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Editorial

Classification, Biochemistry of Depression and the Mode of Action of Antidepressant Drugs

Depression is the most common emotional disorder afflicting approximately 3% of the world population according to W.H.O. statistics (1976) and 50% of North American and Western Europeans at one time or another. The depressive syndrome is the problem in approximately half of all admissions to psychiatric institutions. The National Institute of Mental Health recently warned that 15% in about 20 million people between the ages of 18—74 years in the U.S.A. may be suffering from serious depressive disorders in any given year. Affective disorders represent 24.5% of all attendances at the psychiatric out-patient clinic of Ain Shams University distributed as 10.7% reactive depressive, 8.6% manic depressive psychosis and 5.2% involutional melancholy (Okasha, 1977). Manic-depressive illnesses were represented as 16.4% in a Kasr El-Aini sample (Rakhaway, 1978)

The difference observed in various epidemiological studies is due to many factors, the most important of which is the nosology of depression. The classification is complex and controversial. Despite half a century of discussion, there still exists many outstanding and opposing views.

The contemporary classification of depression after Kendell (1976) may reflect these discrepancies and similarities.

A) Simple Typologies

1. **One category (Lewis)**

   Depressive illness is one continuum and there is no real difference between neurotic and endogenous depression.

2. **Two categories**

Roth (1965)	**Pollit** 1965)	**Van Praag** (1965)
Endogenous depression	Physiological (S)	Vital depression
Neurotic depression	Psychological (I)	Personal depression

3. **Three categories**

I C D - 6	**Overall** (1966)
Manic-depressive	Anxious tense depression
Involutional melancholy	Hostile depression
Neurotic depressive reaction	Psychotic depression

4. **Four categories**

I C D - 8	**Paykell** (1971)
Manic-depressive psychosis (depressive type)	Psychotic depression
Involutional melancholy	Anxious depression
Depressive neurosis	Hostile depression
Reactive depressive psychosis	Young depressives with personality disorder

B) **Tiered Typologies**

Winokur (1974)

(Affective disorders)

I. Primary : 1 — Unipolar
a) Pure depressive
b) Depressive spectrum
2 — Bipolar

II. Secondary

Kielholz (1972)

I. Somatic depression	—	a) Schizophrenic depression
	—	a) Organic depression
II. Endogenous depression	—	b) Symptomatic depression
		b) Cyclic depression
		c) Periodic depression
		d) Involutional depression
III. Psychogenic depression	—	a) Neurotic depression
		b) Exhaustion depression
		c) Reactive depression

The Egyptian manual of psychiatric disorders (D M P — 1) in 1975 classifies the manic and depressive illnesses as follows:

— Acute or chronic reactive and situational depressive illness
— Depressive neurosis
— Manic-depressive illness: Depressed type
Manic type
Circular type
Mixed type
— Involutional melancholy
— Depressive illness not elsewhere specified
— Others

Owing to this extensive variation in the classification Klein (1976) suggested a different approach to the depressive syndrome in an attempt to simplify diagnosis under the term 'dysphoria'.

Dysphoric Disorders

I. **Primary**

A. Endogenomorphic depression where there is impairment of the of the capacity to experience pleasure.

B. Reactive or situational depression

C. Schizo-affective illness.

II. **Secondary**

A. Secondary to schizophrenia or schizoid states

B. Secondary to personality disorders and neurosis

1. **Endogenomorphic**

a) Phobic anxious

b) Obsessive, compulsive

c) Passive-dependent and antisocial personality

2. **Dysphorias**

a) Hysteroid dysphoria : sudden mood changes

b) Emotionally unstable character, mood lability several times per day

c) Hystrionic character disorder : self-dramatization

d) Inadequate and hypochondriacal personality where the patient seeks security through the sickness role behaviour

C. Dysphorias secondary to organic or toxic illness

i. Chronic brain syndrome

ii. Temporal lobe epilepsy

iii. Hypothyroidism

iv. Covert alcohol and/or drug abuse

v. Antipsychotic akinesia (secondary to neuroleptic medication)

vi. Others

Biochemistry of Depression

The review will not include the genetical, environmental, analytical and humanistic approaches in the aetiology of depression. We shall focus on head-lines on neuroendocrine and biochemical studies in depression.

Adrenocortical functions: A relatively large number of studies of adrenal cortical function in depressed patients have been reported (Rubin and Mandell, 1966; Davies **et al,** 1972; Sachar, 1973). In summary there is evidence of increased adrenocortical activity. This includes: elevation of plasma cortisol, of urinary free cortisol, of C.S.F. free cortisol, of urinary 17-hydrocorticosteroids, resistance to dexamethasone suppression and flattening of the diurnal curve for plasma cortisol. This reflects an abnormality of hypothalamic control of pituitary function. There many be a failure to inhibit the mechanism which normally stops the release of corticotrophin factor in depressives.

Thyroid hormones: There had been several studies of thyroid function in depressives with no clear evidence of abnormal function emerging. Patients with thyroid disease do have associated psychiatric abnormalities with symptoms of depression. L-triiodothyronine (T3) accelerates the antidepressant response to imipramine in females (but not in males (Prange **et al.,** 1969). Recently reports have shown that thyrotropic releasing hormones (TRH) produce significant temporary symptomatic response in some depressed patients (Kastin **et al.,** 1972).

Sex hormones: There is considerable evidence that depression is more prevalent in females than in males especially unipolar depression and is more likely to occur at times of endocrine change — pre-mensturally, post-partum, at the menopause and in association with contraceptive pills. There may be sex-related differences in the activity of MAO which may lead to alterations in amine functions (Belmaker, 1974).

Electrolyte metabolism: Depression and mania are presumably associated with an alteration in neuronal function, so an abnormality of electrolytes may be of importance in their development. Increase of residual sodium by 50% in depression and 200% in mania was observed in many studies (Coppen, 1967). It has been suggested that there may

be an alteration in calcitonin activity in depression (Flach, 1964) and also increased calcium retention in those who improve. There are reports of alterations in plasma and erythrocyte magnesium concentration in depressives (Mendel, 1974).

Biochemical Aspects of Depression

1. **Catecholamine theory:** (Noradrenaline — Dopamine) (Schildkraut, 1973)

Some, if not all, depressions are associated with an absolute or relative deficiency of CA, particularly NA at functionally important adrenergic receptor sites in the brain. Elation conversely may be associated with an excess of such amines. Treatment with precursors failed to produce any relief, i.e. Tyrosine or Dopamine (Bunny **et al.**, 1972).

2. **Indolamine theory:** (5 hydroxytryptamine) (Coppen, 1972)

Depression is secondary to a functional deficit of brain 5HT. Treatment with precursors succeeded, i.e. tryptophane. Most studies have shown 5HIAA in C.S.F. of depressives to be reduced, whereas equivocal data have been obtained for HV and MHPG (Ridges, 1975). Post-mortem studies of brains of suicidal depressives showed reduction of 5HT levels in the raphe nuclei dorsalis and centralis inferior, (Bourne **et al.**, 1968).

3. **Permissive amine hypothesis:** (Prange **et al.**, 1974)

Central 5HT deficiency may represent a vulnerability to affective illness and this predisposition may separate the depressive patient from the normal individual. Lowered CA is correlated with the depressive episode (no difference between the clinical depressive and the momentarily depressed normal individuals). Certain changes in VMA and MHPG may occur with changes in the affective state, whereas other abnormalities in monoamine metabalism (decreased 5HIAA in C.S.F.) may represent enduring constitutional factors in some patients with affective disorders.

4. **Cyclic AMP**

This is the second messenger for each of the amines DA, NA, 5HT. Receptor stimulation causes an activation of adenylate cyclase and cyclic AMP formation. Cyclic AMP is claimed to increase in mania and diminish in depression, but it seems to be correlated with muscular activity versus retardation respectively. It may be an index of the functional stage of adrenergic neurones (Eccleston, 1973).

5. A functional balance between acetylcholine and catecholamines exists in the brain. We should not forget that raised central brain cholinergic functions is consistent with depressive symptoms. The same applies to anticholinergie symptoms and antidepressant effects (Janowsky **et al.**, 1972). Further research should involve the role of acetylcholine.

A classification of Anti-depressant and Related Drugs

I. **Amphetamine-related sympathomimetic stimulants:** (Scheel-Kruger and Randrup, 1967)

a) Releasers of non-granular amine stores: (+) —amphetamine
methamphetamine
ephedrine
cocaine

b) Releasers of granular and non-granular amine stores: (Handley and Sayers, 1973)
methylphenidate
phenmetrazine
fencamfamin

c) Agents excerting postsynaptic agonist action at dopamine receptors: (Anden, 1967)
apomorphine
piribedil

d) Agents acting by inhibiting re-uptake of DA (and NA)
nomifensine

II. **MAO inhibitors:**

a) Hydrazines with acute stimulant effects:

iproniazid
isocarboxazid
phenoprazine
phenelzine

..... without acute stimulant effects:

nialamide

b) Non-dydrazines with acute stimulant effects:

tranylcypromine
a-ethyltryptamine

..... without acute stimulant effects:

pargyline

III. **Membrane-pump inhibitors:**

Tricyclics: a) first generation:

(tertiary amines) imipramine
amitriptyline

(secondary amines) desipramine
nortriptyline
protriptyline

b) second generation: clomipramine
maprotiline
viloxazine
nomifensine

IV. **Naturally occurring agents:**

a) Amino acid precursors of transmitter amines:

L-3,4-dihydroxyphenylalanine
L-tryptophan
L-5-hydroxytryptophan

b) Lithium salts: e.g. Lithium carbonate.

V. **Miscellaneous agents :**

Relatively recent synthetic agents : iprindole
mianserin
tandamine

Not all agents are practical antidepressants, nor is the table intended to be exhaustive. Agents have been classified according to the major pharmacological property believed to be responsible (where applicable) for the clinical activity observed.

Antidepressant Drugs

Nomifensine : There is evidence that this agent exerts a dual action at DA and NA synapses in the brain, causing both a release of DA (Braestrup and Scheel-Kruger, 1976) and — perhaps much more important — an inhibition of the re-uptake of both DA and NA (Hunt **et al.,** 1974; Gerhards **et al.,** 1974). There seems to be no effect on 5-HT re-uptake mechanisms (Samanin **et al.,** 1975). It is already possible to say, however, that nomifensine has properties intermediate to those of amphetamine (predominantly a release of both catecholamines) and imipramine (predominantly an inhibitor of NA and 5-HT uptake). The neuropharmacological properties (release of DA with inhibition of uptake of both DA and NA) should provide a drug with interesting clinical properties.

MAO inhibitors : These are effective inhibitors of the mitochondrial enzyme MAO. The fact is that a cessation of treatment and recovery of MAO activity parallels the synthesis of a new enzyme. MAO is involved in the intracellular breakdown of the amines, DA, NA, and 5-HT, its function being to control neuronal pools of these transmitters. It follows that inhibition of MAO is accompanied by an increase in tissue levels of all three amines. It is believed that anti-depressant activity results from the spontaneous spilling over of these amines into the neuronal synape, but it can also be argued that more amines are available for release by specific neuronal activity, particularly if previously amine synthesis and/or storage was impaired.

Apart from the mechanism of this effect, MAO inhibitors differ from the imipramine-like drugs in another major aspect; MAO inhibitors also promote the effects in the brain of DA, a property not possessed by first and second generation tricyclics.

Tricyclics and non-tricyclics: The pharmacological effects of imipramine are largely, if not wholly, explained by their ability to inhibit the presynaptic uptake of transmitter amines, thereby enhancing their postsynaptic activity which is most marked against NA and 5-HT uptake, and relatively weak against DA. Imipramine is a tertiary amine, and the secondary amine (metabolite), desipramine shows greater potency against NA uptake. This is true of all secondary amines. Some second generation tricyclics have been introduced with greater specificity of action, chlomipramine being the most potent 5-HT uptake inhibitor, whereas maprotiline is an almost "pure" inhibitor of NA uptake.

Viloxazine also exhibits a number of differences from the imipramine group. Thus, it possesses no anticholinergic activity and causes moderate transient increases in the brain levels of all three amines, DA NA and 5-HT. On the electroencephalogram (EEG) of the rat, viloxazine produces an arousal effect more reminiscent of the amphetamines, yet in the septal rat the preparation viloxazine affords significant protection against the typical violent, aggressive episodes, a feature reminiscent of the benzodiazepines (minor tranquillizers generally) and not found in any other antidepressant group.

From animal studies, it has a pharmacological profile reminiscent of both the amphetamines and the imipramines with additionally some evidence of minor tranquillizer properlies. Viloxazine epitomises the earlier suggestion that new drugs should go forward for clinical evaluation, not because of presence or absence of activity in one or two specific tests of antidepressant activity, but because of an interesting and unique profile of neuropharmacological activity.

Although the amphetamine-like drugs are effective anti-depressants,

a number of important side-effects preclude their clinical use. A property which the amphetamines and the MAO inhibitors possess, which the tricyclics do not, is the ability to enhance brain DA activity; yet very little is known of the involvement of DA in clinical depression.

After this brief description, the mode of action of various antidepressants can be summarized by the following table :

Tricyclic : (Tertiary amines)			
Imipramine	(Tofranil)		
Amitriptyline	(Tryptizol)		
Chlorimipramine	(Anafranil)	———	Potent inhibitors of 5HT uptake
Doxepin	(Sinequan)		
Dothiepin	(Prothiaden)		
Trimipramine	(Surmontil)		
Dibenzepine	(Noveril)		
Noxiptyline	(Agendal)		
Tricyclic : (Secondary amines)			
Desipramine	(Pertofran)		
Nortriptyline	(Aventyl)	———	Potent inhibitors of NA uptake
Protriptyline	(Concordin)		
Tetracyclic :			
Maprotiline	(Ludiomil)	———	Pure inhibitors of NA uptake
Mianserin	(Bolvidon)		
Non-Tricyclics :			
Viloxazine	(Vivalan)	———	Transient increase in the DA, NA, 5HT
Nomifensin		———	Potent inhibitor of DA and less of NA uptake

We can even correlate the effects of antidepressants, their pharmacological and clinical actions into three phases :

Phase I. Psychomotor activation and increase in drive which are correlated with inhibition of NA uptake, e.g. pertofran, concordin, ludiomil.

Phase II. Brightening of mood which is correlated with inhibition of 5HT uptake, e.g. tofranil, tryptizol, anafranil.

Phase III. Relief of anxiety and tranquilizing action, e.g. tryptizol and other neuroleptics. This is probably correlated with central atropine-like effects.

Recently, attempts to correlate plasma level of antidepressants with clinical response have given variable results. Some claim that higher doses of antidepressants produce better clinical response than lower dosages. Others state that poor clinical response results from excessive increase or decrease of the plasma levels of antidepressants.

Greater than 80% of MAO inhibition is associated with clinical improvement and the response of patients with lower levels cannot be distinguished from the placebo. It is different with tricyclics. The Scandinavians report a curvilinear relationship with improvement occurring at moderate levels (Kragh-Sorensen **et al, 1973).** English and American groups find positive correlation with higher levels associated with improvement and vice versa. (Simpson, 1973; Braithwaite **et al.,** 1972). Australians find no relationship at all, (Burrows **et al.,** 1974).

The above data should give us a sense of humility about our present knowledge of the biochemistry of depression, cerebral amines and the mode of action of antidepressants.

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