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Current status of imipramine

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THE CURRENT STATUS OF IMIPRAMINE

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I. INTRODUCTION

The introduction of the phenothiazine tranquilizer chlorpromazine in 1954 marked the advent of a new era in the medical treatment of emotional illnesses. The phenothiazines became the first psychopharmacologic agents to show significant value in the field of psychiatry. These drugs have produced a vast decline in the patient census in our mental hospitals which in recent years have become transformed into wards in general hospitals and mental therapy centers.

The latest contribution to the rapidly expanding family of psychoactive drugs are the antidepresants, the most effective of which are analogs of the phenothiazines. The wide acceptance of chlorpromazine led to increased investigation of similar compounds, and, in 1958, imipramine (Tofranil), an isostere of the phenothiazines, was introduced as an antidepressant agent.

Imipramine is not a phenothiazine, although it is closely related chemically and has many similar effects. It was chosen as the subject of this thesis by virtue of its unique history, peculiar relationship to the phenothiazines, and effectiveness in the treatment of depression. It is the purpose of this thesis to present a complete, concise, and current evaluation of the pharmacological status of imipramine and its present application in the treatment of depression by the psychiatrist and the

family physician. The role of the family physician has changed considerably with the rapid progress in the field of psychopharmacology, and the drugs which are now available have made him an important member of the team in the treatment of emotional illnesses.(31)

II. HISTORY

Iminodibenzyl is the parent compound of imipramine and was synthesized in 1899. It received no further attention or investigation until 1948, when Geigy Chemical Laboratories in Switzerland became interested in the compound. At this time it was used as a starting chemical in a project involving synthesis of basically substituted heterocyclic compounds in a search for new drugs with potential sedative, analgesic, and anti-Parkinson activity. It was a continuation project of earlier work on antihistaminics.[10,15,19,25]

This project gained importance when chlorpromazine, a phenothiazine compound, was found to be effective in the treatment of psychiatric disorders, since the iminodibenzyl derivatives being studied were quite similar to the phenothiazines. G 22355 (Imipramine) was one of these derivatives and did display special therapeutic value in the treatment of depression, a condition in which the phenothiazines did not appear to be of any value. In 1958, imipramine was introduced in Europe under the tradename of Tofranil (Geigy).

Many articles have appeared in the world literature on imipramine since 1958 in regard to differences in therapeutic effect yet close structural resemblance to phenothiazine drugs. Many authors have speculated as to whether the antidepressant

action of imipramine is a similar mode of action to that of the phenothiazines or some unique indirect effect. At the present time only theories have been put forth in regard to mode of action as linked with similar compounds, and the activity of imipramine remains an enigma.

Imipramine appears to have stood the test of time in the therapy of depression, quite unlike many of the monamine oxidase inhibitors which were taken off the market due to hazzardous side effects. It has substantially displaced the CNS stimulants (amphetamines, methylphenidate, etc.), and reduced the need for electroshock therapy (E.S.T.) in the modern treatment of depression.[1,3,11]

III. CHEMISTRY

(a) General: Imipramine hydrochloride is a white, crystalline substance with a molecular weight of 316.5 and a melting point of 171-174°C. It is freely soluble in water, fairly soluble in acetone or alcohol, and nearly insoluble in ether.

Imipramine is an iminodibenzyl derivative and a member of the dibenzazepine group of antidepressants.[6] The drug is chemically designated as 5(3-dimethylaminopropyl)-10, 11-dihydro-5H-dibenz(b,f) azepine hydrochloride appearing structurally as shown in Figure 1.[10]

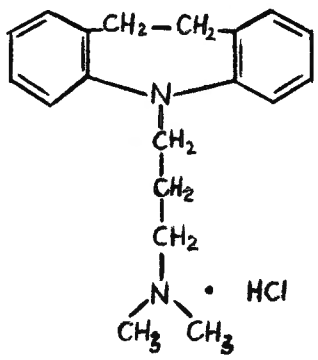

Fig. 1. Imipramine hydrochloride

(b) Structural Comparison with Phenothiazines: As previously described, the chemical structures of the phenothiazines (promazine, chlorpromazine, etc.) and imipramine are quite similar. Since the therapeutic activity of these two groups of drugs are quite different, much investigation

has evolved in the realm of structure-activity relationships. From a structural standpoint the similarities between the phenothiazines, especially promazine, and imipramine are obvious as shown in Figure 2. In comparing the formulas of

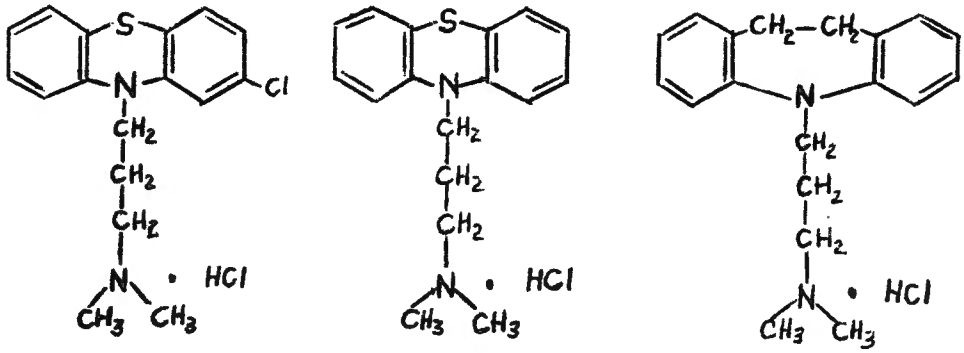

Figure 2. Chlorpromaxine (left), Promazine, and Imipramine (right).

these drugs, it is apparent that the side chains are identical. Imipramine is distinguished by the presence of the iminodibenzyl ring structure with a CH_2-CH_2 bond instead of a sulfur atom in the middle ring. In a chemical sense, the phenothiazine ring system with its sulfur atom allows conjugation of the benzene rings to extend over the bridge; whereas, imipramine, with its CH_2-CH_2 bond, does not permit conjugation.[10] It is to be noted also that promazine is a spacially symmetrical molecule, while imipramine is asymmetrical due to twisting of the benzene rings against one another as can be demonstrated with the use of molecular models.[10] Therefore, it seems only logical that these structural differences must account for the differences in the

biological activity of these drugs, but at the present time the mechanisms involved remain to be elucidated. Claims are made that certain phenothiazine derivatives possess weak antidepressant qualities and perhaps future investigation will establish the exact mode of action involved.

(c) Amitriptyline Structurally Related to Imipramine:

The success enjoyed by imipramine stimulated much research and investigation in the dibenzazepine-related compounds. As a result of this interest, amitriptyline was synthesized and found to be a useful agent in the treatment of depression. It is chemically a dibenzocycloheptadiene derivative but classified by standard pharmacology texts as a dibenzazepine antidepressant due to its close chemical relationship.[6] The molecule is identical to imipramine except the side chain is attached by a double bond to the iminodibenzyl type ring structure as shown in Figure 3.

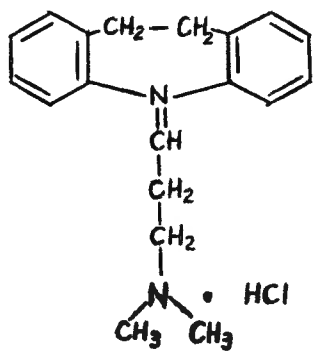

Figure 3. Amitriptyline

(d) Desmethylimipramine and Desmethylamitriptyline: The most active metabolites of imipramine and amitriptyline were synthesized by N-demethylation of the parent compounds in search of antidepressant activity with a more rapid onset of action.[6] These compounds are chemically desmethylimipramine and desmethylamitriptypline, with generic names of desipramine and nortriptyline respectively: their structures are illustrated in Figure 4.

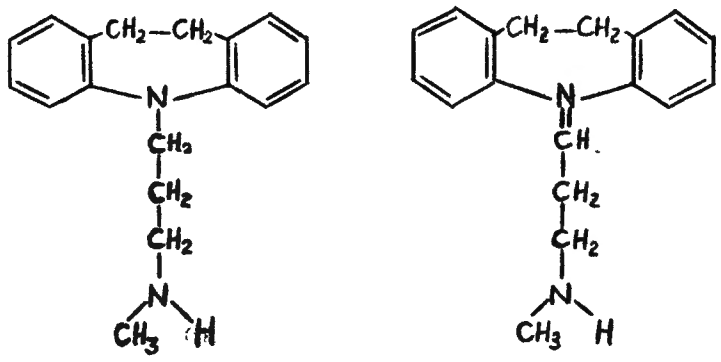

Figure 4. Desmethylimipramine (left) and Desmethylamitriptyline (right).

It is pharmacologically quite interesting that demethylation of certain non-analeptic and sedative tertiary amines have produced antidepressant compounds. Although both these drugs have antidepressant activity similar to the parent compounds, it has not been clearly demonstrated that they are superior in any respect.[5,6,13,22]

IV. MECHANISM OF ACTION

The mechanism of action of imipramine remains a mystery despite the various complex theories thus far advanced on the subject. At the present time, it is concluded by most investigators that imipramine is not a monamine oxidase inhibitor (MAOI) nor a phenothiazine tranquilizer with regard to mode of action. Both of these groups bear marked similarity in respect to such properties as chemical structure, therapeutic responses, activity, etc.; however, it is established that imipramine is a unique psychotropic drug.

Investigators, including Sigg, Stein and Seifter, Brodie, Angyal, and others[19] have presented hypotheses to explain the mechanism of action for the antidepressant action of imipramine; essentially these are as follows:

(1) Adrenergic Sensitization (Sigg): This hypothesis concludes that the antidepressant action of imipramine is the result of sensitization of central adrenergic synapses. This effect is thought to be localized mainly in the activating reticular formation. Similar theories concerned with an increase in excitability of adrenergic structures have corroborated this theory; it may also serve to elucidate the antidepressant effects of other drugs such as the sympathomimetic amines (i.e., amphetamine, methylphenidate, etc.) also used in

treating depressive states. In addition it appears that EEG studies lend some support to this hypothesis.(19,25)

(2) Imipramine-Serotonin Antagonism (Brodie): This hypothesis suggests that an antagonism between imipramine and serotonin in the central nervous system is the mechanism for the antidepressant action of imipramine. It is based on the central antireserpine effect of imipramine and the concept that serotonin is the mediator of reserpine's sedative action. In essence, imipramine inhibits serotonin thereby releasing central inhibition and abolishing depression.(19)

These two theories are at present the most widely accepted, and work done by most investigators serves to support them. Although they appear different in regard to mediator mechanisms, their positions are brought closer together by the assumption that the antidepressant action of imipramine is based on an equilibrium shift between the central adrenergic and serotoninergic systems resulting in a predominance of the former.(19,25)

Other authors have expressed the opinion that imipramine's antidepressant effect may not be related so much to the direct action on the reticular activating system but to an indirect influence on the structures which inhibit the activation. It is felt that psychic depression is functionally correlated to

an increased activity of separate portions of the limbic system, and the action of imipramine results in the suppresion of this activity. (19)

Imipramine's mechanism of action, although quite diverse and complex, is believed to be a result of a direct or indirect action upon the activating reticular system. This is in sharp contrast to the action of the monamine oxidase inhibitors which depend upon the accumulation of noradrenalin and serotonin in the brain for their antidepressant effect. Imipramine does not have MAOI activity.(6,17,19,25,30)

In conclusion, one must keep in mind the possibility that imipramine's antidepressant action may be the result of a combination of the mechanisms discussed.

V. EFFECT ON ORGAN SYSTEMS

The effects of imipramine on the various organ systems will be largely confined to the human subject. Although the literature is filled with the results of much elaborate experimentation with laboratory animals, much of the material is contradictory and for expedience sake will not be included here.

(a) Nervous System: Imipramine in very high dosage displays the properties of a weak phenothiazine on the central nervous system.(25) It possesses weak tranquilizing action, etc., but does not control hyperkinesis and produces marked euphoria in contrast to the phenothiazines.(6) Imipramine in high dosage will increase narcotic effect and potentiate the action of chlorpromazine.(19) It is well known that imipramine possesses low sedative and hypnotic properties. Cases of marked stimulation have been reported, but there is doubt whether the stimulation was disease or drug related; the former was probably the case since dosage was not a factor.

Fortunately the thymoleptic (mood lifting) effect of imipramine is attainable at quite low dosage. This property is responsible for the analeptic and antidepressant activity of imipramine and is not shared to any extent by the phenothiazines.(10,19) At dosage levels used therapeutically, imipramine

does not affect motor activity appreciably, but fatigue, concentration impairment, and sleepiness have been observed.[18] Tremors, Parkinsonian manifestations, and other nervous system conditions attributed to imipramine are discussed under toxicity.

Imipramine exerts weak anticholinergic properties in respect to the autonomic nervous system.[25] Vagal blocking action, transient hypotensive effect, and spasmolytic activity are among these properties. Blood pressure responses to acetylcholine, histamine, and serotonin are decreased by imipramine.[17,25] The autonomic effects of reserpine are thought to be surpressed by imipramine as discussed in mechanism of action; however, such has been observed readily only in animals. Reports of catecholamine potentiation by imipramine consistent with the adrenergic sensitization hypothesis also discussed under mechanism of action have been submitted. It is evident that the autonomic activity of imipramine is also quite diverse and complex; it would seem likely that the drug exerts a two-stage activity, probably affecting the cholinergic processes first, with adrenergic sensitization occurring second.[19]

(b) Respiratory System: No significant effects are exerted by imipramine upon respiration. In respect to imipramine's similarity to the phenothiazines, one would expect very

little respiratory effect.[19]

(c) Gastrointestinal and Hepatic Systems: The gastrointestinal disturbances observed with imipramine are generally mild and quite rare. It seems likely any effect would be due to the mild anticholinergic activity of the drug. It is interesting to note that patients receiving imipramine who were previously anorexic respond with an increased appetite. This response is unique since they generally do not gain weight, as has been the experience with chlorpromazine; the explanation probably lies in the fact that the psychic indications for the two drugs are quite different.

Controlled studies have been made on rather large numbers of patients receiving imipramine with regard to hepatic function.[11,7] Although liver function tests, etc., appeared normal in patients receiving imipramine, jaundice has been reported by several investigators. The jaundice experienced is considered similar to phenothiazine-produced jaundice and is relieved by discontinuation of the drug.[3,6,12.18] The incidence of jaundice and imipramine therapy will be discussed under toxicity.

(d) Skeletal-Muscle: Imipramine does not possess muscle relaxant properties, nor does it inhibit or influence mono- or poly-synaptic spinal reflexes. A muscle weakening effect occurs at very high dosage.[17,19]

(e) Circulatory System and Blood: Due to its atropine-like action on various neurovisceral centers, imipramine usually produces a slight decrease in blood pressure; it is more marked in patients with hypertension where decreases of 30-50 mm. Hg. were observed. Accompanying the blood pressure changes, there is usually a slight increase in pulse rate. Blood pressure increases have occurred with imipramine administration, but are the exception.(8,18,28)

In addition to blood pressure changes, myocardial infarction has occurred during imipramine therapy. It is difficult to know whether the drug was the cause of myocardial infarction or not; nevertheless, imipramine is administered with caution to patients over 65 years of age or with a history of cardiovascular disease.(20)

Imipramine appears to have very little effect on the blood picture except for slight increases in eosinophile leukocyte counts. In general, eosinophile counts range from 5% to 12% as observed in studies by Kuhn.(18) High doses of imipramine have reportedly produced granulocytopenia.(3,8) Thrombosis also has been observed, but no incidences of pulmonary embolism have yet been recorded; patients receiving high doses of imipramine should be required to ambulate daily as a precaution.(18)

(f) Genitourinary System: Although such complaints as urinary retention, urinary frequency, etc., have been observed with patients taking imipramine, it is felt that such are a result of the anticholinergic action of the drug or the emotional disorder itself.

(g) Metabolic and Endocrine: Imipramine has a marked effect upon electrolyte metabolism in emotionally ill patients. It increases the excretion of calcium, potassium, sodium, and magnesium; the most constant of these changes is the intensification of calcium excretion.(19)

It is thought a relationship may exist between the function of the thyroid gland and the action of imipramine. The eosinophilia observed in patients receiving imipramine does not occur when the thyroid gland has been removed.(19) At the same time, imipramine reduces acoustic and adrenalin stimulated eosinophilia. (19)

Other miscellaneous endocrine effects of imipramine include prevention of lowering ascorbic acid levels in the adrenals, reduction of glycosuria and hyperglycemia in diabetic patients, and a peripheral gonadotropic-like action in menopausal women. These effects require much more intensive investigation, but may prove to be of great value in the treatment of such disorders as depression and melan-

cholia of the menopause, etc.[19]

(h) Skin and Allergy: Not unlike the phenothiazines, imipramine exerts a local anesthetic action. Hypersensitivity reactions have not been reported, but minor erythemas which were transitory in nature have been observed along with itching and occasional urticarial rashes.[17,18,19,28]

VI. FATE AND DISTRIBUTION

(a) Absorption and Distribution: Imipramine is well absorbed from all parenteral sites, orally, and rectally.[18] It disappears rapidly from the blood, but penetrates all organs reported examined; these organs include the brain, cerebellum, spinal medulla, liver, kidneys, lungs, heart, and spleen. Tissue analysis in animals and from human suicidal victims who ingested imipramine reveal highest concentrations of the drug in vascular tissues such as lungs, spleen, liver, adrenals, heart, and kidneys.[19]

(b) Metabolism: In the body imipramine undergoes rapid chemical breakdown and six metabolites have been chemically identified. The most significant of these metabolites are I and III; they reduce acetylcholine destruction by the pseudocholinestrase of the blood in vitro. Metabolite I (3-hydroxy-imipramine) alone will inhibit the cholinestrase of the brain. These metabolites also sensitize the nictitating membrane of the cat to adrenalin, noradrenalin, and serotonin (the classical method for studying adrenergic reactions); this effect correlates with the adrenergic sensitization hypothesis.[19]

Metabolite III (the monomethyl analog desipramine) of imipramine is assumed responsible for the antireserpine effect previously discussed. Much study has centered around metabolite III

since it is believed to be responsible for the major portion of the antidepressant effect of imipramine. It is now marketed as desipramine (Pertofrane, Norpramin) and advertized as an antidepressant with a more rapid onset of action than imipramine. Desipramine will be discussed in more detail in a later chapter.

(c) Excretion: Imipramine and its metabolites are excreted mainly via the kidneys. It is fortunate that a rather simple test is now available for the determination of urinary imipramine from which the approximate dose taken can by calculated. This test is inexpensive and the test solution can be prepared by any pharmacy or hospital laboratory. The test solution is mixed with a urine specimen which produces various shades of green which are then matched with a color chart to determine the approximate dosage. More sophisticated apparatus such as a spectrophotometer or a photoelectrocolorimeter make it possible to perform a quantitative analysis of urinary imipramine. Since depressive patients are rather reluctant to ingest any type of medication, a rapid urine color test may prove of great value to imipramine therapy. For more detailed information on this color test, see Forrest[9].

VII. ADMINISTRATION AND DOSAGE

(a) Route of Administeration: Imipramine can be administered by coated tablet, suppository, or intramuscular injection; it is also possible to give the drug by the intravenous route, but this method has not been adequately investigated at this time. The oral route has proven satisfactory in a large percentage of cases and the route of choice when feasible.(18)

(b) Dosage: Various dosage regimens have been recommended by investigators for imipramine in the treatment of depression; however, the concensus of opinion only will be presented in this paper. It has been found advantagous to give small doses more frequently than large doses less frequently daily, as has been the practice with phenothiazine drugs.(18)

In hospitalized patients, a 100 mg. divided daily dose of imipramine is generally given to initiate therapy; it is preferred by many to begin with intramuscular administration.(18) The dosage may be increased by increments of 25 mg. every few days until a response is obtained or a daily dose of 200-250 mg. is reached. If after a period of two weeks no response is obtained, the dosage can be increased to 300 mg. daily; it should be kept in mind that dosage levels above

200 mg. increase the incidence of toxic effects considerably. After two weeks of imipramine therapy the intramuscular route, some clinicians suggest replacing one 25 mg. injection with two 25 mg. tablets. If relapse should occur on this plan, injections should be resumed; oddly enough, it has been observed in some cases that the treatment only proved successful when injections were followed by oral administration of the drug. (18)

In outpatients, doses of 75-100 mg. of imipramine daily in divided doses are used to initiate therapy. This dosage may be increased to 150 mg. if necessary, and some recommend up to 200 mg. daily. In general, doses over 150 mg. daily in outpatients should be exercised with great caution, and dosages over 200 mg. daily are not recommended.(18,20,24,30)

Maintenance doses of imipramine depend largely on the response of the individual patient. After response is noted, it is generally attempted to lower the dosage to between 25 and 150 mg. daily. It is important to continue maintenance therapy without interruption during the active phase of depression; premature withdrawl of the drug is generally followed by relapse. It is now recommended that imipramine maintenance therapy continue until at least a month after clinical symptoms disappear or even longer. Maintenance

therapy by injection has been carried out up to one year and orally for as long as three years safely.[18,20,28]

For adolescent and elderly patients, lower initial and maintenance doses must be administered. They generally do not tolerate doses in excess of 100 mg. of imipramine, and they respond usually to lower dosages. Initial daily doses of from 20 to 50 mg. are recommended with 10 mg. increases according to individual patient responses.

(c) Overdosage: Symptoms of overdosage with imipramine include drowsiness, tachycardia, ataxia, hypotension, restlessness, agitation, hallucinations, hyperpyrexia, hyperactive reflexes, severe perspiration, mydriasis, and muscle rigidity.[1,3,6,8,11,14,17-20,24,28,30] In severe cases, athetoid movements occur followed by convulsions, coma, and death; signs of cardiac arrhythmia and congestive heart failure may also occur.[4] Treatment includes emesis and gastric lavage, as there is not any known antidote for imipramine. It is wise to keep the patient in a dark, quiet room to prevent convulsions, etc. Symptomatic treatment might include parenteral barbiturates for hyperirritability, digitilization for congestive heart failure, cold packs for hyperpyrexia, etc. In the event of suicidal attempts with imipramine, urinary imipramine measurements by the method previously discussed could prove invaluable in determining the amount of the

drug ingested.

(d) Tolerance: In general, imipramine is well tolerated by patients. In doses ranging from 75 to 125 mg. daily orally or 75 mg. daily intramuscularly, patients were able to work both physically and intellectually once they became accustomed to the drug. Patients receiving imipramine reportedly have been able to return to responsible jobs and function well as soon as four to five weeks after initiation of therapy.(18)

VIII. TOXICITY

The incidence of serious side reactions to imipramine are relatively low provided dosage is kept below 200 mg. daily. As discussed, elderly patients and children require even lower dosage schedules. In general, adequate responses are obtained at these dosage levels or even lower.

(a) Side Effects: The most common side effects noted with imipramine are the result of the drug's atropine-like activity. Transient hypotension and urinary retention are common even in low oral dosage, and more prone to occur in elderly patients, especially women. Other anticholinergic side effects which are not too uncommon include dry mouth, excessive perspiration, tachycardia, constipation, disturbances in accommodation, and even urinary frequency. All of these side effects are usually mild and tend to disappear as the patient becomes accustomed to the drug. On occasion, dosage must be adjusted to aleviate these effects. It has been observed by some investigators that the incidence of side effects is less in patients receiving the drug by intramuscular injection as compared with oral administration.[18]

Other side effects reported due to imipramine occur most generally in elderly patients. Investigators have described the following: Palpitation with an increased pulse rate

(these usually occur in sudden attacks), slight vertigo and dizziness, nausea and vomiting, and a Parkinson-like syndrome (much like the pseudoparkinsonism ascribed to the phenothiazines). (1,3,6,11,20,24,26,28)

One of the more rare but alarming side effects of imipramine is jaundice. All cases reported have been transient, responding to discontinuation of the drug. It is thought to be a cholestatic jaundice as occurs occasionally with the phenothiazines. (3,4,6,11,12,17,18,20,24)

The most hazzardous side effect known to occur with imipramine is agranulocytosis. Bone marrow depression is quite rare with an incidence of less than 1% and probably about 0.1%. Blood studies should be performed at routine intervals on patients taking the drug especially if fever or signs of infection should develop. (6,18)

Sensitization has been observed occasionally with imipramine. In patients receiving the drug allergic actions noted thus far have been minor. Photosensitization, skin rashes, transitory erythemas, and eosinophilia do occur. It is recommended that patients receiving the drug avoid sun bathing, etc. There have not been any hypersensitivity reactions, serious skin conditions, or eye damage reported in association with imipramine.(18)

Side effects observed in patients with more complex emotional disorders than simple depression syndromes receiving imipramine include hypomanic or manic syndromes, agitation, and psychotic symptoms. It is thought the drug may unmask underlying schizophrenic reactions, etc. In such cases it is advisable to administer a tranquilizer.[3,18,21,24]

(b) Contraindications: Imipramine and imipramine-like drugs are incompatable with monamine oxidase inhibitors (MAOI); these drugs used cocomitantly are capable of producing death.[2,3,6] It is presently recommended that at least a duration of one week be allowed to elapse between the discontinuation of one drug and the initiation of the other. It is preferable to allow more time as the clinical condition permits in the judgement of the clinician.[2,4,6]

Due to its atropine-like activity, imipramine is contra-indicated in patients with glaucoma. In these patients, an ophthomologist should be consulted prior to consideration of this drug.[3,6,11,17,18,24]

Imipramine is generally contraindicated in patients with severe cardiovascular disease and must be administered with caution in moderate cases. Cases of myocardial infarction and cardiac arrhythmias have occurred in suseptible individuals. ECG changes, including flattening of T-waves, also have

been reported.[4,20]

The cocomitant use of sympathomimetic amines (epinephrine, amphetamine, methylphenidate, etc.) are also contraindicated with imipramine. These compounds, which are used extensively in weight control, etc., are potentiated by imipramine.[17,19,20]

(c) Precautions: As previously discussed under dosage, imipramine should be used with caution in elderly patients and children. These age extremes tolerate the drug poorly and hazzardous side effects may occur with doses over 100 mg. daily.

Imipramine, like certain phenothiazines, is capable of activating seizures in epileptic patients; this effect has been confirmed by EEG studies in various experimental animals. It is believed by many investigators such phenomena occur only with very high doses of the drug and is not necessarily a contraindication. Imipramine, at any rate, should be used with caution in any patient with a history of epilepsy.[6,19,20]

The threat of suicide in seriously depressed patients must be considered a constant danger with patients receiving imipramine, especially in the early phases of therapy. These patients should be hospitalized under close supervision where

EST is abailable, etc.[3]

Caution must be observed in patients with hyperthyroidism or receiving any type of thyroid medication in addition to imipramine.[19] Reports of cardiac arrhythmias in such cases appear in the literature.[24]

Imipramine should hot be used in the first trimester of pregnancy as studies concerning its teratongenicity are inconclusive at the present time. If the drug is deemed necessary at this time, the clinician must be aware of the risks involved, etc.

(d) Addiction Liability: Withdrawl symptoms following the discontinuation of imipramine have been reported.[16,18] The symptoms cited include nausea, vomiting, dizziness, coryza, muscular pains, and malaise. These symptoms were first regarded by observers as conversion phenomena, but after several repetitions these effects were thought due to a physiological withdrawl. It was first thought by some clinicians to be a return of anxiety and representative of imminent relapse.

Just how important imipramine is to patient stability is unknown, and the various reports on withdrawl phenomena are inconsistent. At the present time it is felt by most that a physiological addiction in the true sense of the word

is quite unlikely. It is only logical that a psychological dependance could exist and account for the symptoms observed when the drug is discontinued. It is also noteworthy that withdrawl phenomena have been observed only in patients receiving large doses (over 200 mg. daily) of the drug. In conclusion, it is doubtful there is a true addiction to imipramine.

IX. USE IN THE TREATMENT OF DEPRESSION

Imipramine is presently considered by most clinicians as the drug of choice in properly selected cases of depression. As with any drug, it is not effective in every case which has a depressive component, nor does it replace EST, insulin therapy, etc.

(a) Types of Depression and Imipramine: The drug appears to be most effective in the treatment of typical endogenous depressions. This includes those disturbances which occur during the menopause in which the dominant component involves a vital depression. The effect of imipramine will be more uncertain and more incomplete the older the patient and the longer the duration of the depression. The best therapeutic results have been obtained in patients with endogenous depression displaying mental and motor retardation in addition to feelings of guilt and despair.(3,6,11,15,17,18,19,20,24,26,30)

The depressions associated with organic brain damage and schizophrenic reactions do not respond as well to imipramine.(3,24) Neurotic and reactive depressions are also more refractory to the drug, but in a few cases good results have been obtained.(24) Various cure rates appear in the literature with regard to imipramine therapy from studies conducted in this country and Europe. They vary considerably, but in general boast a cure

rate of from 40 to 60% overall in the treatment of various types of depression, while specifically diagnosed cases of endogenous depression reflected rates between 70 and 85%.(30) The unusually high rates of cure are probably misleading, as the studies involved intensive treatment with high dosage regimens; most practitioners would not employ doses over 200 mg. daily.

(b) Electroshock Therapy (EST) and Imipramine: In the treatment of endogenous depression, EST acts most rapidly and undoubtedly is the most effective. Due to the fact that electroshock is distasteful to patients, the antidepressant drugs have offered an alternative, assuming a dominant role in recent years in the treatment of depression.(3,11)

Many studies have compared the drugs of the imipramine group with EST. Some clinicians feel they are equally effective, while others prefer one or the other. One must keep in mind that EST does produce rapid action, while imipramine requires up to 3 weeks to be effective; this factor may be lifesaving where suicidal tendencies are present.

It does appear that combining EST and imipramine may be effective in the treatment of endogenous depression. Some investigators feel that imipramine affects more aspects of behavior than EST. By virtue of these effects, it is felt that

imipramine markedly reduces the incidence of relapse when used in combination with EST. It does not reduce the number of electrical treatments required or have any potentiation activity on their effect, despite some opinions to the contrary. Many clinicians refuse to combine EST with any type of drug therapy.(3,11,22,23,28,29)

(c) Imipramine and Phenothiazine Tranquilizers: There are not any known contraindications to the use of a phenothiazine tranquilizer in combination with imipramine in the treatment of depressive syndromes where anxiety or agitation are present. Commercial preparations are now available which contain just such a combination. Perhaps these combinations will enlarge the range of effectiveness of both groups of drugs. (3,7,30)

(d) Imipramine and Desipramine: Although the role of despramine (metabolite III) in the action of imipramine is considered responsible for the major portion of the antidepressant action of the drug, it has no particular advantage over the parent compound. The response to desipramine is supposedly more prompt than that of imipramine, but this is not always the case; it is probably not as potent nor as long acting as the latter. The dosage regimen generally applied to desipramine is the opposite of imipramine as a high initial

dose is employed which is reduced as dictated by the response. Most studies dealing with comparing the two drugs reveal very little difference, with imipramine being more effective in most instances.[5,13,22]

(e) Imipramine and Amitriptyline: Although amitriptyline is almost identical to imipramine chemically, it differs in activity in that it imposes some sedative properties.[3] It can be substituted for imipramine as the evening medication in patients with insomnia. Amitriptyline also can be used in combination with phenothiazines, etc.

(f) Imipramine and Enuresis: Imipramine has found some use in the field of pediatrics in the control of enuresis. It has been found to be of value in the treatment of enuresis in children, but not adults. Many encouraging reports have been found in the literature concerning this unusual property of imipramine, but in the past year these claims have received close scrutiny. It appears at the present time that imipramine's role in enuresis is uncertain.[27]

Various dosage regimens have been suggested for imipramine in treating enuretics. Some prefer to initiate therapy with 10 mg. doses at bedtime, with daily increases of 10 mg. until a response is obtained or a total dose of 50 mg. is reached. Others simplify the dosage with 25 mg. doses for children under

twelve years of age and 50 mg. for those older. Discontinuation of the drug after 2 to 4 weeks to test if control is permanent is the general practice; if relapse occurs, dosage is resumed at its prior level and the child tested again in 2 to 4 weeks. As with any drug, many cases are entirely refractory to treatment.

Side effects observed in children receiving imipramine include dermititis, nervousness, nightmares, and visual disturbances. All of these side effects are amendable to a reduction in dosage.(27)

In conclusion, it appears that imipramine's value in the treatment of enuresis remains to be decided. More conclusive studies will be required to establish the drug in this field of therapy.

X. SUMMARY

The current literature concerning the efficacy of the antidepressant drug imipramine has been presented, and certain aspects of this drug deserve special mention, as follows:

(1) Imipramine is closely related chemically to the phenothiazine tranquilizers, yet displays a unique therapeutic effect of antidepression not shared by the latter group to any extent.

(2) The mechanism of action of imipramine is poorly understood, and at this time several hypotheses offer only logical explanations; future studies on this subject may expand the field of psychopharmacology to much greater dimensions.

(3) Imipramine exerts the majority of its effects upon the CNS where its chief activity is the antidepressant action of mood lifting now termed thymoleptic effect.

(4) Imipramine breaks down into six metabolites in the body. Metabolite III, which is desmethylimipramine (desipramine), is responsible for the major portion of the antidepressant activity of the parent compound; it also has found use in the treatment of depression.

(5) In general, imipramine is effective in dosage ranges

between 50 and 150 mg. daily, which is far below toxic levels. The oral route is prefered and usually adequate, yet many clinicians favor intramuscular dosage of the drug.

(6) Signs of toxicity usually do not occur in doses below 200 mg. daily except in patients at age extremes or those with cardiovascular diseases.

(7) There are certain contraindications to the use of imipramine and one in particular with which every clinician should be acquainted. Cocommitant use with monamine oxidase inhibitors can prove lethal and patients must be free of these drugs for at least a week prior to initiation of imipramine therapy.

(8) It appears that endogenous depressions respond most favorably to imipramine, while other types of depression respond less consistently.

(9) Imipramine has markedly reduced the need for EST, but it must be noted that imipramine does not replace EST. The latter is still the treatment of choice in emergency cases of depression where suicide poses a constant threat.

(10) Recently imipramine has found use in the field of pediatrics in the control of enuresis. Much enthusiasm has been generated for this use of the drug, but its status in enuresis remains uncertain for the present time.

XI. CONCLUSION

Of the psychopharmacologic drugs now available for the treatment of depression, imipramine is the drug of choice. It has attained this status as a result of extensive use and investigation over the last eight years.

Generic and Trade Names of Drugs:

Imipramine --- Tofranil (Giegy)

Desipramine --- Pertofrane (Giegy), Norpramin (Lakeside)

Amitriptyline --- Elavil (Merk, Sharpe and Dome)

Nortriptyline --- Aventyl (Lilly)

Promazine --- Sparine (Wyeth)

Chlorpromazine --- Thorazine (Smith, Kline and French)

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