DRUG TREATMENT IN PSYCHIATRY

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Modern drug treatment in psychiatry dates back only ten years when Delay and Deniker in France introduced Chlorpromazine. This followed the observation of the anaesthetists that patients under the influence of this drug, though fully conscious of the surroundings, became indifferent to the surgical procedure. In 1952, Swiss scientists analysed and synthesised Reserpine, a drug which had been used for centuries by Indian physicians for the relief of high blood pressure and insanity. Berber introduced Meprobamate in 1954 and Kuhn observed the euphoriant effect of Imipramine in spite of the drug's structural resemblance to Chlorpromazine. In 1957 Kline reported his observation that tuberculous patients put in Iproniazid, a substance related to I.N.A.H., became very elated irrespective of their clinical condition. It will be noted that these break-throughs were due to keen clinical observations. The physician, by the bed-side, and not the research worker in the laboratory, deserved most of the credit. The advent of these drugs created a new interest in the mental patient. The 'therapeutic frustration' was dissipating and the main symptoms of disease were being controlled. The patient could be treated at home, while at work and without the 'stigma' of hospitalization. Vast reforms in the mental hospital followed, chief among which one could mention the 'open ward system', the general hospital psychiatric unit, and the rehabilitation and occupation centres. The follow-up out patient clinic, the Psychiatric Social Workers, and the participation of the General Practitioner made Community Care a working possibility.

CLASSIFICATION OF PSYCHIATRIC DRUGS

"The burgeoning flood of reports on drugs almost defies analysis; the physician, unfortunately, has difficulty finding adequate guide lines and objective information and the only good method to date for identifying a new drug type is skilled clinical observation." Wortis Jean Delay has classified psychiatric drugs into: —

GROUP I. DEPRESSORS OF MENTAL ACTIVITY (PSYCHOLEPTICS)
- a) Depressors of Vigilance (Hypnotics)
- b) Depressors of Affect (Tranquillizers)

GROUP II. STIMULANTS OF MENTAL ACTIVITY (PSYCHO-ANALEPTICS)
- a) Stimulants of Vigilance (Dexamphetamine)
- b) Stimulants of Affect (Anti-depressants)

GROUP III. DISTURBERS OF MENTAL ACTIVITY (PSYCHO-DYSLEPTICS)
Hallucinogenic Drugs.

HYPNOTICS

Hypnotics may be Barbiturates or non-Barbiturates. The former are the most commonly used drugs in psychiatry. When prescribing a barbiturate preparation the physician should keep in mind: —

i) The real danger of addiction, and one uses them for the shortest possible time.

ii) The real danger of suicide amongst depressed patients, and one should trust them in the care of a responsible relative after explaining the reality of the danger.

iii) Side effects like rashes, confusional states, vertigoes, peripheral tremors, ataxia and double vision are all rare, but one takes the precaution of advising the patient not to drive on the first few days of taking the drugs.

iv) In the elderly the barbiturates may stimulate instead of sedate and can give rise to a confusional state. A preparation containing Chloral is usually preferred.

v) The effect of the barbiturate is often enhanced by simultaneous administration of Phenothiazines, Antidepressants and Alcohol.

TRANQUILLIZERS

MINOR TRANQUILLIZERS

Chlordiazepoxide (Librium) and Meprobamate (Equanil) are the two most widely used drugs of this group. Chlordiazepoxide in doses of 10 to 20 mgms t.d.s. has been used in Anxiety states, Obsessive Compulsive Neurosis and Psycho-Somatic disorders. It has claimed a place in the attenuation of alcoholic craving. It is a very safe drug and the reported side effects of ataxia and rage reaction have been encountered very rarely. Its use with antidepressants has been favourably commented upon especially in the hysterical type of depression. Valium (2 & 5 mgm tablets) has recently been introduced but the effects are quite similar to Chlordiazepoxide. Meprobamate (Miltown, Equanil) is a muscle relaxant which has had explosive vogue in the U.S.A. following its introduction. Various side effects like rashes, purpura and bone marrow depression have been reported but they must be extremely rare. The dose is in the region of 400 mgm, t.d.s. Both these drugs may lead to habituation.

MAJOR TRANQUILLIZERS

i) The Rauwolfia Alkaloid Group

ii) The Phenothiazine Group

Piperazine Group (Trifluoperazine-Stelazine)
Promazine Group (Chlorpromazine-Largactil, Thioridazine-Melleril, Promazine-Sparine).

iii) The Butyro-phenon Group

Haloperidol-Serenace.

The Rauwolfia Alkaloids (Reserpine 1 to 4 mgm tabs) have been superseded by the phenothiazines.

The Phenothiazines are very widely used drugs. They do not cure diseases but they reduce agitation and tension. Probably they diminish the 'hold' which delusions and hallucinations have on the patient. Possibly they remove apathy and make the patient more cooperative. Their use is mainly confined to the psychoses. Chlorpromazine (Largactil) is the drug of choice in restless and aggressive patients because of its added soporific or sedative effect. It is the best studied drug and has withstood the test of time. It calms the patient while leaving him fully conscious and

thus claims the name 'tranquillizer'. Where there is agitation, whether schizophrenic, depression or organic psychotic state, Chlorpromazine has been found useful. Dosage ranges between 25 to 200 mgms t.d.s. Promazine (Sparine) in equivalent dosage is probably milder and has fewer side effects and is indicated in the elderly psychotic Thioridazine (Melleril) in the same scale of doses has little effect on blood pressure and is suitable for outpatient practice. In fact one often uses them quite interchangeably. Whenever we use these drugs we take the following precautions:

i) Check the blood pressure especially on initiation of treatment.

ii) Routine W.B.C. every 15 days and emphatic warning to the patient and his relatives to report any fever or sore throat.

iii) to report at once in case of abdominal pain and icterus.

Trifluoperazine (Stelazine) in doses of 1 to 5 mgm t.d.s. is a very effective and potent phenothiazine and is probably the drug of choice in the withdrawn apathetic schizophrenic and the Paranoid type. In actual fact because most of its side effects are not serious and all are reversible it is the first to be prescribed in all forms of Schizophrenias in the young. It has a high failure rate and if there is no response in ten days of adequate dosage one thinks of alternative therapy. Thiopropazate (Dartal) in 5 to 10 mgms t.d.s. has the same spectrum of activity but is reputed to work satisfactorily in Huntington's Chorea and Obsessive Compulsive Neurosis.

Haloperidol (Serenace) in doses of 1.5 mgm to 10 mgm/day is mostly used in Manias but it has proved its worth in the Schizophrenias, diminishing the delusions and hallucinations.

When prescribing the above drugs one should anticipate extra-pyramidal syndromes and one may give anti-parkinsonian drugs beforehand.

Side Effects of Tranquillisers

On the whole the tranquillizers are relatively safe drugs, but like all potent drugs they carry therapeutic hazards which make the physician measure up the benefit from the drugs as against the risks. In spite of the side effects the Tranqillizers have proved themselves to be effective therapeutic devices to combat the miseries of mental illness.

The chief side effects can be grouped into three categories: —

i) Those that are due to idiosyncrasy and independent of dosage:

a) skin manifestations—papular rashes, erythemas, desquamation, light sensitization.

b) blood dyscrasias, chiefly leukopenia which might lead to agranulocytosis.

c) liver damage in the form of ball thrombi in the bile canaliculi leading to obstructive jaundice.

ii) Those which depend on dosage and/or the physiological action of the drug:

a) Autonomic disturbances—dryness of mouth, micturition difficulties, visual blurring, constipation, sexual difficulties and hypotension.

b) Extrapyramidal Syndromes—akinesia, dyskinesia, akathisia, Parkinsonism.

iii) Alleged effects on the foetus in animals.

As a rule, the more potent the phenothiazine the commoner and more persis-

tent are the extrapyramidal effects but the less the autonomic or blood or liver damage, and vice-versa. Thus while Trifluoperazine (Stelazine) if given in adequate dosage will invariably produce extrapyramidal symptoms, but will not produce hypotension or leukopenia, Promazine (Sparine) will, though rarely, produce hypotension and marrow depression, but only with massive doses will it produce extrapyramidal effects.

1) Agranulocytosis:

This is the most serious complication estimated as occurring in 1 every 100 cases and carrying a 36% mortality. It is an extremely rare complication in our practice, never encountered with Trifluoperazine. It is said to be more frequent in women beyond the age of 40 and manifests itself in the 40th to the 70th day of treatment. It may occur as a progressive leukopenia (and a white count of less than 4000 calls for revision of treatment) or as an 'agranulocytosis out of the blue'.

2) Obstuctive jaundice:

Occurs in 1 to 2 per thousand of cases on Chlorpromazine or Promazine after the first month of treatment and usually clears up spontaneously in 4 weeks. It is heralded by chills, fever, abdominal pain, persistent nausea with occasional vomiting, and pruritus. In hospital practice this complication has been seen only rarely.

3) Hypotension:

Likely to occur with large doses of the weaker phenothiazines or with parenteral administration of the drug. The patient feels dizzy and may collapse. This is particularly dangerous in the elderly, as a cerebral or coronary thrombosis might be precipitated. The patient should be nursed flat in bed but may have to be given a Noradrenaline-Saline drip. Contrary to previous belief, Mephentermine in large doses is found effective.

4) Parkinsonism and Extrapyramidal Syndromes:

i) Akinesia: The patient is aware of feeling very tired whatever he does. He complains of weakness and muscular fatigue in a limb used for any activity.

ii) Dyskinesia: This takes the form of torsion spasms, myoclonic twitchings, torticollis, speech and swallowing defects and involuntary protrusion of the tongue. Usually a transitory phenomenon appearing in the first 5 days of treatment and responds to lowering of dose.

iii) Akathisia: the patient complains of jitters, and is compelled to pace the floor, smack his tongue and perform all sorts of bizarre chewing movements. It is common in females in the first 15 days of treatment. Antiparkinsonian drugs will help.

iv) Parkinsonism: The usual triad of cog wheel rigidity, tremors and autonomic disturbances (salivation, oculogyric spasm and difficulty in accomodation) occur in the elderly group (over 50) and respond well to antiparkinson drugs (Artane, Disipal, Akineton) In patients over 60 iatrogenic parkinsonism may be very resistant to any form of treatment. With the strong Phenothiazines (Trifluoperazine) and also with Haloperidol it may be forestalled by initiating a combination of antiparkinsonian drugs together with the Phenothiazines from the start.

5) Effects on Human Foetus

These are deduced from animal experiments. Reserpine and Chlorpromazine can cause foetal death in experimental animals and can significantly affect birth weight. Chlorpromazine can retard embryonic growth in salamanders; it depresses both foetal and maternal brain oxygen in gravid guinea pigs. All these suggest caution in the use of tranquillizers during pregnancy. As a rule one uses drugs which are compatible with safety and which yield the best therapeutic results. One realizes that in pregnancy the risks to be reckoned with include the vulnerability of the foetus and one cannot condemn too strongly the use of any drugs unless there is adequate indication; but if there is (and a schizophrenic or depressive episode can be really serious) one should not hesitate to take this calculated risk.

STIMULANTS

Amphetamines and Allied Substances

Dexamphetamine Sulphate (Dexedrine) in 5 mgm tables is widely used as a stimulant and an appetitie suppressant. Often it is combined with a barbiturate (Drinamyl or Purple Hearts) and as such it is widely used. Recently it was found that large quantities of the drug were being consumed by youngsters in search of excitement or an easy way out of the problems of life. It is a drug of addiction and its prolonged use gives a clinical picture very much like that of paranoid schizophrenia (ideas of reference, paranoid ideas, auditory hallucinations and facile affect.) Dexedrine should be used under medical supervision as a short term treatment in transitory depressive reactions. When prescribed to inadequate persons the danger of psychological dependence should be kept in mind. In children Dexamphetamine is a sedative and has been used successfully in behaviour disturbances. In enuresis it is said to help.

Antidepressants

Antidepressants fall into two groups:

(i) Iminodibenzyl group — Imipramine (Tofranil) 25mgm. tabs.
Amitriptyline (Tryptizol, Laroxyl, Saroten) 25mgm.
Nortriptyline (Aventyl, Allegron) 25 mgm. tabs.

(ii) Monamino-oxidase-inhibitor group—
Nialamide (Niamid) 25mgm.
Phenelzine (Nardil) 15mgm.
Isocarboxazid (Marplan).
Tranylcypromine (Parnate).

It is usual (though admittedly very difficult) to divide the depressive syndrome into Endogenous and Neurotic depression. Endogenous group (which includes the M.D.P. and Agitated Depression) is characterised by disturbances in *mood* (depression which is persistent, usually unprovoked, unmodified by changes in the environment), *behaviour* (retardation or agitation, insomnia, loss of appetite and refusal to eat, somatic effects like bradycardia, constipation and fatigue), and *thought* (hypochondriasis, ruminations, ideas of unworthiness, suicidal ideas, and phobias.)

Quite characteristic of endogenous depression are the following features: past history of mood swings or frank manic episode; depression worse in the morning with slight improvement towards the afternoon; late insomnia.

The Neurotic group is said to have the following features: good previous personality which has broken down under stress; fluctuation in mood; preoccupation with the lack of emotional control; cannot fall off to sleep; very irritable, with a tendency to exaggerate the symptoms. Probably the drugs of Iminodibenzyl group (Imipramine, Amitriptyline) are the more effective in the endogenous type of depression, while the Monamino-oxidase inhibitor type are to be preferred in the neurotic type. These drugs are believed to be "mood lifters" as they relieve the depression, but the agitation is not well controlled. For this reason they are very often combined with a phenothiazine.

a) When using the Iminodibenzyl group (Tofranil or Amitriptyline) we keep in mind: —

(i) Start with small dosage and work smartly up to a maximum e.g. 25 mgm t.d.s. up to 50 mgm t.d.s. within a week (if one starts with maximum dosage the patient will not cooperate owing to side effects).

(ii) These drugs take 2 to 3 weeks to exert maximum effect and if the patient is actively suicidal this point will work in favour of hospitalization or the more rapidly acting Electric-Convulsive Therapy.

(iii) These drugs do not cure the depression but alleviate symptoms — early withdrawal or sudden stoppage of the drugs by the patient may precipitate an acute psychotic episode.

(iv) Imipramine works well in M.D.P. but in 30% of cases the patients are pushed into the manic phase.

(v) Always check for urinary obstruction (prostatism) or glaucoma because these two conditions constitute the only contraindication at outset.

(vi) The two groups of drugs are never to be used together (i.e. never use Imipramine with any of the M.A.O. inhibitor drugs).

(vii) If these drugs are taken for suicidal purposes, they are highly toxic and so far no antidote is known, therefore one must never trust a suicidal patient with them but they should be entrusted to the care of a responsible relative.

Amitriptyline is said to have caused paralytic ileus in a few cases. On starting treatment the patient will often complain of drowsiness (especially with Amitriptyline), some dizziness, dryness of mouth, constipation, difficulty in starting micturition, blurring of vision, tachycardia, hot flushes and heavy sweating.

b) When using the M.A.O. inhibitor group of drugs one should remember:

(i) These drugs have been subjected to a torrential amount of criticism and one hesitates to use them until one hears more about their effects and side effects (e.g. the drugs Catron, Monase and Drazine have been withdrawn from the open market for further study owing to alleged toxicity).

(ii) Maximum effect is reached within 2 to 3 weeks, a fact which should be borne in mind in dealing with suicidal patients.

(iii) Never couple them with drugs of the Imipramine series (3 weeks must pass before a patient who was having these drugs can be safely put on Imipramine or Amitriptyline).

(iv) Patients on these drugs should be warned that they are not to have any drugs of the pethidine, morphine group and they are to tell the doctor before 'any injections'.

(v) Sympatheticomimetic amines like adrenaline, ephedrine, caffeine, benzedrine may have untoward reactions owing to blod pressure changes.

(vi) Serious side effects may follow the use of these drugs—toxic hepatitis occurring on the 30th to 40th day with 20 to 30% mortality has been reported. There is considerable controversy at the moment. Rees says that toxic hepatitis in U.K. never occurred with Nialamid or Isocarboxazid. Definitely there are no cases reported with Tranylcypromine. Sargant believes that the hepatitis is in fact due to viral infection and the drugs have nothing to do with it or if they do they just lower the patient's resistance.

(vii) Blood pressure changes and headaches like those due to subarachnoid haemorrhages have been reported with Tranylcypromine (Parnate), especially if cheese containing tyramine is ingested (Camembert and Stilton cheese).

THE PSYCHODYSLEPTICS

We have no experience with these drugs like Lysergic acid, Mescal, Phencyclidine, etc. They produce hallucinations, skinesia, distort the sense of time, remove the customary inhibitions in respect of speech, fantasy, feeling and action or may induce a state of perplexity or confusion.

Phencyclidine (Sernyl) has been used in the management of Obsessive Compulsive Neurosis and mixed neurotic conditions; it is alleged that Lysergic Acid Diethylamide deepens insight by the patient into his illness during therapeutic sessions. Psilocybine has been utilised for diagnostic purposes.

CONCLUSION

There is no doubt that the advent of psychotherapeutic drugs has marked a step forward for the mental patient. As soon as they appeared the ever increasing hospital admission and overcrowding have been halted and the trend reversed. The patient came to expect control of symptoms while still in the community and even if admitted his stay in hospital became shorter. We notice that mental ill-health became very much the concern of the research worker as well as the legislator. There is hope that in the future the psychoses as we know them today will be entirely the business of the general practitioner, and the mental hospital will tackle the thorny problem of the psychopath, the juvenile delinquent, the addict and the degenerative conditions like the senile dementias and even senescence itself. However that may be, these drugs are potentially dangerous and should be accorded the respect we usually attach to potent therapeutic agents. At a symposium in New York marking the 10th anniversary of the coming of the tranquillizers, Dr. F. Ayd estimated that 200 million people around the globe have been given tranquillizers. In the U.S.A. tranquillizers compete with antibiotics and barbiturates as the fastest selling pharmaceutical compound. We should however be very much on the alert lest "the milder tranquillizers are used sort of like vitamins. If the doctor can't quite pin a person's problem down, he's apt to write a tranquillizer prescription." Nothing could do greater harm to psychiatry than this attitude, rightly condemned by Dr. Greiner of Bailer University,