Antidepressants: From MAOIs to SSRIs and more

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The era of antidepressants started with isoniazid, an antitubercular agent, which was accidentally found to have euphoric effects in patients with tuberculosis who were receiving this drug. The mood elevating property of the drug, considered to be a side effect, became the primary effect in depression and heralded the synthesis of generations of newer antidepressants. It also shifted the focus of psychiatrists from psychodynamic processes to a biological basis of the illness.[11]

Isoniazid belongs to a group of hydrazine compounds, which were synthesized by Fischer in the 1870's. Isonicotinyl hydrazine (isoniazid) was synthesized by Meyer and Malley at Prague from these hydrazine compounds. Forty years later it was re-synthesized by another group of scientists. By chance, it was found to be an effective antitubercular agent. In 1952, Zeller discovered that iproniazid, another hydrazine derivative, inhibited monoamine oxidase (MAO) enzyme, so named by a group of scientists led by Blaschko and Richter in 1937. The enzyme caused the oxidation of adrenaline, a monoamine and was inhibited by ephedrine. However, Mary Hare had observed similar results in 1928 with an enzyme, tyramine oxidase, which later was found to be MAO. The MAO enzyme acts on a number of endogenous and exogenous amines (serotonin, catecholamines, tyramine, beta-phenylethylamine, benzylamine). In the year 1952, Selikoff and Robidzek observed that iproniazid had greater psychostimulatory effects than isoniazid in patients with and without tuberculosis. Subsequent studies by Smith, Kamman, and del Pino found similar stimulatory effects. The effects were described as mood elevating. The patients showed increased vigor and appetite, weight gain, improved sleep, and sociability. In some cases, it caused psychomotor agitation, hypersexuality and psychoses, behavior described as “dancing in the hall”. Lurie, a private psychiatrist, coined the term “antidepressant” for the psychostimulatory effects of isoniazid in depressed patients. Until then various terms such as “thymeretics” and “psychic energizers” were used to describe these effects. Kline, Loomer, and Saunders found a correlation between the effects of the antitubercular agents and their inhibitory action on MAO and used iproniazid for the first time on a group of patients with depression. They recorded significant improvement in 70% of the patients. Later studies showed that its MAO-inhibiting property increased serotonin levels in the brain similar to the effects seen with 5-hydroxytryptophan, a precursor of serotonin, which crosses the blood-brain barrier. This was also substantiated by the reversal of reserpine-induced depression by iproniazid, as reserpine depletes biogenic amines. These studies showed promising results in depression through clinical and biochemical observations. Iproniazid was launched as an antitubercular agent because of disagreements among psychiatrists and also due to its hepato and nephrotoxicity. The drug and some other hydrazine derivatives were later taken off of the market.[2,3]

The above findings paved the way to the development of the first class of exclusive MAO inhibitors such as isocarboxazid, tranylcypromine, phenelzine, mebanazine, nialamide, pheniprazine, and etryptamine (an indole derivative). In the meantime, the enzyme MAO was reported by Johnston, in 1968, to exist in two isomeric forms. MAO-A deaminated adrenaline, noradrenaline, and serotonin, whereas MAO-B acted on benzylamine and tyramine, beta-phenylethylamine, and other amines. In the year 1952, Selikoff and Robidzek observed that iproniazid had greater psychostimulatory effects than isoniazid in patients with and without tuberculosis. Subsequent studies by Smith, Kamman, and del Pino found similar stimulatory effects. The effects were described as mood elevating. The patients showed increased vigor and appetite, weight gain, improved sleep, and sociability. In some cases, it caused psychomotor agitation, hypersexuality and psychoses, behavior described as “dancing in the hall”. Lurie, a private psychiatrist, coined the term “antidepressant” for the psychostimulatory effects of isoniazid in depressed patients. Until then various terms such as “thymeretics” and “psychic energizers” were used to describe these effects. Kline, Loomer, and Saunders found a correlation between the effects of the antitubercular agents and their inhibitory action on MAO and used iproniazid for the first time on a group of patients with depression. They recorded significant improvement in 70% of the patients. Later studies showed that its MAO-inhibiting property increased serotonin levels in the brain similar to the effects seen with 5-hydroxytryptophan, a precursor of serotonin, which crosses the blood-brain barrier. This was also substantiated by the reversal of reserpine-induced depression by iproniazid, as reserpine depletes biogenic amines. These studies showed promising results in depression through clinical and biochemical observations. Iproniazid was launched as an antitubercular agent because of disagreements among psychiatrists and also due to its hepato and nephrotoxicity. The drug and some other hydrazine derivatives were later taken off of the market.[2,3]
β-phenylethylamine. Dopamine and tyramine were the substrates for both of the isoforms. The classical MAO inhibitors such as tranylcypromine and phenelzine inhibited both the isoenzymes. Tranylcypromine, a derivative of cyclopropylamine, was first used in 1959 as an antidepressant, and soon MAO inhibitors became frequently prescribed antidepressants. Later on, there were several reports of these drugs being associated with hepatotoxicity and death due to hypertensive crises and intracranial hemorrhages. The hypertensive crisis was particularly seen with the concomitant administration of sympathomimetics. This was first described by Blackwell and he called it the “cheese effect”, as it was associated with the consumption of certain types of cheese. This rise in the blood pressure was because of irreversible inhibition of MAO-A (published as the first psychiatric pearl in IJP). The necessity to avoid this side effect resulted in the synthesis of selective inhibitors such as l-deprenyl (selective, irreversible inhibitor of MAO-B) and moclobemide (selective, reversible inhibitor of MAO-A) to avoid the fatal hypertensive crisis. L-Deprenyl was not a particularly effective antidepressant, but proved useful in treatment of Parkinson’s disease; however, recently it has been used as an antidepressant given transdermally[6]. Currently, MAO inhibitors are not first choice antidepressants, and are usually used only when there is intolerance or lack of response to the newer drugs, refractory depression or when ECT is contraindicated.[1]

The tricyclic antidepressants are derived from antihistaminic compounds, which were the precursors of phenothiazines, the discovery of which was a revolution in the history of biological psychiatry. In 1948, Halfinger and Schindler, working at Geigy, synthesized 42 products from iminodibenzyl. Kuhn headed the experiments on G-22150. After the initial animal and human studies, he found no sedative effects but observed that the drug had some positive effects on psychiatric patients. In 1952, Deniker and Delay had a breakthrough with chlorpromazine as an effective antipsychotic. Kuhn wanted to test the efficacy of G-22150 as an antipsychotic but was given G-22355 (imipramine) instead due to G-22150’s intolerable side effects. In 1956, Kuhn used imipramine, which had a similar side chain as chlorpromazine, on patients with depressive psychosis and witnessed a remarkable improvement within a few weeks. Extended studies for a year showed that the drug was very effective and the finding was published in a Swiss journal in 1957. Once again the product had to face skepticism, like chlorpromazine. During those times, the hypothesis of depression stemming from intrapsychic conflicts was firmly held, and hence it was believed that the antidepressants could only result in symptomatic relief. Geigy introduced imipramine onto the market in 1957 and named it “Tofranil”. The drug continued to be a success in patients with depression and Kuhn started to give lectures on recommendations regarding the indications, dosage and duration of treatment. This was followed by two publications in the American Journal of Psychiatry. Kuhn’s observations were confirmed by other studies, including those of Lehmann who agreed with Kuhn about the significance of imipramine in depressive illnesses. Hence, Roland Kuhn is considered one of the pioneers in biological psychiatry and psychopharmacology. In 1961, a second tricyclic antidepressant, amitriptyline, was synthesized and Frank Ayd Jr showed that this compound had similar effects to imipramine; amitriptyline was launched as “Elavil”. Series of tricyclics followed, desipramine, nortriptyline, trimipramine, and doxepin. Clomipramine, synthesized in 1958, was also found to be effective in obsessive compulsive disorder after a series of studies in 1967 and the drug was launched in 1975. The first tetracyclic antidepressant, maprotiline, was developed by Wilhelm and Schmidt in 1967 and clinical studies conducted by Kuhn found it to be an effective antidepressant. Mianserin, another tetracyclic, is presently being used in depression in the elderly and for pain modulation.[2]

The comparable effects of both MAO inhibitors and tricyclics led to the hypothesis by Sulser and Axelrod in 1960 that despite different mechanisms, the final mode of action was common, i.e., increased availability of free serotonin and catecholamines in the brain.[3] is also worth mentioning here the effectiveness of these agents in other medical illnesses such as various anxiety disorders, migraine, chronic pain, irritable bowel syndrome, and chronic urticaria.

The above discoveries led to a new era in the development of psychotropics, i.e., the era of rational drug development, in which the molecules are designed to act on a particular site, receptors or enzymes or reuptake pumps. This approach avoids the undesirable side effects of serendipitously discovered drugs, which often have actions on multiple sites such as cholinergic, alpha-adrenergic, histaminic, and fast sodium ion channels. Dr. Arvid Carlsson was the first one to develop the antidepressant compound, zimeldine, which was the first selective serotonin re-uptake inhibitor (SSRI). The precursor of this drug was brompheniramine. Here, one should note that he also did substantial work on the synthesis and metabolism of 5-hydroxytryptamine (serotonin) in the central nervous system.[4,5] Zimelidine produced a serious neurological side effect, Guillian-Barre syndrome, in a few patients and thus was withdrawn from the market.[6]

Five new SSRI antidepressants were designed by five different pharmaceutical companies[7]. They were fluoxetine, fluvoxamine, paroxetine, sertraline, and citalopram (which is now also marketed as S-enantiomer). These drugs act on serotonergic neurons, thus inherently causing side effects related to serotonin function namely sexual dysfunction, nausea, incoordination, tremors, akathisia, and the serotonin syndrome, which can be fatal. The ever increasing knowledge of pathophysiological mechanisms of depression
has led to the synthesis of other drugs, which affect both serotonin and norepinephrine reuptake (SNRIs: venlafaxine, duloxetine). These drugs inhibit norepinephrine and dopamine reuptake (bupropion and its metabolites), and antagonize serotonin-2 receptor (trazodone) or presynaptic α2 adrenergic receptors (mirtazapine) in addition to inhibiting serotonin reuptake. Currently, the indications for many Antidepressant drugs have broadened to a wide variety of psychiatric illnesses such as panic disorder, obsessive compulsive disorder, generalized anxiety disorder, phobic disorders, and premature ejaculation.\[8\]

At present, SSRIs and SNRIs are the first drugs of choice for most psychiatrists to treat depressive illness but the antidepressants also have an undeniable place in the management of depression. Sometimes the combination of SSRIs with tricyclic antidepressants is of great value in the management of treatment-resistant depression.

Knowledge of brain function and of the neurobiology of depression has increased enormously in recent years and has increased awareness that the biogenic amines cannot be considered in isolation with regard to the etiology and pharmacotherapy of depression. Exciting new targets, which are being investigated with regard to antidepressant drug development, include the amino acids GABA and glutamate, neuroactive steroids, corticotrophin releasing factor (CRF), and substance P, cytokines, neurotrophic factors, and melatonin receptors. Some atypical antipsychotics now appear to be useful antidepressants when combined with standard antidepressants or even on their own. These new developments in antidepressant research have been reviewed recently.\[9-11\]

REFERENCES


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