

chapter 33

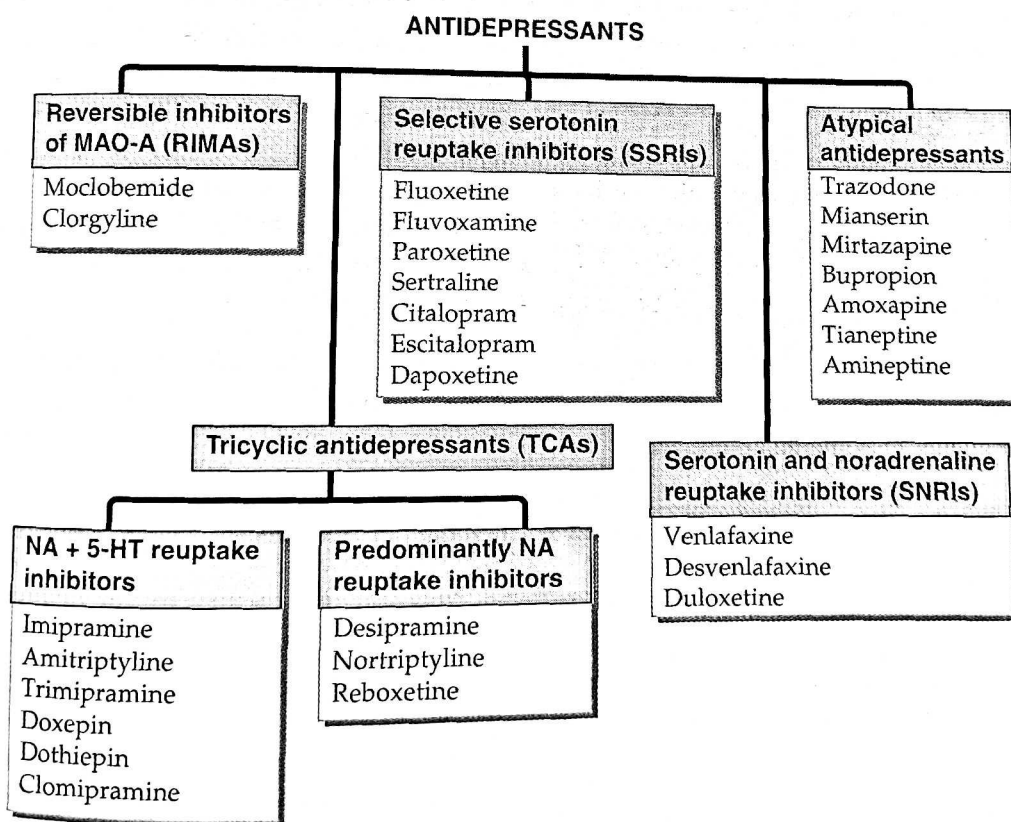
Drugs Used in Mental Illness: Antidepressant and Antianxiety Drugs

Major depression and mania are two extremes of *affective disorders* which refer to a pathological change in the 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 cyclic 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



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

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. A working classification has been presented above.

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.

Dopamine is degraded equally by both isoenzymes.

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

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

Distribution of MAO-A and MAO-B 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 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 interaction with foods and other drugs, they have become unpopular.

These MAO inhibitors frequently produce postural hypotension, restlessness, insomnia and interfere with sexual function (impotence, loss of libido, anorgasmia). More importantly they interact with many foods and drugs.

- **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.

Similar reaction can occur with cough and cold remedies which contain ephedrine or similar drugs, as well as with tricyclic antidepressants, SSRIs, SNRIs and levodopa. Hallucinations and atropine poisoning like symptoms occur with anticholinergics. Alcohol, sedative-antihistaminics,

barbiturates and opioids are potentiated; they may cause respiratory failure. Pethidine administered to MAO inhibited patients has produced fever, sweating, excitation, delirium, convulsions and respiratory depression. The mechanism of this interaction is:

MAO inhibitors retard hydrolysis of pethidine but not its demethylation. Thus, excess of *norpethidine* (normally a minor metabolite—see p. 503) is produced which has excitatory actions.

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

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 insignificant, and dietary restrictions are not required. Clinical trials have shown moclobemide to be an efficacious antidepressant, 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 an alternative 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 is also useful in social phobia.

TRICYCLIC ANTIDEPRESSANTS (TCAs)

Imipramine, an analogue of chlorpromazine (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 reuptake into neurones. A large

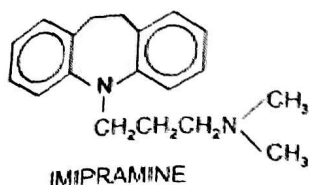
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number of congeners were soon added and these together are called *tricyclic antidepressants* (TCAs). In addition to uptake blockade, these early developed compounds have direct effects on adrenergic, cholinergic and histaminergic receptors, and are referred to as 'first generation antidepressants'.

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 and platelet membrane. They also interact with a variety of receptors viz. muscarinic, α adrenergic, histamine H_1 , 5-HT $_1$, 5-HT $_2$ and occasionally dopamine D $_2$. 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.

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 euphoric 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. Respiration is depressed in overdose only.

Mechanism of antidepressant 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 by increasing their availability in the synaptic cleft (see Fig. 33.1). Antidepressants, however, differ markedly in their selectivity and potency for different amines, and are classified on this basis. 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. Tentative conclusions drawn are:

- Inhibition of NA and 5-HT uptake is associated with antidepressant action.
- Inhibition of DA uptake correlates with stimulant action.

Monoaminergic hypothesis of depression

This hypothesis supposes that depression is caused by deficient noradrenergic and/or serotonergic transmission in the brain (mainly in cortical and limbic areas). This hypothesis is supported by the observation that reserpine depletes NA and 5-HT from brain and produces depression; and that all classes of antidepressants (TCAs, SNRIs, SSRIs, atypical) enhance

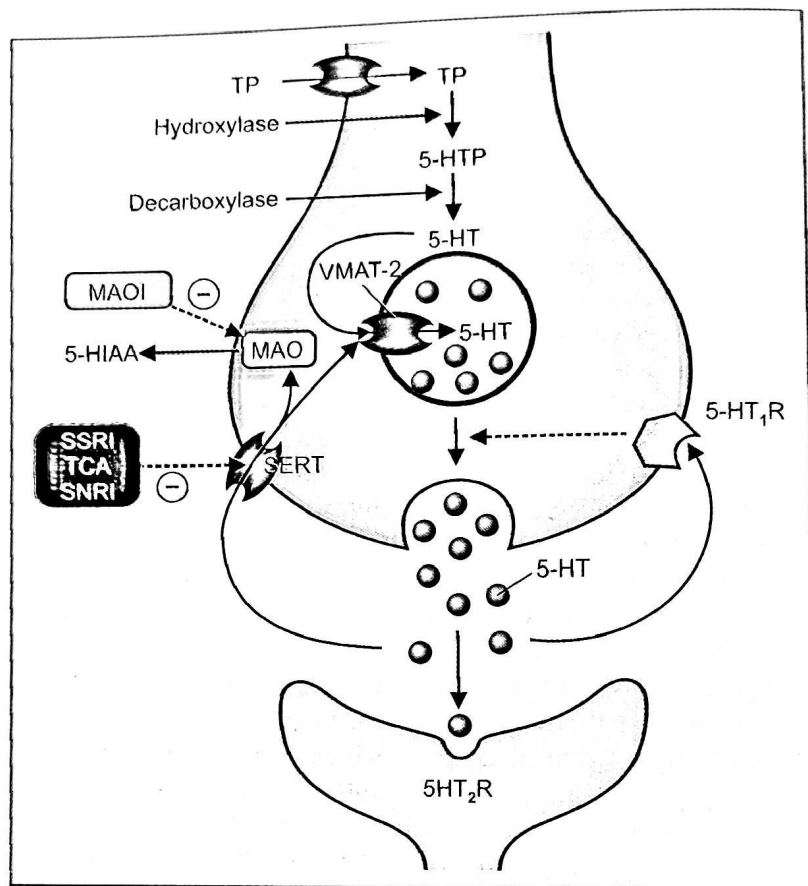


Fig. 33.1: Schematic depiction of cerebral serotonergic synapse and sites of action of tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors (MAOIs)

TP—Tryptophan; 5-HTP—5-Hydroxytryptophan; VMAT-2—Vesicular monoamine transporter-2; MAO—Monoamine oxidase; 5-HIAA—5-Hydroxy indole acetic acid; SERT—Serotonin transporter; 5-HT₁-R / 5-HT₂-R — 5-HT₁ and 5-HT₂ receptors.

synaptic availability of NA or 5-HT or both, in one way or the other. However, uptake blockade does not appear to be directly responsible for the antidepressant effect, because uptake blockade occurs quickly, while antidepressant effect develops over several weeks. Explanation offered for this discrepancy is—initially the presynaptic α_2 and 5-HT₁ 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 postsynaptic NA and/or 5-HT receptors as well as in amine turnover of brain, the net effect of which is enhanced noradrenergic and serotonergic transmission. Thus, uptake blockade appears to initiate a series of time-dependent changes that culminate in antidepressant effect.

Neurotrophic hypothesis of depression This hypothesis proposes that depression is associated with deficiency of brain derived neurotrophic factor (BDNF) and other nerve growth factors (NGFs) in brain areas regulating feelings, emotion, cognition, hedonia, behaviour, etc., and that

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NGFs act
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antidepressants promote elaboration of NGFs. The NGFs activate receptor tyrosine kinases (RTKs) and enhance axonal/dendritic growth, promote synaptic connection and improve neural plasticity. Reduction of BDNF levels and neural mass in the limbic areas has been demonstrated in depression, while prolonged antidepressant treatment has been found to elevate BDNF levels as well as enhance neurogenesis and synaptic connections.

The monoaminergic and neurotrophic hypotheses have been reconciled by contending that enhancement of monoaminergic transmission by prolonged antidepressant therapy indirectly promotes neurogenesis in critical brain areas by increasing BDNF production. These growth factors activate RTKs and initiate axonal/dendritic proliferation and formation of synaptic connections. The therapeutic response is delayed due to the time taken for neurogenesis to occur.

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.

The TCAs 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 become 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 in ECG. Arrhythmias occur in overdose mainly due to interference with intraventricular conduction. The NA potentiating + cholinergic 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.

Addiction to 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 tricyclic and related antidepressants. Metabolites are excreted in urine over 1–2 weeks. The plasma $t_{1/2}$ of amitriptyline, imipramine and doxepin range between 16–24 hours. The $t_{1/2}$ is longer for some of their active metabolites. Because of relatively long $t_{1/2}$ s, 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).

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.

Table 33.1: Comparative properties of antidepressants

Drug	Sedation	Anti-muscarinic	Hypotension	Cardiac arrhythmia	Seizure precipitation	Daily dose (mg)
<i>Tricyclic antidepressants (TCAs)</i>						
1. Imipramine	+	++	++	+++	++	50–200
2. Amitriptyline	+++	+++	+++	+++	++	50–200
3. Trimipramine	+++	++	++	+++	++	50–150
4. Doxepin	+++	++	++	+++	++	50–150
5. Clomipramine	++	++	+	+++	+++	50–150
6. Dothiepin (Dosulepin)	++	++	++	++	++	50–150
7. Nortriptyline	+	++	+	++	+	50–150
<i>Selective serotonin reuptake inhibitors (SSRIs)</i>						
1. Fluoxetine	±	—	—	—	±	20–40
2. Fluvoxamine	±	—	—	—	—	50–200
3. Paroxetine	+	+	—	—	—	20–50
4. Sertraline	—	—	—	—	—	50–150
5. Citalopram	—	±	—	+	—	20–40
6. Escitalopram	—	±	—	—	—	10–20
<i>Serotonin and noradrenaline reuptake inhibitors (SNRIs)</i>						
1. Venlafaxine	±	—	—	±	—	75–150
2. Duloxetine	+	++	—	—	—	30–80
<i>Atypical antidepressants</i>						
1. Trazodone	+++	—	+	±	—	50–200
2. Mianserin	++	+	++	+	++	30–100
3. Bupropion	—	—	—	—	+++	150–300
4. Amoxapine	+	+	++	++	++	100–300
5. Mirtazapine	+++	+	±	—	—	15–45

+ to +++ indicates increasing intensity of that action; — indicates absence of that action

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. Probably, these are cases of bipolar depression, the other pole being unmasked by the antidepressant.
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.
10. Rashes and jaundice due to hypersensitivity are rare. Mianserin is more hepatotoxic.

Acute poisoning Poisoning with TCAs is frequent; usually self-attempted for suicide, 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.

2. TCAs potentiate *CNS depressants*, including alcohol and antihistaminics.
3. *Phenytoin, phenylbutazone, aspirin and CPZ* can displace TCAs from protein binding sites and cause transient overdose symptoms.
4. *Phenobarbitone* competitively inhibits as well as induces imipramine metabolism. Carbamazepine and other enzyme inducers enhance metabolism of TCAs.
5. SSRIs inhibit metabolism of several drugs (*see later*) including TCAs—dangerous toxicity can occur if the two are given concurrently.
6. By their anticholinergic property, TCAs delay gastric emptying and retard their own as well as other drug's absorption.
7. *MAO inhibitors*—dangerous hypertensive crisis with excitement and hallucinations has occurred when given with TCAs.

Preparations of TCAs

1. Imipramine: DEPSONIL, ANTIDEP 25 mg tab, 75 mg SR cap.
2. Amitriptyline: AMLINE, TRYPTOMER, SAROTENA 10, 25, 75 mg tabs.
3. Trimipramine: SURMONTIL 10, 25 mg tab.
4. Doxepin: SPECTRA, DOXIN, DOXETAR 10, 25, 75 mg tab/cap.
5. Clomipramine: CLOFRANIL 10, 25, 50 mg tab, 75 mg SR tab. CLONIL, ANAFRANIL 10, 25 mg tab
6. Dothiepin (Dosulepin): PROTHIADEN, EXODEP 25, 50, 75 mg tab.
7. Nortriptyline: SENSIVAL, PRIMOX 25 mg tab.
8. Reboxetine: 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.
- 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 at therapeutic doses, as well as safety 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, panic, 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-HT₃ 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, 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 the 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.

Because of freedom from psychomotor and cognitive impairment, SSRIs are preferred over TCAs 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, it is the first SSRI to be introduced, and the longest acting. Its plasma $t_{1/2}$ 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 with 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.

FLUDAC 20 mg cap, 20 mg/5 ml susp., FLUNIL, FLUPAR, PRODAC 10, 20 mg cap.

Fluvoxamine It is a shorter-acting SSRI with a $t_{1/2}$ of 18 hours and no active metabolite. It has been specifically recommended for generalized anxiety disorder (GAD) and OCD.

Relatively more nausea, dyspepsia, flatulence, nervousness and discontinuation reactions have been reported with fluvoxamine.

Fluvoxamine SOREST 50, 100 mg tabs.

Paroxetine Another short acting SSRI ($t_{1/2}$ 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. Sedation and antimuscarinic effects are mild.

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 sertraline. Its plasma $t_{1/2}$ is 26 hours and it produces a still longer-lasting active metabolite.

SERENETA, SERLIN, SERTIL 50, 100 mg tabs., ZOSERT 25, 50, 100 mg tabs.

Citalopram This SSRI shares with sertraline a lower propensity to cause drug interactions. Its $t_{1/2}$ is 33 hours and no active metabolite is known. However, Q-T prolongation and 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 dysphoric disorder (PMDD).

FELIZ, CITADEP, CELICA 10, 20, 40 mg tabs.

Escitalopram It is the active S(+) enantiomer of citalopram, effective at half the dose, with similar properties, but Q-T prolongation is not reported. Currently, it is a popular SSRI for anxi-depressive disorders. Modest relief from menopausal hot flashes has been obtained in women who cannot take estrogens. Side effects are milder and safety is improved.

Dapoxetine This SSRI is being promoted particularly 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 of sexual distress due to early ejaculation. 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, PMDD, 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 flashes in menopausal syndrome, social 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.

VENLOR, SENTOSA 25, 37.5, 75 mg tabs., VENIZ-XR 37.5, 75, 150 mg ER caps.

2. Desvenlafaxine It is desmethylvenlafaxine, an active metabolite of venlafaxine with similar actions, uses, and side effects.

Dose: 50-100 mg/day;

D-VENIZ, NEWVEN, VENZ-OD 50, 100 mg tabs.

3. Duloxetine A newer SNRI similar to venlafaxine. It is mildly sedating with some antimuscarinic effects, but not an antihistaminic or α blocker. Side effects, including g.i. and sexual problems are milder, but agitation, insomnia and rise in BP can occur in few. Antidepressant efficacy is comparable to TCAs. Duloxetine is particularly indicated in diabetic and other types of neuropathic pain, fibromyalgia and stress urinary incontinence in women (because it increases urethral tone). It has also been used for maintenance therapy in panic disorder.

CYMBALTA 20, 30, 60 mg tab, DELOK, DULANE 20, 30, 40 mg caps.

ATYPICAL ANTIDEPRESSANTS

1. Trazodone It is the first atypical antidepressant; less efficiently blocks 5-HT uptake, but has prominent α adrenergic and weak 5-HT₂ antagonistic actions. However, its metabolite is a strong 5-HT₂ blocker. Antidepressant effect is modest. It is sedative but not anticholinergic, causes bradycardia rather than tachycardia, does not interfere with intracardiac conduction, therefore less prone to cause arrhythmia. Nausea is felt, especially in the beginning. 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. Trazodone is infrequently used now in depression; unless associated with insomnia.

TRAZODAC 25, 50 mg tab, TRAZONIL, TRAZALON 25, 50, 100 mg tabs.

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-HT₂, 5-HT_{1c} as well as H₁ 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.

TETRADEP, SERIDAC 10, 20, 30, mg tabs.

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-HT₁ receptor action is achieved by concurrent blockade of 5-HT₂ and 5-HT₃ 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 H₁ blocker and moderately strong sedative, but only mildly antimuscarinic and not antidopaminergic. Efficacy in mild as well as severe depression is reported to be comparable to TCAs. 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.

MIRT 15, 30, 45 mg tabs, MIRTAZ, MATIZ 15, 30 mg tab.

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 equivalent smoking abstinence and quitting rates as nicotine replacement, and higher than placebo. 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, while it can cause insomnia, agitation, dry mouth and nausea, but not sexual side effects. Seizures occur in overdose 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 except those with atypical features, or it may be added to a SSRI as an augmenting drug. It is not suitable for treatment of anxiety disorders. SMOQUIT 150 mg tab.

5. 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; may be used for patients with psychotic depression unresponsive to other antidepressants. Risk of extrapyramidal side effects is also there. Seizures (including status epilepticus) occur in its overdose. DEMOLOX 50, 100 mg tab.

6. 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 or insomnia, tremor and bodyache. Dose: 12.5 mg BD-TDS; STABLON 12.5 mg tab.

7. 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 tabs.

USES

1. Endogenous (major) depression: The aim of therapy is to relieve symptoms of depression and restore normal social behaviour. While antidepressants are not the answer to every grief, loss, set-back or 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 in depressive illness. Major depression clearly requires antidepressant medication and these drugs are of proven value, but 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, and past history of drug response, if available. 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 advantages. The only antidepressants clearly shown to be effective in juvenile depression are fluoxetine and sertraline. The TCAs are now used only 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 may succeed in nonresponsive cases. However, few patients fail any single antidepressant. In such cases, augmenting the initially selected drug (usually a SSRI) with an atypical antidepressant like bupropion or with valproate/lithium is an option. Another option is to add a second generation antipsychotic drug in refractory cases.

Psychotic depression needs to be treated with a combination of a SSRI with an atypical antipsychotic like olanzapine, aripiprazole or quetiapine. In case of bipolar depression, it is essential to combine the antidepressant (SSRI/SNRI/TCA/atypical) with valproate or lithium or lamotrigine to avoid the risk of switching over to mania.

After a depressive episode has been controlled, continued treatment at maintenance doses 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 effect of the antidepressant is developing, because no antidepressant has been clearly demonstrated to act fast enough to prevent suicide.

Moclobemide, a reversible inhibitor of MAO-A, is a relatively well tolerated option for mild-to-moderate depression and atypical depression. It is less risky than TCAs for patients with cardiovascular risk factors.

2. **Obsessive-compulsive disorder (OCD):** The SSRIs, particularly fluoxetine, are the drugs of choice due to better patient acceptability. TCAs, especially clomipramine, are also highly effective in OCD. Over 50% patients obtain significant improvement in OCD rating scale, but longer response time of 2–3 months and relatively higher doses are generally needed than for depression. 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 and SNRIs, exert a delayed but sustained beneficial effect in many patients of *social anxiety* and *generalized anxiety disorder*. They may be used along with a short course of BZDs, which act rapidly, to cover exacerbations. They have also proven helpful in *phobic disorders*, long term treatment of *panic attacks* and in *post-traumatic stress disorder (PTSD)*. Mood swings and hot flashes in menopausal women may be partly relieved by certain SSRIs when HRT is contraindicated.
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 the first line drug for diabetic neuropathy, fibromyalgia, etc. Other drugs useful in neuropathic pain are pregabalin and 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. **Smoking cessation:** Only bupropion is approved as an aid to smoking cessation, though some TCAs have also been found to reduce craving, albeit inconsistently. In controlled trials, quitting rates were significantly higher in bupropion recipients, than among placebo recipients. Abstinent subjects on bupropion experienced fewer distress symptoms and mood swings. Benefits were comparable to those with nicotine gum, and the two were additive.
8. **Enuresis:** In children above 5 years, imipramine 25 mg at bedtime is effective, but bed wetting may again start when the drug is stopped. Elderly subjects with bed wetting have also benefited.
9. **Migraine:** Amitriptyline has some prophylactic value, especially in patients with mixed headaches.
10. **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. Somatic symptoms like anorexia, breathlessness, palpitation, paresthesias, etc. often accompany. 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 (PTSD) 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.

BENZODIAZEPINES

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

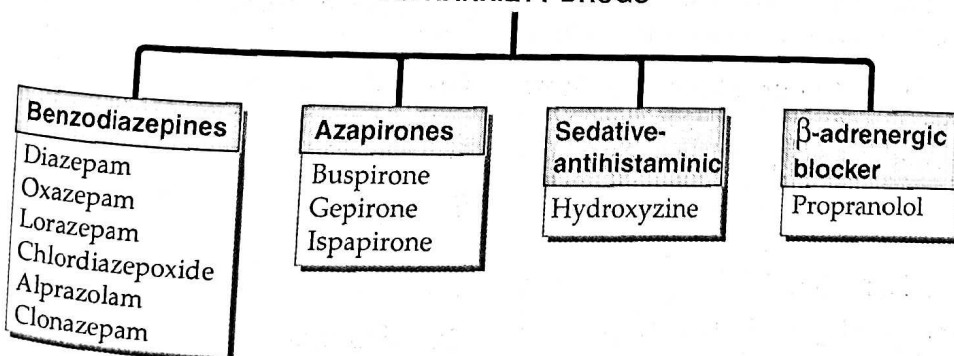
Some members have a slow and prolonged action, relieve anxiety at low doses without producing significant CNS depression. They have a selective taming effect on aggressive animals and suppress induced aggression. They also suppress the performance impairing effect of punishment. In contrast to barbiturates, 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,
- Benzodiazepines are presently one of the most 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.

ANTIANXIETY DRUGS



In addition to the above drugs, antidepressants, especially the SSRIs and SNRIs are effective in OCD, phobias, panic, PTSD and severe generalized anxiety disorder (GAD).

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 BZD medication. 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 $t_{1/2}$ 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 $t_{1/2}$ 1 hr, elimination phase $t_{1/2}$ 20–30 hours). The biological effect $t_{1/2}$ is still longer due to production of active metabolites. It is preferred in acute panic states and anxiety associated with organic disease.

Daily dose: 5–20 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 $t_{1/2}$ 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 $t_{1/2}$ 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. Lorazepam 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 $t_{1/2}$ 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.

6. Clonazepam This high potency BZD has prominent anticonvulsant activity and is described in Ch 30. It is also highly effective

for urgent treatment of acute panic attack. In patients with recurrent panic disorder, a SSRI should be started concurrently and continued for sustained benefit while the BZD is gradually withdrawn. Patients with severe GAD may also be treated with clonazepam, but use should be limited to short term, till the maintenance drug (SSRI/SNRI) has taken effect.

Dose: 0.5–1.0 mg OD–TDS;

CLONAPAX, RIVOTRIL, LONAZEP 0.5, 1.0, 2.0 mg tabs.

OTHER ANTIANXIETY DRUGS

Buspirone It is the first azapirone, a class of selective 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 dependence; no rebound anxiety or withdrawal symptoms on stoppage.
- Does not suppress BZD or barbiturate withdrawal syndrome.
- Has no muscle relaxant or anticonvulsant activity.

Buspirone relieves generalized anxiety of mild-to-moderate intensity, but is ineffective in severe cases and in those showing panic reaction. Buspirone, in relatively higher doses, has also been used to augment the therapeutic effect of SSRIs in OCD. The beneficial effect in anxiety develops slowly; maximum benefit may be delayed up to 2–3 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-HT₂ receptors may occur.

Buspirone is rapidly absorbed; undergoes extensive first pass metabolism; (bioavailability <5%), one metabolite is active and excretion

occurs both in urine and faeces; t_{1/2} is 2–3.5 hrs. Side effects are minor: dizziness, nausea, abdominal discomfort, 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 H₁ 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 somatic 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 for acute anxiety 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 larger 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 $t_{1/2}$ 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, but is not suitable for acute cases due to delayed effect. The SSRIs and SNRIs are now extensively used in most forms of chronic anxiety disorders.

However, they 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 long term treatment of GAD, social anxiety, OCD, eating disorders and PTSD.

Panic attacks are initially treated with a rapidly acting BZD (e.g. diazepam, alprazolam, or i.m. lorazepam), but BZDs are not suitable for maintenance therapy. SSRIs, venlafaxine and duloxetine are the drugs of choice for maintenance 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 tranquilizers 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)