

MONO-AMINE THEORY AND THE EVOLUTION OF ANTIDEPRESSANT THERAPY

D. Hackett

Neuroscience Clinical Research and Development, Wyeth Research, Paris,
France.

INTRODUCTION

The evolution of antidepressant therapy has until the mid 1990s tended to focus on improvements in tolerability and safety. Current antidepressants, however, achieve remission of symptoms in fewer than 50% treated patients, and improving efficacy must remain a vital developmental aim. The first antidepressants were discovered serendipitously in the clinic, from which followed the monoamine theory. Subsequent antidepressant development relied upon this theory itself with additional refinement and adaptation. Although, neither the pathophysiology of depression nor the regulation of normal mood may yet be said to be precisely understood, the monoamine theory has proven invaluable in the development of therapies for the treatment of depression and other mood or anxiety disorders. The considerable, and almost overwhelming, problems arising from the variability and inconsistency of the signal coming from clinical trials of antidepressants in patients (1) has prevented reliable comparisons of therapeutic options. To overcome this problem, in recent years there has been an increase in the meta-analyses of comparative studies of antidepressant trials in order to determine whether antidepressants with differing mechanisms differ in their efficacy.

DEVELOPMENT OF THE MONO-AMINE THEORY

While searching to find "chlorpromazine-like" compounds to treat schizophrenia, imipramine was recognized by Kuhn (1957) (2) for its antidepressant properties. With the introduction of imipramine, the first monoamine uptake inhibitor antidepressant, and iproniazide, the first monoamine oxidase inhibitor antidepressant (Loomer, Saunders and Kline, 1957) (3), the theory and treatment of depression changed. These early studies still summarise much of our current knowledge of the therapeutic effects of antidepressant treatments. For example, Andersen & Kristiansen in 1959 (4) studied imipramine in doses up to 350 mg/day, primarily in patients with endogenous depression. They found that 84% patients "improved" and that 54% were "cured". Tolerability and side effects were rather well characterised (even from today's perspective), and the need for maintenance therapy to prevent relapse was identified. The presence of withdrawal symptoms in 17% patients was described.

The activity of these agents was later hypothesised to be catecholamine based. This postulated that depression arises as a consequence of a deficiency of noradrenaline (Schildkraut, 1965) (5). The strength of this hypothesis was that it incorporated the possibility of experimental testing, e.g. by depleting catecholamine in animals using reserpine and the reversal of these effects by antidepressants. The

catecholamine hypothesis was later modified to take into account the extensive data that implicated serotonin in the aetiology of depression (van Praag & Korf, 1971 (6); Coppen et al, 1972 (7)).

Subsequent to the introduction of imipramine, a large number of drugs with a similar pharmacological profile were synthesized. Over the 2 decades following the introduction of imipramine, at least ten structurally similar and ten structurally different groups of non-tricyclic monoamine reuptake inhibitor antidepressants were identified. Today, monoamine reuptake inhibitors are the most extensively used group of drugs to treat depression.

The recognition that some mono-amine antidepressants were neither reuptake inhibitors nor mono-amine oxidase inhibitors brought to attention a third mechanism, that of direct activity at receptors that regulates monoamine transmission. For example, enhancement of noradrenaline availability at the synaptic gap can be obtained through blockade by mianserin of the presynaptic alpha₂-autoreceptors that modulate the release of noradrenaline (8).

CURRENT CLASSES OF ANTIDEPRESSANTS BASED ON MONO-AMINE THEORY

The monoamine theory of depression “proposes that depression is due to a deficiency in one or another of three monoamines, namely serotonin, noradrenaline (noradrenaline) and or/dopamine” (Stahl, 2000) (9). Antidepressant therapy aims to correct these deficiencies.

The evolution of antidepressant therapy has been primarily one of increasing specificity of effect, and manipulation of selectivity of mechanism. “Specificity” is used here to denote activity only on the principle of the putative therapeutic mechanism (i.e. removing extraneous activities), and “selectivity” to denote activity on a subset of one or more of the therapeutic mechanism(s).

It is clear from early theory and substantiated by subsequent progress that the wide range of receptor activities (particularly histamine₁, alpha₁-adrenergic, antimuscarinic, etc) associated with the early tricyclics are not necessary to their therapeutic action, but contribute significantly to side effects. Most developments of therapy have sought to remove these properties. There were also attempts to increase the specificity of effect of monoamine oxidase inhibitors.

With the possible exception of clomipramine that showed some selectivity for serotonin, early antidepressants were either non-selective or were selective for noradrenaline. Newer antidepressants, such as fluoxetine, sertraline, and paroxetine, show selectivity for 5-HT reuptake inhibition. Recently a specific and selective noradrenaline reuptake inhibitor, reboxetine, has been approved for use in many markets. This allows for the exploration of the roles of noradrenaline vs. serotonin using treatments that are devoid of confounding receptor activities. Conscious targeting of more than one neurotransmitter activity followed next e.g. of serotonergic and noradrenergic mechanisms, or of noradrenaline and dopamine, while retaining specificity. Examples are venlafaxine, milnacipran, duloxetine and bupropion. Finally, therapies were developed that aimed to act more directly on one or other of the processes of receptor adaptation thought to underlie the final common pathway of antidepressant action, such as mianserin and mirtazepine.

One evident problem of the original monoamine model was that while enhancement of mono-aminergic function occurs almost immediately, chronic administration of antidepressants is needed before clinical efficacy is attained (10, 11). It is generally considered that the therapeutic effect of an antidepressant is observed after a period of 3 to 6 weeks of treatment. This suggests that certain adaptive changes that occur with chronic administration of these drugs may be important for their antidepressant action. This concept has been the motivating force for much of the evolution of monoamine theory (12). Over the years, mechanisms such as down-regulation of beta-adrenergic receptors, desensitisation of presynaptic alpha-2 adrenoceptors, increased postsynaptic serotonin receptor sensitivity, down regulation of 5-HT₂ receptors and desensitisation of presynaptic 5-HT_{1A} receptor have been cited as the final common pathway or, more modestly, as one of many possible final common pathways (13, 14).

There are now at least 9 different clinically proven classes of antidepressant therapies (9) based upon the mono-amine theory: These are variously grouped according to chemical structure (the TCAs), specificity of effect, mechanism and/or selectivity of mechanism: mono-amine oxidase inhibitors (MAOIs), reversible inhibitors of MAO type A (RIMA), selective serotonin re-uptake inhibitors (SSRIs), selective noradrenaline reuptake inhibitors (sNARI or NARI), serotonin and noradrenaline reuptake inhibitor (SNRI), noradrenaline and dopamine reuptake inhibitor (NDRI), alpha 2 antagonism, alpha 2 antagonism with other receptor activity (noradrenergic and specific serotonergic antidepressant or NasSA), or serotonin antagonist and reuptake inhibitor (SARI). A possible 10th class that appears to run counter to the current theory is that of serotonin reuptake stimulants. Unlike other antidepressant agents, tianeptine, a modified tricyclic, stimulates the uptake of serotonin in rat brain synaptosomes and rat and human platelets and reduces serotonergic-induced behaviour, and is an effective antidepressant (15).

MONOAMINE THEORY AND THE PATHOPHYSIOLOGY OF DEPRESSION

While most evidence supports a role for increased mono-amine neurotransmission in the therapy of depressive disorders, it is not clear whether impairments in mono-amine function are actually responsible for the clinical signs of depression.

Recent studies appear to confirm that the anti-depressive action of antidepressants is indeed a function of their monoamine activity. Firstly, administration of parachlorophenylalanine, a 5-HT synthesis inhibitor, produced relapse in depressed patients successfully treated with imipramine or tranylcypromine, while administration of α -methyl-paratyrosine, which reversibly inhibits the rate-limiting step in the synthesis of dopamine and noradrenaline, did not (Shopsin et al, 1975 (16); 1976 (17)). Secondly, studies have been conducted which decrease serotonin by dietary manipulation of tryptophan. The synthesis of serotonin in the brain is dependent upon the availability of its amino acid precursor tryptophan from plasma. It is possible to produce a rapid lowering of tryptophan availability to the brain by replacing a normal balanced diet with an amino acid mixture lacking tryptophan. This lowers the concentration of tryptophan in plasma and inhibits transport across the blood-brain barrier. As a result serotonin synthesis and release are decreased. It has been found that such a procedure reverses the therapeutic effects

of treatment with antidepressants that have predominantly serotonin reuptake inhibitory activity (e.g. fluoxetine), but less so with those which have predominantly noradrenaline reuptake inhibitory activity (e.g. desipramine) (18). Thirdly, alpha-methyl-paratyrosine (AMPT), which causes a rapid depletion of catecholamines, reverses the therapeutic effects of desipramine more than that of fluoxetine or sertraline (19).

These studies show that in patients, the mechanism of action of SSRIs, at least as immediately manifest, does not *critically* involve noradrenaline; while the mechanism of action of NARIs does not *critically* involve serotonin. These conclusions further suggest that there may be more than one type of depression, i.e. that a broad spectrum antidepressant may be effective in a wider range of patients than a more selective agent, and/or that a broad spectrum agent may improve a wider range of symptoms.

Recent data provides evidence that clinical depression is due to a deficiency in these same mono-amines. It was initially found that a tryptophan-free diet had no effect on the mood of normal volunteers. However, Smith et al (1997) (20) showed that a tryptophan free diet could precipitate clinically depressive symptoms in women who had suffered recurrent episodes in depression, but who were currently well and no longer on drug treatment.

DO DIFFERENT MECHANISMS PROVIDE DIFFERENT EFFICACY?

Differences in general tolerability of different classes of antidepressants and in their side effects profiles are well known and generally accepted. Compared with TCAs, SSRIs cause significantly more nausea, diarrhoea, agitation, anorexia, insomnia, nervousness and anxiety, while TCAs caused more dry mouth, constipation, dizziness, sweating, blurred vision (21). These profiles do not just differ: there is also consistent evidence that SSRIs as a group are better tolerated than TCAs (21).

Despite pharmacological differences in the type of mono-amine neurotransmission mechanisms of the different classes of antidepressants, the general view taken is that all antidepressants are of equal efficacy. Only within the last 10 years has this general assumption come under serious challenge, from comparisons of antidepressants with a dual mechanism of action compared with those with a single mechanism of action (eg 22, 23, 24, 25, 26 and as exemplified by the work of Lars Gram presented at a previous Euro-conference on this same topic (27)).

There are many reasons why differences in efficacy of antidepressants are difficult to detect, and more importantly reproduce. Using standard assessment instruments the signal in double-blind controlled trials is not as strong as we might imagine. On average, a difference of less than 3 points on the standard Hamilton (28) rating scale of severity of depression (the HAM-D) between active drug and placebo is found across a range of studies; and there is a failure rate greater than 50% in studies to show a statistically significant difference from placebo (1). If being able to reliably detect a difference from placebo is difficult, then finding differences between antidepressants can be seen to be formidable, even if they exist, under the normal conditions of clinical trials.

One method to overcome these problems that is being increasingly adopted is by the use of meta-analyses. In a classical meta-analysis, the unit of analysis is the study and the analysis uses summary statistics of the results of each study from which

to draw conclusions. In the pooled analysis (or mega analysis) (29), the original data from each subject is the unit of analysis, and allows for a more sophisticated and detailed analysis of the individual characteristics that might mediate the effects. A number of such pooled analyses are now available. Some of the meta-analyses reported have involved groups of more than 100 studies, though many have much fewer studies.

The weakness of the meta-or mega-analysis is the fact that combining trials that have been conducted over the last few decades inevitably means combining studies that may vary in their methodological exactness, including a lack of consistent intention to-treat samples - especially in the earlier studies.

Various questions have been addressed in these analyses: amongst many others, the comparable efficacy and tolerability of SSRIs and TCAs (30), of RIMAs and TCAs (31), of the SNRI, venlafaxine, with SSRIs and other antidepressants (32), of paroxetine with TCAs (33). Freemantle et al (34) have specifically attempted to examine the factor of pharmacological profile of mechanism. Mega-analyses of large databases have been reported for venlafaxine (comparative rates of remission) by Thase (35), and for mirtazapine (comparative onset of action) by Van Oers (36).

A comprehensive review of meta-/mega-analyses up until 2001, has been provided by Anderson (21). On the basis of the results of the meta-analyses as well as the perceived strengths and limitations of these meta-analyses, according to the number and quality of the studies, and their variations in design and study population, conclusions drawn by the author were grouped by levels of higher or lower confidence. Amongst the higher confidence conclusions were that SSRIs are generally as effective as TCAs, that fluoxetine has a slower onset of therapeutic action than other SSRIs, that venlafaxine is more effective than SSRIs, that SSRIs are better tolerated than TCAs. Conclusions with a lower confidence conclusion were that TCAs are more effective than SSRIs in in-patients; amitriptyline is more effective than SSRIs, but that mirtazapine is as effective as amitriptyline.

Additional to general differences in efficacy there have always been suggestions that efficacy based upon a noradrenergic effect would have a different profile from that based upon a serotonergic effect. The possibility exists to evaluate this concept more thoroughly given the availability of the NARI, reboxetine. In addition, increasing attention is currently being paid to more detailed examination of the precise effects of antidepressants rather than to single total score figures on rating scales (e.g. 37). These more detailed assessments may begin to reveal in a systematic way, differences in the efficacy profiles of antidepressant therapies across a range of symptoms, as well as across different dimensions of improvement e.g. social adaptation. The use of analyses of itemised symptoms from the HAM-D, using pooled databases will allow such profile comparisons to be systematised. Already such methods have found differences between venlafaxine and SSRIs (e.g. 38). Single studies of reboxetine already point to the possibility that the noradrenergic mechanism may offer better efficacy compared with the serotonin mechanism in improving patient motivation and self-perception in patients (Massana, 1999) (39).

These meta-analyses are beginning to have an impact on published guidelines for the treatment of depression (e.g. 40), and we should expect further confirmation of comparative conclusions. It is probable that we are entering a period when improvements in methodology will allow a more pre-eminent role of clinical research in the evaluation and further development of the monoamine theory of antidepressant therapy.

REFERENCES

- 1** Storosum JG, Elferink AJA, Van Zwieten BJ, et al. Short-Term Efficacy of Tricyclic Antidepressants Revisited. A Meta-Analytic Study. *European Neuropsychopharmacology*, 11:173-180, 2001.
- 2** Kuhn R. Über Die Behandlung Depressives Zustände Mit Einem Iminobenzylderivat (G 22,355). *Schweiz. Med. Wschr.* 87:1135-1140;1957.
- 3** Loomer HP, Saunders JC, Kline NS. A Clinical and Pharmacodynamic Evaluation of Iproniazid as a Psychic Energizer. *Psychiat. Res. Rep. Amer. Psychiat. Ass.* 8:129-141,1957.
- 4** Andersen H, Kristiansen ES. Tofranil Treatment of Endogenous Depressions. *Acta Psych. Et Neurol Scand.* 34:387-397, 1959.
- 5** Schildkraut JJ, Klerman GL, Hammond R et al. Excretion of 3-Methoxy-Mandelic acid (VMA) in Depressed Patients Treated with Antidepressant Drugs. *J Psychiatric Research* 2:257-266;1965.
- 6** van Praag HK, Korf J. Endogenous Depression With and Without Disturbance of 5-Hydroxytryptamine Metabolism: A Biochemical Classification? *Psychopharmacology* 19:148-152;1971.
- 7** Coppen A, Prange AJ, Jr., Whybrow PC, Noguera R. Abnormalities of Indoleamines in Affective Disorders. *Arch Gen Psychiat* 26:474-478;1972.
- 8** Leonard BE, O'Connor WT. Effects of Isomers of The 6-Aza Derivative of Mianserin on Behaviour and Noradrenaline Metabolism in Bulbectomised Rats. *Br. J Pharmacology* 82:246;1984
- 9** Stahl SM. *Psychopharmacology of Antidepressants*. ISBN 1-85317-513-7, Martin Dunitz Publisher, London.
- 10** Oswald I, Brezinova LE, Dunleavy DLF. On the Slowness of Action of Tricyclic Antidepressant Drugs. *Br J Psychiatry.* 120:673-677;1972.
- 11** Bradshaw CM, Roberts MHT, Szabadi E. Comparisons of the Effects of Imipramine and Desipramine on Single Cortical Neurones. *Br J Pharmacology* 52:349-358;1974.
- 12** Leonard BE. Neurotransmitter Receptors, Endocrine Responses and the Biological Substrates of Depression: A Review. *Human Psychopharmacology* 1:3-21;1986.
- 13** Brunello N, Mendlewicz J, Kasper S et al. The Role of Noradrenaline and Selective Reuptake Inhibition in Depression. *European Neuropsychopharmacology* 12:461-475;2002.
- 14** Blier P, de Montigny C. Current Advances and Trends in the Treatment of Depression. *Trends in Pharmacological Sciences.* 15:220-6;1994.
- 15** Ginestet D. Efficacy of Tianeptine in Major Depressive Disorders With or Without Melancholia. *European Neuropsychopharmacology* 7(Suppl 3):S341-345;1997
- 16** Shopsin B, Gershon S, Goldstein M et al. Use of Synthesis Inhibitors In Defining a Role for Biogenic Amines During Imipramine Treatment in Depressed Patients. *Psychopharmacology Communication* 1:239-249;1975.
- 17** Shopsin B, Friedman, E, Gershon S: Parachlorophenylalanine Reversal of Tranylcypromine Effects in Depressed Patients. *Arch Gen Psychiatry* 33:811-819;1976.
- 18** Delgado PL, Price LH, Miller HL et al. Serotonin and the Neurobiology of Depression. Effects of Tryptophan Depletion in Drug-Free Depressed Patients. *Arch Gen Psychiatry* 51:865-874;1994.
- 19** Miller HL, Delgado PL, Salomon RM, et al. Clinical and Biochemical Effects of Catecholamine Depletion on Antidepressant-Induced Remission of Depression. *Arch Gen Psychiatry* 53:117-128;1996.
- 20** Smith KA, Fairburn CG, Cowen PJ. Relapse of Depression After Rapid Depletion of Tryptophan. *Lancet* 349:915-919;1997.
- 21** Anderson IM. Meta-Analytical Studies on New Antidepressants. *Br Med Bull* 57:161-178;2001.
- 22** Guelfi JD, White C, Hackett D, et al. Effectiveness of Venlafaxine in Patients Hospitalized for Major Depression and Melancholia. *J Clin Psychiatry* 56:450-8;1995.
- 23** Benkert O, Grunder G, Wetzel H, Hackett D. A Randomized, Double-Blind Comparison of a Rapidly Escalating Dose of Venlafaxine and Imipramine in Inpatients with Major Depression and Melancholia. *J Psychiatr Res.* 30:441-51;1996.

-
- 24** Clerc GE, Ruimy P, Verdeau-Palles J. A Double-Blind Comparison of Venlafaxine and Fluoxetine in Patients Hospitalized for Major Depression and Melancholia. The Venlafaxine French Inpatient Study Group. *Int Clin Psychopharmacology* 9:139-43;1994.
- 25** Lecrubier Y, Bourin M, Moon CA, Schifano F, Blanchard C, Danjou P, Hackett D. Efficacy of Venlafaxine in Depressive Illness in General Practice. *Acta Psychiatr Scand*. 95:485-93;1997.
- 26** Goldstein DJ, Mallinckrodt C, Lu Y, Demitrack MA. Duloxetine in the Treatment of Major Depressive Disorder: a Double-Blind Clinical Trial. *J Clin Psychiatry* 63:225-231;2002.
- 27** Gram LF. Antidepressant Drugs for the 21st Century. SSRI Versus Serotonin/Noradrenaline Inhibitors. Institut Pasteur, October 1995.
- 28** Hamilton M. A Rating Scale for Depression. *J Neurol Neurosurg Psychiatry* 23:56-62;1960.
- 29** Olkin I. Meta-Analyses Reconciling the Results of Independent Studies. *Statist Med* 14:457-472;1995.
- 30** Anderson IM. Selective Serotonin Re-Uptake Inhibitors Versus Tricyclic Antidepressants: A Meta-Analysis of Efficacy and Tolerability. *J Affect Dis* 58:19-36;2000.
- 31** Lotufo-Neto F, Trivedi M, Thase ME. Meta-Analysis of the Reversible Inhibitors of Monoamine Oxidase Type A Moclobemide and Brofaramine for the Treatment of Depression. *Neuropsychopharmacology* 20:226-247;1999.
- 32** Smith D, Dempster C, Glanville J, Freemantle N, Anderson I. Efficacy and Tolerability of Venlafaxine Compared With Selective Serotonin Reuptake Inhibitors and Other Antidepressants: A Meta-Analysis. *Br J Psychiatry* 180:396-404;2002.
- 33** Montgomery SA. A Meta-Analysis of The Efficacy and Tolerability of Paroxetine Versus Tricyclic Antidepressants in the Treatment of Major Depression. *Int Clin Psychopharmacology* 16:169-178;2001.
- 34** Freemantle N, Anderson IM, Young P. Predictive Value of Pharmacological Activity for the Relative Efficacy of Antidepressant Drugs. Meta-Regression Analysis. *Br J Psychiatry* 177:292-302;2000.
- 35** Thase ME, Entsuah AR, Rudolph RL. Remission Rates During Treatment with Venlafaxine or Selective Serotonin Re-Uptake Inhibitors. *Br J Psychiatry* 178:324-241;2001.
- 36** van Oers H, Schutte AJ, van Hensbeek I. Mirtazapine Versus Other New-Generation Antidepressants: Pooled Analysis on the Onset of Action. *J Eur Coll Neuropsychopharmacology* 12(Suppl3):S187;2002 (abstract).
- 37** Meoni P, Salinas E, Brault Y, Hackett D. Pattern of symptom improvement following treatment with venlafaxine XR in patients with generalized anxiety disorder. *J Clin Psychiatry*. 62:888-93;2001.
- 38** Entsuah R, Shaffer M, Zhang J. A Critical Examination of the Sensitivity of Unidimensional Subscales from the Hamilton Depression Rating Scale to Antidepressant Drug Effects. *J Psychiatric Res* 36:437-448;2002.
- 39** Massana J. Reboxetine: A Double-Blind Comparison With Fluoxetine in Major Depressive Disorder. *Int Clin Psychopharmacology* 14:73-80;1999.
- 40** Anderson IM, Nutt DJ, Deakin JFW. Evidence-Based Guidelines for Treating Depressive Disorders with Antidepressants: A Revision of the 1993 British Association for Psychopharmacology Guidelines. *J Psychopharmacology* 14:3-20;2000.