Biochemistry and Treatment Strategies for Depression

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Major depressive disorder is a relatively common illness. Many depressed patients are seen by a primary care physician and not a psychiatrist. Several lines of evidence suggest a biochemical etiology for depression. Some research suggests at least two distinct biochemical depressions, one involving an abnormality of the norepinephrine neurotransmitter system and the other involving an abnormality of the serotonin system.

Individual tricyclic antidepressants appear to have differential effects on these two neurotransmitters. This may explain why some depressed patients respond better to one tricyclic than to another. This factor also provides a treatment rationale for switching a nonresponsive depressed patient from one tricyclic, after an adequate trial, to the "opposite" tricyclic.

Pretreatment levels of 3-methoxy-4-hydroxyphenylglycol (MHPG) separate depressed patients quite accurately into two groups: imipramine responders and amitriptyline responders. Future research in this area may lead to clinically useful laboratory tests for the treatment of depression.

Major depressive disorder is a relatively common illness. Estimates of incidence range from 2 percent[1] to as high as 20 percent.[2] If less severe depressions are included, the incidence is increased even further. While approximately 60 percent of persons suffering a major depressive disorder have only a single episode, the other 40 percent of affected patients will have two or more episodes. Many depressed patients are seen by their primary care physician and not by a psychiatrist. A study of successful suicides revealed that 73 percent of patients with affective disorder were seen by a physician for their psychiatric illness during the year before their successful suicide, but only 29 percent were seen by a psychiatrist.[3]

The DSM-III diagnosis of major depressive disorder includes the following:

1. dysphoria;
2. at least four of the following symptoms:
   a. poor appetite or weight loss or increased appetite or weight gain,
   b. insomnia or hypersomnia,
   c. energy loss,
   d. psychomotor agitation or retardation,
   e. loss of interest or decreased sexual drive,

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f. self-reproach or excessive guilt,
g. difficulty concentrating or thinking,
h. thoughts of death or suicide;

3. illness duration of at least two weeks;
4. no symptoms suggesting schizophrenia, organic mental disorder, or uncomplicated bereavement.

Biochemical Etiology for Depression

Several lines of evidence suggest a biochemical etiology for depression. More specifically, abnormalities of the monoamine neurotransmitters norepinephrine and serotonin have been implicated as etiological agents in depression.

Reserpine has been estimated to cause depressions in 10 to 20 percent of hypertensives taking the drug.[4] Reserpine depletes central nervous system stores of both norepinephrine and serotonin. All currently available tricyclic antidepressant drugs are known to block the reuptake on norepinephrine, serotonin, or both. This is probably not their mechanism of action. While the reuptake blocking activity is an immediate effect, these drugs usually take at least two weeks to effect improvement of depressive symptoms. This indicates the tricyclics do not work by simply blocking the reuptake of a neurotransmitter. A recent report suggests a possible mechanism of action for tricyclic antidepressants.[5] Norepinephrine has been shown to decrease its own release by stimulating a presynaptic receptor. Desipramine (a tricyclic antidepressant) was noted to gradually decrease the sensitivity of a norepinephrine presynaptic receptor. A decrease in receptor sensitivity allows for greater norepinephrine release. This effect was noted after three weeks of desipramine administration, but not after one day. This time course approximates the onset of clinical action for tricyclics. However, reuptake blocking activity was maximal at one day.

The monoamine oxidase inhibitors (MAOIs), a second class of antidepressants, block one route of metabolism for norepinephrine and serotonin. Whether this is the mechanism of action of MAOIs is not certain, but it is another piece of evidence suggesting a role of monoamines in depression.

Lithium is effective in the treatment of some depressions.[6] Lithium has been found to inhibit the release of norepinephrine and serotonin from brain slices. Lithium has also been found to alter the central nervous system metabolism of norepinephrine in animals.

Various materials presented thus far suggest that norepinephrine and serotonin are involved in depressive disorders. Information will now be presented that suggests the likelihood of at least two distinct biological depressive disorders, one involving an abnormality in norepinephrine function and the other, serotonin function.

Several lines of evidence suggest that 3-methoxy-4-hydroxyphenylglycol (MHPG) (Figure 1) is the major metabolite of central nervous system norepinephrine in man and other species. MHPG is conjugated and excreted in the urine. Peripheral sources also contribute to urinary MHPG.

Previous investigations have demonstrated the mean levels of urinary MHPG in 24-hour urine collections to be statistically significantly lower for depressed bipolars (patients with previous mania) than for a control group.[7] Twenty-four-hour MHPG levels in unipolar depression are not as uniform (ie, they have greater variability). This suggests unipolar depression is a more heterogeneous group.

Several clinical investigations[8-10] have demonstrated that patients with low pretreatment urinary MHPG responded well to imipramine and poorly to amitriptyline. The reverse response was noted in patients who had normal or elevated MHPG, (ie, good response to amitriptyline and poor response to imipramine).

The major metabolic product of serotonin (Figure 1) is 5-hydroxyindoleacetic acid (5-HIAA). The peripheral contributions of 5-HIAA are so great that urine measurements of it are not useful. Previous studies have focused on cerebrospinal fluid levels of 5-HIAA. Several studies have shown a decreased level of cerebrospinal fluid 5-HIAA in depressed patients when compared to various control groups, but others have not been able to confirm this.[7]

Maas[11] has postulated there are two biochemically and pharmacologically identifiable subgroups of depressed patients. One group is characterized by: (1) low pretreatment urinary MHPG; (2) a favorable response to treatment with imipramine or desipramine; (3) failure to respond to amitrip-

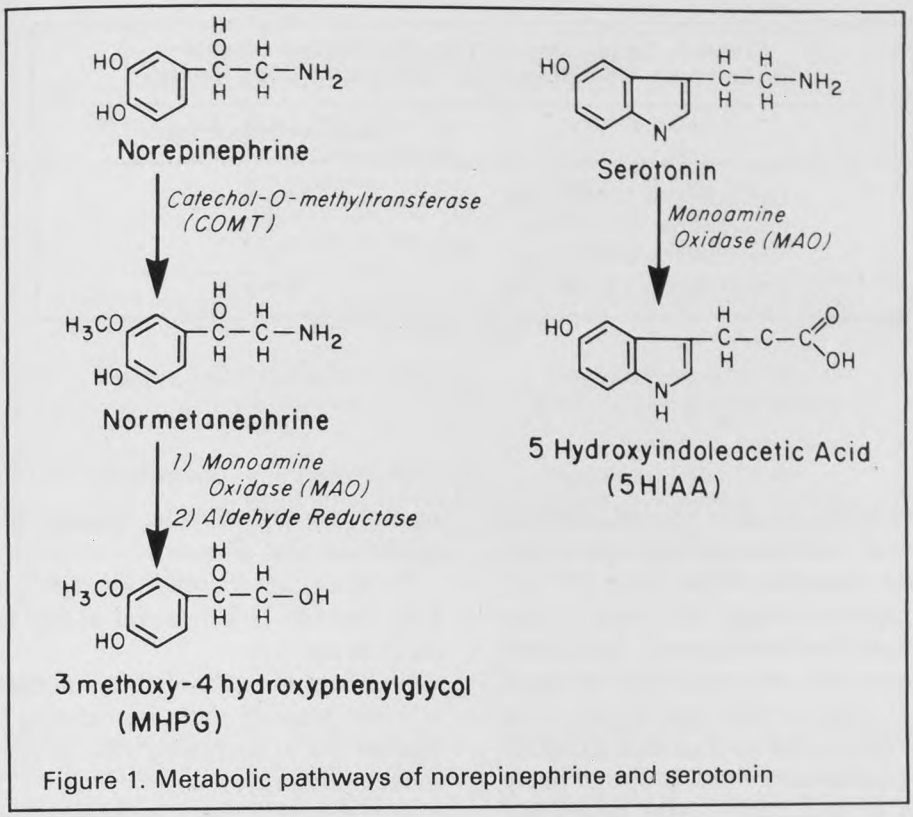

Figure 1. Metabolic pathways of norepinephrine and serotonin

tyline; and (4) transient improvement of depressive symptoms when given a trial of dextroamphetamine. The other group is characterized by: (1) normal or high pretreatment levels of urinary MHPG; (2) favorable response to treatment with amitriptyline; (3) failure to respond to imipramine or desipramine; and (4) no change in depressive symptoms when given a trial of dextroamphetamine.

Since imipramine, desipramine, and dextroamphetamine all have predominant effects on norepinephrine, and amitriptyline has effects primarily on serotonin, it is plausible that the former drugs effect improvement in depressions in which an abnormality of the norepinephrine system is present and amitriptyline would effect improvement in depressions in which there was an abnormality of the serotonin system. This "abnormality" could involve such things as deficient neurotransmitter production, production of a "false" neurotransmitter, or hypo- or hypersensitivity of pre- or postsynaptic receptors.

Treatment of Depression

Laboratory Tests

At the present time, the MHPG assay is not a readily available laboratory test. The necessity of several days of a special diet while collecting the urine may limit its clinical usefulness. However, the amount of treatment time wasted in choosing the "wrong" tricyclic may promote the use of the MHPG assay in special circumstances (eg, hospitalized patients).

Recently, quantitative tricyclic serum levels

Table 1. Comparison of Tricyclic Antidepressants for Common Side Effects and Therapeutic Dose Ranges

	Common Side Effects
Desipramine 150-300 mg Imipramine 150-300 mg Nortriptyline 50-100 mg Amitriptyline 150-300 mg	Fewer ↓ More

have become available. To date several studies[12] have examined the relationship between serum levels and clinical response. While there are suggestions of therapeutic ranges for some of the tricyclics, the results are inconclusive. Aside from identifying patients who are either slow or rapid metabolizers of tricyclics, these drug levels at the present time should be used with caution in deciding a definitive treatment course. It seems likely that future research will clarify these issues and provide useful laboratory aids for the treatment of depression.

Treatment Strategies

Currently, a reasonable approach to the treatment of depression should involve a selection of one of the tricyclics based on the individual drug's side effects. Table 1 lists four common tricyclics and compares them for the common side effects of sedation, dry mouth, and orthostatic hypotension.

Patients with very bothersome insomnia could be started on the more sedating tricyclics. Retarded patients or patients very sensitive to the various drugs' side effects (eg, elderly patients) could be started on the less sedating tricyclics. Doxepin (Sinequan) is closely related to the tricyclics and is rather sedating but has been suggested to have fewer cardiovascular side effects.

A recent review[13] suggests the following relative to the cardiovascular effects of tricyclics.

1. Two large surveys yielded conflicting views on the risks of tricyclic therapy in patients with cardiovascular diseases.

2. Tricyclics increase PR, QRS, and QTc intervals, and the H-V interval in His bundle electrocardiogram.

3. There is not available a definitive answer to whether patients with pre-existing bundle branch disease are at increased risk to AV block during tricyclic therapy.

4. Tricyclics have quinidine-like effects and thus have antiarrhythmic effects on atrial and ventricular premature depolarizations.

Using imipramine as an example, Table 2 illustrates dosage guidelines in treatment of depression. The gradual build-up in dosage in the first week is to avoid the unpleasant side effects that may result if the full dose was given the first night.

If a patient does not show any evidence of responding after two or three weeks of maximal dosages (eg, imipramine 300 mg), then a switch to an "opposite" tricyclic should be made. In the illustration given, a switch to amitriptyline would be indicated. It is usually not necessary to start the new tricyclic gradually. The amitriptyline could be started at 150 mg a day after the imipramine was discontinued. The same guidelines in Table 2 could then be followed with the amitriptyline.

A review of the literature[14] reveals an approximate response rate of 70 percent for depressions treated with tricyclics. Patients failing to respond to the tricyclics may be considered for other forms of somatic treatment including electroconvulsive treatment or monoamine oxidase inhibitors.

The necessity of accurate diagnosis is obvious. The differential diagnosis of major depressive disorders is beyond the scope of this discussion but

Table 2. Treatment Guidelines

Weeks 1-2	Imipramine 50 mg	Treatment Day 1
	Imipramine 50 mg	Treatment Day 2
	Imipramine 100 mg	Treatment Day 3
	Imipramine 100 mg	Treatment Day 4
	Imipramine 150 mg	Treatment Days 5-14

If return appointment at 2 weeks reveals no improvement and no problem with side effects, then increase dose to:

Weeks 3-4	Imipramine 200 mg	Treatment Days 15-28

If minimal or no improvement at the end of 4 weeks then:

Weeks 5-7	Imipramine 300 mg	Treatment Days 29-49

If minimal or no improvement at 7 weeks, consider switching to the "opposite" tricyclic (eg, amitriptyline)

can be found in various sources.[14,15] Suffice it to say that accurate diagnosis of psychiatric conditions can be difficult, especially on a cross-sectional basis.

Summary

There are many lines of evidence to suggest that the monoamines norepinephrine and serotonin are involved in the etiology of major depressive disorders. Use of MHPG levels may, in the future, aid the clinician in the choice of antidepressant drugs. The present state of knowledge does suggest a rationale for switching depressed patients who have not responded to adequate doses of one tricyclic to an "opposite" tricyclic.

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