are safer in this regard.

Tolerance and dependence

Tolerance to the anticholinergic and hypotensive effects of imipramine-like drugs develops gradually, but antidepressant action is sustained.

Psychological dependence on these drugs is rare, because their acute effects are not pleasant.

There is some evidence of physical dependence occurring when high doses are used for long periods—malaise, chills, muscle pain may occur on discontinuation and have been considered withdrawal phenomena. Gradual withdrawal is recommended, but antidepressants do not carry abuse potential.

PHARMACOKINETICS

The oral absorption of TCAs is good, though often slow. They are highly bound to plasma and tissue proteins, therefore have large volumes of distribution (~20 L/kg). They are extensively metabolized in liver; the major route for imipramine and amitriptyline is demethylation whereby active metabolites—desipramine and nortriptyline respectively are formed. Both these metabolites predominantly block NA reuptake. Few other TCAs also produce active metabolites. Inactivation occurs by oxidation and glucuronide conjugation. Various CYP isoenzymes like CYP2D6, CYP3A4, CYP1A2 and others metabolise tricylic and related antidepressants. Metabolites are excreted in urine over 1–2 weeks. The plasma t½ of amitriptyline, imipramine and doxepin range between 16–24 hours. The t½ is longer for some of their active metabolites. Because of relatively long t½s, once daily dosing (at bed time) is practicable in the maintenance phase.

An unusual *therapeutic window* phenomenon has been observed, i.e. optimal antidepressant effect is exerted at a narrow band of plasma concentrations (between 50–200 ng/ml of imipramine, amitriptyline, nortriptyline). Both

TABLE 33.1 **Comparative properties and preparations of tricyclic and related antidepressants**

Drug	Sedation	Anti-muscarinic	Hypotension	Cardiac arrhythmia	Seizure precipitation	Daily dose (mg)	Preparations
Tricyclic antidepressants (TCAs)							
1. Imipramine	+	++	++	+++	++	50–200	DEPSONIL, ANTIDEP 25 mg tab, 75 mg SR cap.
2. Amitriptyline	+++	+++	+++	+++	++	50–200	AMLINE, SAROTENA, TRYPTOMER, 10, 25, 75 mg tabs.
3. Trimipramine	+++	+++	++	+++	++	50–150	SURMONTIL 10, 25 mg tab.
4. Doxepin	+++	++	++	+++	++	50–150	SPECTRA, DOXIN, DOXETAR 10, 25, 75 mg tab/cap.
5. Clomipramine	++	+++	++	+++	+++	50–150	CLOFRANIL, 10, 25, 50 mg tab, 75 mg SR tab. CLONIL, ANAFRANIL 10, 25 mg tab.
6. Dothiepin (Dosulpin)	++	++	++	++	++	50–150	PROTHIADEN, DOTHIN 25, 75 mg tab.
7. Nortriptyline	+	++	+	++	+	50–150	SENSIVAL, PRIMOX 25 mg tab.
8. Amoxapine	+	+	++	++	++	100–300	DEMOLOX 50, 100 mg tab.
Selective serotonin reuptake inhibitors (SSRIs)							
1. Fluoxetine	±	—	—	—	±	20–40	FLUDAC 20 mg cap, 20 mg/5 ml susp. FLUNIL 10, 20 mg caps; FLUPAR, PRODAC 20 mg cap.
2. Fluvoxamine	±	—	—	—	—	50–200	FLUVOXIN 50, 100 mg tab.
3. Paroxetine	±	±	—	—	—	20–50	XET 10, 20, 30, 40 mg tabs.
4. Sertraline	±	—	—	—	—	50–150	SERENATA, SERLIN, SERTIL 50, 100 mg tabs.
5. Citalopram	—	—	—	—	—	20–40	CELICA 10, 20, 40 mg tabs.
6. Escitalopram	—	—	—	—	—	10–20	ESDEP, FELIZ-S 5, 10, 20 mg tabs.
Serotonin and noradrenaline reuptake inhibitors (SNRIs)							
1. Venlafaxine	—	—	—	±	—	75–150	VENLOR 25, 37.5, 75 mg tabs, VENIZ-XR 37.5, 75, 150 mg ER caps.
2. Duloxetine	—	—	—	—	—	30-80	DELOK, DULANE, DUZAC, 20, 30, 40 mg caps.
Atypical antidepressants							
1. Trazodone	+++	—	±	±	—	50–200	TRAZODAC 25, 50 mg tab, TRAZONIL, TRAZALON 25, 50, 100 mg tabs.
2. Mianserin	++	+	++	+	++	30–100	TETRADEP 10, 20, 30 mg tab, SERIDAC 10, 30 mg tab.
3. Bupropion	–, -	—	—	—	+++	150–300	SMOQUIT 150 mg tab.
4. Mirtazapine	+++	—	±	—	—	15–45	MIRT 15, 30, 45 mg tabs, MIRTAZ 15, 30 mg tab.

below and above this range, beneficial effects are suboptimal.

Wide variation in the plasma concentration attained by different individuals given the same dose has been noted. Thus, doses need to be individualized and titrated with the response, but plasma concentrations are not a reliable guide for adjusting the dose of TCAs.

ADVERSE EFFECTS

Side effects are common with TCAs because of which SSRIs, SNRIs and atypical antidepressants have become the first line drugs.

1. Anticholinergic: dry mouth, bad taste, constipation, epigastric distress, urinary retention (especially in males with enlarged prostate), blurred vision, palpitation.
2. Sedation, mental confusion and weakness, especially with amitriptyline and more sedative congeners.
3. Increased appetite and weight gain is noted with most TCAs and trazodone, but not with SSRIs, SNRIs and bupropion.
4. Some patients receiving any antidepressant may abruptly '*switch over*' to a dysphoric-agitated state or to mania. Most likely, these are cases of bipolar depression, the other pole being unmasked by the antidepressant. Patients receiving higher doses, especially of TCAs, are at greater risk than those receiving lower doses and SSRIs or bupropion.
5. Sweating (despite antimuscarinic action) and fine tremors are relatively common.
6. Seizure threshold is lowered—fits may be precipitated, especially in children. Bupropion, clomipramine, amoxapine have greater propensity, while desipramine, SSRIs and SNRIs are safer in this regard.
7. Postural hypotension, especially in older patients. It is less severe with desipramine-like drugs and insignificant with SSRIs/SNRIs.
8. Sexual distress: especially delay or interference with erection, ejaculation and occasionally with orgasm.
9. Cardiac arrhythmias, especially in patients with ischaemic heart disease. Arrhythmias may be responsible for sudden death in these patients. Amitriptyline and dosulpin are particularly dangerous in overdose; higher incidence of arrhythmia is reported with them.
10. Rashes and jaundice due to hypersensitivity are rare. Mianserin is more hepatotoxic.

Acute poisoning Poisoning with TCAs is frequent; usually self-attempted by the depressed patients, and may endanger life. Manifestations are:

Excitement, delirium and other anticholinergic symptoms as seen in atropine poisoning, followed by muscle spasms, convulsions and coma. Respiration is depressed, body temperature may fall, BP is low, tachycardia is prominent. ECG changes and ventricular arrhythmias are common.

Treatment is primarily supportive with gastric lavage, respiratory assistance, fluid infusion, maintenance of BP and body temperature. Acidosis must be corrected by bicarbonate infusion.

Diazepam may be injected i.v. to control convulsions and delirium. Most important is the treatment of cardiac arrhythmias, for which propranolol/lidocaine may be used. The class IA and IC antiarrhythmics and digoxin themselves depress cardiac conduction; are therefore contraindicated.

INTERACTIONS

1. TCAs potentiate directly acting *sympathomimetic amines* (present in cold/asthma remedies). Adrenaline containing local anaesthetic should be avoided. However, TCAs attenuate the action of indirect sympathomimetics (ephedrine, tyramine).
2. TCAs abolish the antihypertensive action of *guanethidine* and *clonidine* by preventing their transport into adrenergic neurones.
3. TCAs potentiate *CNS depressants*, including alcohol and antihistaminics.
4. *Phenytoin, phenylbutazone, aspirin and CPZ* can displace TCAs from protein binding sites and cause transient overdose symptoms.

5. *Phenobarbitone* competitively inhibits as well as induces imipramine metabolism. Carbamazepine and other enzyme inducers enhance metabolism of TCAs.
6. SSRIs inhibit metabolism of several drugs (*see* later) including TCAs—dangerous toxicity can occur if the two are given concurrently.
7. By their anticholinergic property, TCAs delay gastric emptying and retard their own as well as other drug's absorption. However, *digoxin* and *tetracyclines* may be more completely absorbed. When used together, the anticholinergic action of neuroleptics and TCAs may add up.
8. *MAO inhibitors*—dangerous hypertensive crisis with excitement and hallucinations has occurred when given with TCAs.

Amoxapine This tetracyclic compound is unusual in that it blocks dopamine D2 receptors in addition to inhibiting NA reuptake. It is chemically related to the antipsychotic drug loxapine and has mixed antidepressant + neuroleptic properties—offers advantage for patients with psychotic depression. Risk of extrapyramidal side effects is also there. Seizures (including status epilepticus) occur in its overdose.

Reboxetine This is a newer selective NA reuptake blocker with weak effect on 5-HT reuptake. Antimuscarinic and sedative actions are minimal. It appears to produce fewer side effects and may be safer in overdose than the older TCAs. Usual side effects are insomnia, palpitation, dry mouth, constipation, sexual distress and urinary symptoms.

Dose: 4 mg BD or 8 mg OD.

NAREBOX 4, 8 mg tab.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

The major limitations of TCAs (first generation antidepressants) are:

- Frequent anticholinergic, cardiovascular and neurological side effects.
- Relatively low safety margin. They are hazardous in overdose; fatalities are common.
- Lag time of 2–4 weeks before antidepressant action manifests.
- Significant number of patients respond incompletely and some do not respond.

To overcome these shortcomings, a large number of newer (second generation) antidepressants have been developed since 1980s. The most significant of these are the SSRIs and SNRIs which selectively inhibit membrane associated SERT or both SERT and NET. Though, some patients may not respond even to these drugs, the efficacy of second generation antidepressants is rated higher than older TCAs and RIMAs. Some patients not responding to one type of drug may respond to another type. More importantly the newer drugs have improved tolerability, both in therapeutic dose as well as in overdose. It has been claimed that certain drugs (bupropion, venlafaxine, mirtazapine) have faster onset of antidepressant action, but this has not been unequivocally established.

The relative safety and better acceptability of SSRIs has made them 1st line drugs in depression and allowed their extensive use in anxiety, phobias, OCD and related disorders. The SSRIs produce little or no sedation, do not interfere with cognitive and psychomotor function or produce anticholinergic side effects. They are devoid of α adrenergic blocking action—postural hypotension does not occur, making them suitable for elderly patients. They have practically no seizure precipitating propensity and do not inhibit cardiac conduction—overdose arrhythmias are not a problem. Prominent side effects are gastrointestinal; all SSRIs frequently produce nausea (due to 5-HT_3 receptor stimulation), but tolerance develops over time. Loose motions are due to 5-HT uptake blockade in the gut and activation of 5-HT receptors on enteric plexus neurones. Weight gain is not a problem with SSRIs, but they more commonly interfere with ejaculation or orgasm. A new constellation of mild side effects, *viz.* nervousness, restlessness, insomnia, anorexia, dyskinesia and headache is associated with them, but patient acceptability is good. Increased incidence of

epistaxis and ecchymosis has been reported, probably due to impairment of platelet function. Gastric blood loss due to NSAIDs may be increased by SSRIs.

The SSRIs inhibit drug metabolizing isoenzymes CYP2D6 and CYP3A4: elevate plasma levels of TCAs, haloperidol, clozapine, terfenadine, astemizole, warfarin, β blockers, some BZDs and carbamazepine. '*Serotonin syndrome*' manifesting as agitation, restlessness, rigidity, hyperthermia, delirium, sweating, twitchings followed by convulsions can be precipitated when any serotonergic drug (e.g. MAOIs, tramadol, pethidine) is taken by a patient receiving SSRIs. Some degree of tolerance to antidepressant action of SSRIs has been noted in few patients after months of use. Discontinuation reaction consisting of paresthesias, bodyache, bowel upset, agitation and sleep disturbances occurs in some patients. However, risk of switching over to hypomania during treatment is less with SSRIs than with TCAs.

Some authorities now consider SSRIs to be more effective antidepressants than TCAs. However, some patients not responding to SSRIs may respond to TCAs. The converse is also true, and there is no way to predict which patient will respond to which drug. Because of freedom from psychomotor and cognitive impairment, SSRIs are preferred for prophylaxis of recurrent depression (should be combined with lithium/valproate). Metaanalysis of comparative trials has shown no significant difference in efficacy among individual SSRIs, but there are pharmacokinetic differences and incidence of particular side effects differs somewhat.

Fluoxetine A bicyclic compound, is the first SSRI to be introduced, and the longest acting. Its plasma t½ is 2 days and that of its active demethylated metabolite is 7–10 days. It has been approved for use in children 7 years or older for depression and OCD on the basis of similar efficacy and side effect profile as in adults, but should be given to children only when psychotherapy fails. Agitation and dermatological reactions are more frequent than other SSRIs. Because of slower onset of antidepressant effect, it is considered less suitable for patients needing rapid effect, but is more appropriate for poorly compliant patients. Its stimulant effect could worsen patients showing agitation.

Fluvoxamine It is a shorter-acting SSRI with a t½ of 18 hours and no active metabolite, which has been specifically recommended for generalized anxiety disorder and OCD, rather than for depression. Relatively more nausea, dyspepsia, flatulence, nervousness and discontinuation reactions have been reported with fluvoxamine.

Paroxetine Another short acting SSRI (t½ 20 hours) which does not produce active metabolite. A higher incidence of g.i. side effects, sexual distress, agitation and discontinuation reaction than with other SSRIs has been noted.

Sertraline This SSRI has gained popularity, because in clinical trials fewer patients stopped sertraline due to side effects. Efficacy in juvenile depression has been demonstrated, and it is recommended for anxiety and post-traumatic stress disorder (PTSD) as well. Drug interactions due to inhibition of CYP isoenzymes are less likely to occur with this SSRI. Its plasma t½ is 26 hours and it produces a still longer-lasting active metabolite.

Citalopram This SSRI shares with sertraline a lower propensity to cause drug interactions. Its t½ is 33 hours and no active metabolite is known. However, few deaths due to overdose of citalopram are on record, because of which it is to be avoided in patients likely to attempt suicide. Citalopram is the preferred SSRI for mood disorders in premenstrual syndrome.

Escitalopram It is the active S(+) enantiomer of citalopram, effective at half the dose, with similar properties. Side effects are milder and safety is improved.

Dapoxetine A SSRI which has been developed and is being promoted for delaying premature ejaculation, a property common to many SSRIs

and some TCAs. Dapoxetine acts rapidly and can be taken 1 hour before sexual intercourse. Combined with behavioural therapies, it has been found to help many sufferers. Side effects are nausea, vomiting, loose motions, headache, dizziness and occasionally insomnia.

Dose: 60 mg taken 1 hour before intercourse; older patients 30 mg.

SUSTINEX, DURALAST, KUTUB 30 mg, 60 mg tabs.

Other uses of SSRIs The SSRIs are now 1st choice drugs for OCD, panic disorder, social phobia, eating disorders, premenstrual dysphoric disorder and PTSD. They are also being increasingly used for anxiety disorders, body dysmorphic disorder, compulsive buying, kleptomania and premature ejaculation. Elevation of mood and increased work capacity has been reported in postmyocardial infarction and other chronic somatic illness patients. Thus, SSRIs are being used to improve outlook on life and to feel good, even in apparently nondepressed patients. Wisdom of such use though is questionable.

SEROTONIN AND NORADRENALINE REUPTAKE INHIBITORS (SNRIs)

1. Venlafaxine A novel antidepressant referred to as SNRI, because it inhibits uptake of both NA and 5-HT but, in contrast to older TCAs, does not interact with cholinergic, adrenergic or histaminergic receptors or have sedative property. Trials have shown it to be as effective antidepressant as TCAs and may work in some resistant cases. A faster onset of action is claimed. Mood changes and hot flushes in menopausal syndrome, some anxiety and eating disorders are also benefited by venlafaxine. It does not produce the usual side effects of TCAs; tends to raise rather than depress BP and is safer in overdose. Prominent side effects are nausea, sweating, anxiety, dizziness, impotence and withdrawal reactions on discontinuation.

2. Duloxetine A newer SNRI similar to venlafaxine. It is neither sedative, nor anticholinergic, nor antihistaminic, nor α blocker. Side effects, including g.i. and sexual problems are milder, but some agitation, insomnia and rise in BP can occur. Antidepressant efficacy is comparable to TCAs. Duloxetine is also indicated in panic attacks, diabetic neuropathic pain, fibromyalgia and stress urinary incontinence in women (because it increases urethral tone).

ATYPICAL ANTIDEPRESSANTS

1. Trazodone It is the first atypical antidepressant; less efficiently blocks 5-HT uptake and has prominent α adrenergic and weak 5-HT_2 antagonistic actions. The latter may contribute to its antidepressant effect, which nevertheless is modest. It is sedative but not anticholinergic, causes bradycardia rather than tachycardia, does not interfere with intracardiac conduction—less prone to cause arrhythmia and better suited for the elderly. Nausea is felt, especially in the beginning. Mild anxiolytic effect has been noted and it has benefited cases of OCD. Inappropriate, prolonged and painful penile erection (priapism) occurs in few recipients resulting in impotence in a fraction of these. The α_1 adrenergic blocking property has been held responsible for this effect as well as for postural hypotension. In general, trazodone is infrequently used now in depression.

2. Mianserin It is unique in not inhibiting either NA or 5-HT uptake; but blocks presynaptic α_2 receptors thereby increasing release and turnover of NA in brain which may be responsible for the antidepressant effect. Antagonistic action at 5-HT_2, 5-HT_{1c} as well as H_1 receptors has also been shown. It is a sedative—relieves associated anxiety and suppresses panic attacks. While anticholinergic and cardiac side effects are less prominent, it has caused seizures in overdose. However, overdose fatality is low. Reports of blood dyscrasias and liver dysfunction have restricted its use.

3. Mirtazapine This antidepressant acts by a novel mechanism, *viz*. blocks α_2 auto- (on NA neurones) and hetero- (on 5-HT neurones) receptors enhancing both NA and 5-HT release. The augmented NA further increases firing of

serotonergic raphe neurones *via* α_1 receptors. Selective enhancement of antidepressive 5-HT_1 receptor action is achieved by concurrent blockade of 5-HT_2 and 5-HT_3 receptors which are held responsible for some of the adverse effects of high serotonergic tone. Accordingly, it has been labelled as "*noradrenergic and specific serotonergic antidepressant*" (NaSSA). It is a H_1 blocker and quite sedative, but not anticholinergic or antidopaminergic. Efficacy in mild as well as severe depression is reported to be comparable to TCAs, and given once daily at bed time, it is particularly suitable for those with insomnia. Increased appetite and weight gain is frequent. Sexual dysfunction is not a problem with mirtazapine.

4. Bupropion This inhibitor of DA and NA uptake has excitant rather than sedative property. It is metabolized into an amphetamine like compound which can cause presynaptic release of DA and NA. A sustained-release formulation is marketed as an aid to smoking cessation. In clinical trials it has been found to yield higher smoking abstinence and quitting rates than placebo and equivalent to nicotine replacement. Bupropion may be acting by augmenting the dopaminergic reward function. Better results are obtained when it is combined with nicotine patch. The nicotine withdrawal symptoms were less severe in bupropion recipients. However, long-term efficacy is not known, and it can cause insomnia, agitation, dry mouth and nausea, but not sexual side effects. Seizures occur in over dose and in predisposed patients due to lowering of seizure threshold. The dose of 150 mg BD should not be exceeded. It is contraindicated in eating disorders and in bipolar illness. Bupropion is infrequently used to treat depression; may be added to a SSRI.

5. Tianeptine This antidepressant is reported to increase rather than inhibit 5-HT uptake, and is neither sedative nor stimulant. It has shown efficacy in anxiodepressive states, particularly with psychosomatic symptoms, as well as in endogenous depression. Side effects are dry mouth, epigastric pain, flatulence, drowsiness/insomnia, tremor and bodyache.

Dose: 12.5 mg BD–TDS; STABLON 12.5 mg tab.

6. Amineptine Like tianeptine it enhances 5-HT uptake, and has antidepressant property. It produces anticholinergic side effects including tachycardia, confusion and delirium. Postural hypotension, conduction disturbances and arrhythmias can occur, especially in patients with heart disease.

Dose: 100 mg BD at breakfast and lunch.
SURVECTOR 100 mg tab.

7. Atomoxetine It is unrelated to tricyclic antidepressants, but is a selective NA reuptake inhibitor. It is approved only for treatment of attention deficit hyperactivity disorder (ADHD), and is described in Ch. 35.

USES

1. *Endogenous (major) depression:* The aim is to relieve symptoms of depression and restore normal social behaviour. The tricyclic and related antidepressants are of proven value. Response takes at least 2–3 weeks to appear, full benefits take still longer. Choice of a particular drug for an individual patient depends on the secondary properties (sedative, anticholinergic, hypotensive, cardiotoxic, seizure precipitating, etc.) as described above. The SSRIs are currently used as first choice for their better tolerability, safety and may be higher efficacy as well. The SNRIs and newer atypical agents also offer some advantages. The only antidepressants clearly shown to be effective in juvenile depression are fluoxetine and sertraline. The TCAs are mostly used as alternatives in non-responsive cases or in those not tolerating the second generation antidepressants. Substituting a drug with a different pattern of aminergic action often succeedes in non-responsive cases. However, few patients fail any antidepressant. Moclobemide is a well tolerated option for mild to moderate depression, especially suited for elderly and cardiac patients. However, antidepressants are not the answer to every grief, loss, set back and other sad events that are part of life, but the less toxic and more patient-friendly SSRIs/SNRIs/atypical antidepressants are now more readily prescribed for depressive illness.

After a depressive episode has been controlled, continued treatment at maintenance doses (about 100 mg imipramine/day or equivalent) for months is recommended to prevent relapse. Discontinuation of the antidepressant may be attempted after 6–12 months. Long-term therapy may be needed in patients who tend to relapse. ECT may be given in the severely depressed, especially initially while the effect of antidepressants is developing, because no antidepressant has been clearly demonstrated to act fast enough to prevent suicide. The TCAs or SSRIs must be combined with lithium/valproate/lamotrigine for bipolar depression, and not used alone due to risk of switching over to mania.

Combination of one of the SSRIs with an atypical antipsychotic (such as olanzapine, aripiprazole or quetiapine) is also accepted as a treatment option for bipolar depression.

2. *Obsessive-compulsive and phobic states:* The SSRIs, particularly fluoxamine, are the drugs of choice due to better patient acceptability. TCAs, especially clomipramine, are highly effective in OCD and panic disorders: more than 25% improvement occurs in OCD rating scale and panic attacks are reduced in >75% patients. SSRIs and TCAs also reduce compulsive eating in *bulimia*, and help patients with *body dysmorphic disorder, compulsive buying* and *kleptomania,* though these habits may not completely die.

3. *Anxiety disorders:* Antidepressants, especially SSRIs, exert a delayed but sustained beneficial effect in many patients of *generalized anxiety disorder;* may be used along with a short course of BZDs to cover exacerbations. SSRIs have also proven helpful in *phobic disorders*, sustained treatment of *panic attacks* and in *post-traumatic stress disorder.*

4. *Neuropathic pain:* Amitriptyline and other TCAs afford considerable relief in diabetic and some other types of chronic pain. Amitriptyline reduces intensity of post-herpetic neuralgia in ~50% patients. The SSRIs are less effective in these conditions. Duloxetine, a SNRI, is now a first line drug for diabetic neuropathy, fibromyalgia, etc. Other drugs useful in neuropathic pain are pregabalin or gabapentin. Combination of duloxetine + pregabalin may work if monotherapy is not satisfactory.

5. *Attention deficit-hyperactivity disorder (ADHD) in children:* TCAs with less depressant properties like imipramine, nortriptyline and amoxapine are now first line drugs in this disorder, comparable in efficacy to amphetamine-like drugs, with the advantage of less fluctuating action and fewer behavioural side effects. Atomoxetine is a NA reuptake inhibitor unrelated to both TCAs as well as amphetamine, which is used specifically in ADHD.

6. *Premature ejaculation:* It refers to repeated occurrences of ejaculation before or shortly after penetration, or with minimal sexual stimulation. It is a very common sexual complaint, which is often interpreted as sexual weakness; can cause considerable distress and dissatisfaction in the patient as well as in his partner. Sometimes the subject has unreasonable expectations about the optimal/desirable length of intercourse.

Most SSRIs and some TCAs, especially clomipramine have the common property of delaying and in some cases inhibiting ejaculation (this itself can cause sexual distress). The primary treatment of premature ejaculation is counselling and behavioural therapy, but this can be supplemented by drugs. Dapoxetine is a SSRI which has been specifically introduced for this purpose. It acts rapidly; 60 mg taken 1 hour before intercourse has helped many subjects. Clomipramine 10–25 mg three times a day is a slow acting drug which needs to be taken regularly for maximum benefit. For on demand use, 25 mg may be taken 6 hours before sex.

7. *Enuresis:* In children above 5 years, imipramine 25 mg at bedtime is effective, but bed wetting may again start when the drug is stopped. Eldery subjects with bed wetting have also benefited.

8. *Migraine:* Amitriptyline has some prophylactic value, especially in patients with mixed headaches.

9. *Pruritus:* Some tricyclics have antipruritic action. Topical doxepin has been used to relieve itching in atopic dermatitis, lichen simplex, etc. NOCTADERM 5% cream.

ANTIANXIETY DRUGS

Anxiety It is an emotional state, unpleasant in nature, associated with uneasiness, discomfort and concern or fear about some defined or undefined future threat. Some degree of anxiety is a part of normal life. Treatment is needed when it is disproportionate to the situation and excessive. Some psychotics and depressed patients also exhibit pathological anxiety.

Cardiac neurosis (unfounded fear of heart disease—palpitation, functional precordial pain); g.i. neurosis (fixation on bowel movement, distention, eructation, reflux, acidity); social anxiety (fear of being observed and evaluated by others); obsessive-compulsive disorder (OCD), post-traumatic stress disorder and various forms of phobias are some specific types of anxiety disorders.

Antianxiety drugs These are an ill-defined group of drugs, mostly mild CNS depressants, which are aimed to control the symptoms of anxiety, produce a restful state of mind without interfering with normal mental or physical functions. The anxiolytic-sedative drugs differ markedly from antipsychotics, and more closely resemble sedative-hypnotics. They:

1. Have no therapeutic effect to control thought disorder of schizophrenia.
2. Do not produce extrapyramidal side effects.
3. Have anticonvulsant property.
4. Produce physical dependence and carry abuse liability.
5. Do not selectively block conditioned avoidance response in animals.

CLASSIFICATION

1. *Benzodiazepines*	Diazepam Chlordiazepoxide Oxazepam Lorazepam, Alprazolam
2. *Azapirones*	Buspirone, Gepirone, Ispapirone
3. *Sedative antihistaminic*	Hydroxyzine
4. *β blocker*	Propranolol

In addition to the above drugs, antidepressants, especially the SSRIs and SNRIs are effective in OCD, phobias, panic and many types of severe generalized anxiety disorders.

BENZODIAZEPINES

The pharmacology of benzodiazepines (BZDs) as a class is described in Ch. 29.

Some members have a slow and prolonged action, relieve anxiety at low doses without producing significant CNS depression. They have a selective taming effect on aggressive animals and suppress induced aggression. They also suppress the performance impairing effect of punishment. In contrast to barbiturates, they are more selective for the limbic system and have proven clinically better in both quality and quantity of improvement in anxiety and stress-related symptoms.

At antianxiety doses, cardiovascular and respiratory depression is minor.

Because anxiety is a common complaint and is a part of most physical and mental illness, and because the BZDs—

- have little effect on other body systems
- have lower dependence producing liability than barbiturates and other sedatives; withdrawal syndrome is milder and delayed due to their long half lives
- are relatively safe even in gross overdosage,

they are presently one of the widely used class of drugs. Potent BZDs like lorazepam and clonazepam injected i.m. have adjuvant role in the management of acutely psychotic and manic patients.

BZDs act primarily by facilitating inhibitory GABAergic transmission, but other additional mechanisms of action have been suggested. Higher doses induce sleep and impair performance.

Adverse effects of BZDs noted in their use as hypnotics are described in Ch. 29. *Side effects* that occur in their use to relieve anxiety are—sedation, light-headedness, psychomotor and cognitive impairment, confusional state (especially in the elderly), increased appetite and weight gain, alterations in sexual function. Rashes are uncommon. Some women fail to ovulate while on regular use of BZDs. The major constraint in their long-term use for anxiety disorders is their potential to impair mental functions and to produce dependence.

Differences between individual BZDs recommended for anxiety are primarily pharmacokinetic: choice of one over the other is largely empirical.

1. Chlordiazepoxide It was the first BZD to be used clinically. Oral absorption is slow. A smooth long lasting effect is produced. It is preferred in chronic anxiety states. Chlordiazepoxide is often combined with other drugs in psychosomatic disorders, and has been the commonest BZD used to cover alcohol withdrawal. Its t½ is 6–12 hours, but active metabolites are produced which extend the duration of action. Its anticonvulsant action is weak.

Daily dose: 25–100 mg; LIBRIUM 10, 25 mg tabs; EQUILIBRIUM 10 mg tab.

2. Diazepam It is quickly absorbed; produces a brief initial phase of strong action followed by prolonged milder effect due to a two phase plasma concentration decay curve (distributive phase t½ 1 hr, elimination phase t½ 20–30 hours). The biological effect t½ is still longer due to production of active metabolites. It is preferred in acute panic states and anxiety associated with organic disease.

Daily dose: 5–30 mg; VALIUM, PLACIDOX 2, 5, 10 mg tabs; CALMPOSE 5, 10 mg tab, 2 mg/5 ml Syr.

3. Oxazepam It is slowly absorbed; being relatively polar, its penetration in brain is also slow. The plasma t½ is about 10 hours. It is metabolized only by glucuronide conjugation, therefore no active metabolite is produced. Duration of action is relatively shorter making it preferable for the elderly and in those with liver disease. It has been used mainly in short lasting anxiety states.

Daily dose: 30–60 mg in 2–3 divided portions; SEREPAX 15, 30 mg tab.

4. Lorazepam Has slow oral absorption. Being less lipid-soluble than diazepam, its rate of entry in brain is slower. The plasma t½ is shorter (10–20 hours); no active metabolite is produced, since it is directly conjugated with glucuronic acid, and is suitable for older patients. However, it is quite sedative and capable of producing marked amnesia when injected i.v. Injection site complications are minor. Therefore, it is the only BZD recommended for i.m. use. It has been preferred for short lasting anxiety states, panic, OCD and tension syndromes, as well as for psychosomatic diseases and for i.v. use in status epilepticus.

Daily dose: 1–6 mg; LARPOSE, ATIVAN 1, 2 mg tab. CALMESE 1, 2 mg tabs, 4 mg/2 ml inj.

5. Alprazolam A high potency anxiolytic BZD which in addition has some mood elevating action in mild depression. As such, it is particularly useful in anxiety associated with depression. Good response has been obtained in panic disorders with severe anxiety and autonomic symptoms. Its plasma t½ is about 12 hours, but an active metabolite is produced. Alprazolam is also used as hypnotic. When administered daily as anxiolytic, some patients experience anxiety in between doses, which may be obviated by employing sustained release tablet. Withdrawal symptoms may be more marked on discontinuation than with other BZDs.

Dose: 0.25–1.0 mg TDS; upto 6 mg/day in panic disorder; ALPRAX 0.25, 0.5, 1.0 mg tabs., 0.5, 1.0, 1.5 mg SR tabs; ALZOLAM 0.25, 0.5, 1.0 mg tabs; 1.5 mg SR tab, ALPROCONTIN 0.5, 1.0, 1.5 mg CR tabs. RESTYL 0.25, 0.5, 1.0 mg tabs, RESTYL-SR 0.5, 1.0, 1.5 mg SR tabs.

OTHER ANTIANXIETY DRUGS

Buspirone It is the first azapirone, a new class of antianxiety drugs, distinctly different from BZDs. Buspirone:

- Does not produce significant sedation or cognitive/functional impairment.
- Does not interact with BZD receptor or modify GABAergic transmission.
- Does not produce tolerance or physical dependence.
- Does not suppress BZD or barbiturate withdrawal syndrome.
- Has no muscle relaxant or anticonvulsant activity.

Buspirone relieves mild-to-moderate generalized anxiety, but is ineffective in severe cases, in those showing panic reaction and in OCD. The therapeutic effect develops slowly; maximum benefit may be delayed up to 2 weeks. The mechanism of anxiolytic action is not clearly known, but may be dependent on its selective partial agonistic action on 5-HT_{1A} receptors. By stimulating presynaptic 5-HT_{1A} autoreceptors, it reduces the activity of dorsal raphe serotonergic neurones. Antagonistic action at certain postsynaptic 5-HT_{1A} receptors has also been demonstrated. After chronic treatment, adaptive reduction in cortical 5-HT_2 receptors may occur. Buspirone has weak dopamine D2 blocking action but no antipsychotic or extrapyramidal effects. A mild mood elevating action has been noted occasionally, which may be due to facilitation of central noradrenergic system.

Buspirone is rapidly absorbed; undergoes extensive first pass metabolism; (bioavailability <5%), one metabolite is active and excretion occurs both in urine and faeces; t½ is 2–3.5 hrs. Side effects are minor: dizziness, nausea, headache, light-headedness, rarely excitement. It may cause rise in BP in patients on MAO inhibitors, but does not potentiate CNS depressants. Though most patients on buspirone remain alert, those operating machinery/motor vehicles should be cautioned.

Dose: 5–15 mg OD–TDS:
ANXIPAR, BUSPIN, BUSCALM 5, 10 mg tab.

Hydroxyzine An H_1 antihistaminic with sedative, antiemetic, antimuscarinic and spasmolytic properties. It is claimed to have selective anxiolytic action, but the accompanying sedation is quite marked. Hydroxyzine may be used in reactive anxiety or that associated with marked autonomic symptoms. Due to antihistaminic and sedative property, it is useful in pruritus and urticaria.
Daily dose 50–200 mg;
ATARAX 10, 25 mg tab, 10 mg/5 ml syr, 25 mg/2 ml inj.

β Blockers (*see* Ch. 10)

Many symptoms of anxiety (palpitation, rise in BP, shaking, tremor, gastrointestinal hurrying, etc.) are due to sympathetic overactivity, and these symptoms reinforce anxiety. Propranolol and other nonselective β blockers help anxious patients troubled by these symptoms, by cutting the vicious cycle and provide symptomatic relief. They do not affect the psychological symptoms such as worry, tension and fear, but are valuable in acutely stressful situations (examination fear, unaccustomed public appearance, etc.). They may be used for performance/situational anxiety or as adjuvant to BZDs. The role of β blockers in anxiety disorders is quite limited.

TREATMENT OF ANXIETY

Anxiety is a universal phenomenon, and to experience it in appropriate circumstances is the normal response. It may serve to enhance vigilance and drive. However, if anxiety symptoms are frequent and persist in a severe form, they are a cause of distress/suffering and markedly impair performance. Anxiety should be treated with drugs only when excessive and disabling in its own right.

The established drugs are BZDs which act quickly, while buspirone and SSRIs/SNRIs act only after chronic treatment. The BZDs should be used in the smallest possible dose. The dose has to be found out for each patient by titration with symptoms of anxiety. Acute anxiety states generally respond better than chronic anxiety. The drug should be withdrawn as soon as it is no longer required. However, when large doses have been used for longer periods, withdrawal should be gradual. Long-term use of BZDs is of questionable merit due to cognitive impairment and risk of dependence.

The usual practice is to give 1/2 to 2/3 of the daily dose at bed time to ensure good nightly

rest; the remaining is divided in 2–3 doses given at day time. Though the t½ of BZDs used in anxiety are longer, divided day time doses or SR tab. are required to avoid high peaks.

Buspirone is a nonsedating alternative to BZDs for chronic treatment of less severe forms of generalized anxiety. The SSRIs and SNRIs are now extensively used in most forms of chronic anxiety disorders, but are not good for acute anxiety. They produce a delayed but often gratifying response and can be combined with BZDs. The SSRIs are now drugs of choice for social anxiety, OCD, eating disorders and PTSD in which BZDs, though effective, carry abuse potential on long-term use.

Panic attacks are initially treated with a rapidly acting BZD (e.g. diazepam, alprazolam), but BZDs are not suitable for long-term therapy. SSRIs and duloxetine are the drugs of choice for sustained treatment, which in the initial few weeks may be supplemented by continuing the BZD. Valproate is an alternative to SSRIs. Phobic disorders are mostly treated by a SSRI, such as paroxetine, fluvoxamine or sertraline. In situational phobias, propranolol may be added as and when required. Gabapentin has been used as alternative to SSRI.

Patients with hypertension, peptic ulcer, ulcerative colitis, irritable bowel syndrome, gastroesophageal reflux, thyrotoxicosis, angina pectoris are often given low doses of BZD in addition to specific therapy, though anxiety may not be a prominent manifestation.

Fixed dose combination of tranquillizers with vitamins has been banned.

☞ PROBLEM DIRECTED STUDY

33.1 A businessman aged 35 years suffered loss and his employees left. He became very depressed and stopped taking interest in the business. Gradually he stopped going out and withdrew socially. He felt guilty, worthless and tired all the time, lost interest in pleasure and sex, stopped eating properly and had disturbed sleep. When he showed no sign of recovery even after 3 months, the family members consulted a doctor, who diagnosed him to be a case of major depression and prescribed—

Tab Sertraline 50 mg twice a day, and a multivitamin.

The family members brought him back after one week and complained that there was no improvement. On questioning the patient revealed that he felt more restless, had nausea, pain in upper abdomen, headache and no desire to eat.

(a) What could be the reason for no improvement in the depressive symptoms? Is the choice of drug inappropriate? Does the medication needs to be changed, dose increased or decreased? Should another drug be added at this stage?

(see Appendix-1 for solution)