Depression may be associated with hippocampal volume changes and HPA axis dysfunction: Is treatment to remission the answer?

Roger M Pinder
Vice President Medical Affairs CNS and Thrombosis, NV Organon,The Netherlands

Abstract
Under-treatment of depression is common practice and carries substantial risks of relapse and recurrence while increasing morbidity and mortality in co-morbid medical illnesses. It may also lead to or exacerbate structural brain changes in depression, most particularly in the hippocampus, with an accompanying decline in cognitive functioning. Treatment to full remission of symptoms and maintaining patients in remission is therefore essential. Although all current antidepressants seem to provide comparable efficacy in preventing relapse, some of the newer dual action antidepressants can induce a faster response and produce greater degrees of remission. However, remission rates are low even with the best treatments. There remains a need for treatments that will act quickly to reverse not only the symptoms of depression but also the accompanying brain abnormalities.

Keywords: *Antidepressants, Depression, Hippocampus, HPA Axis, Remission*

Treatment of depression has long been a hit-and-miss affair. Community surveys have consistently shown that only half of patients with depression are properly diagnosed of whom half receive any form of treatment.[1,2] Furthermore, of those who actually receive treatment only half receive adequate doses and durations of therapy. Those patients who achieve remission are a rare breed.[3] Failure to receive adequate treatment to full remission carries considerable risks not only for the evolution of the depressive disorder itself but also for extra morbidity and mortality in a wide range of medical illnesses.[3,4] The economic and social burden of inadequately treated depression is substantial[5] and is considerably greater in the presence of medical comorbidity.[6] Remission of symptoms and a return to full psychosocial functioning has therefore become the new goal of treatment.[7]

At the same time, depression is increasingly being viewed as more of a disease of the brain than of the mind. Neuroimaging studies have revealed structural changes in the brains of depressed patients within the neuroanatomical circuit of Nauta termed the limbic-cortical-striatal-pallidal-thalamic tract.[8] The importance of the hippocampus in depressive pathophysiology is now supported by a large body of evidence suggesting that hippocampal volume is reduced in depressed patients.[9] This reduction in volume and the associated deficits in cognitive functioning may occur at their greatest rates in the early years after onset of illness and be greatest in patients with a chronic and recurrent course. Mechanisms proposed to explain hippocampal volume loss in depression include hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis and associated glucocorticoid neurotoxicity, decreased levels of brain-derived neurotrophic factor (BDNF) and associated diminished neurogenesis, and loss of plasticity.[8]

Correspondence:
Dr RM Pinder,Vice President Medical Affairs CNS and Thrombosis, NV Organon, KA2091, Molenstraat 110, PO Box 20, 5340BH, Oss, The Netherlands
email: roger.pinder@organon.com

Treatment Outcome in Depression

Current definitions of treatment outcome in depression date from the 1990s (Table 1); response, remission, relapse, recovery and recurrence are conceptual definitions which were accompanied by operational outcome criteria such as asymptomatic, fully symptomatic, episode, full remission and recovery.[7,10] Outcome criteria were and are based upon assessment scales like the Hamilton Rating Scale for Depression (HAM-D), the Montgomery Åsberg Depression Rating Scale (MADRS) and the Clinical Global Impressions (CGI). Response is typically defined as a greater than 50% decrease from the baseline score, while remission criteria have finally settled at a HAM-D17 score of 7 or less, MADRS score of 10 or less and a CGI-Improvement score equal to 1.[7] Psychosocial functioning is now regarded as a important outcome measure for full remission which may improve

Table 1. Definitions of Outcomes in Depression[7,10]

Response:	Patient no longer fully symptomatic but evidence of more than minimal symptoms.
Remission:	Patient no longer meets syndromal criteria and has no or minimal symptoms.
Relapse:	A return to a fully symptomatic state that occurs during remission; re-emergence of current episode.
Recovery:	Extended period of remission indicating end of current episode.
Recurrence:	Appearance of a new episode of major depression; occurs only during recovery.

independently of depressive symptoms and therefore require separate evaluation to determine whether patients have truly reached a state of wellness. In the future we may have to evaluate improvement in pathophysiology using neuroimaging techniques as part of the process of remission and recovery.

Effective treatments for depression have been available for half a century, with electroconvulsive therapy (ECT) preceding the development of antidepressant drugs, modern forms of psychotherapy and emerging methods for brain stimulation like vagus nerve stimulation (VNS) and transcranial magnetic stimulation (TMS). ECT needs a specialized setting and trained personnel, while its emotive aspects have restricted its use in many countries or confined it to the treatment of the very ill psychotic, delusional and often elderly patient. The principal forms of psychotherapy, Cognitive Behaviour Therapy (CBT) and Interpersonal Therapy (IPT), also require training and are labour intensive. Certainly VNS, and probably TMS, carries the same baggage. Although the therapeutic efficacy of many of these treatments is comparable[7], the focus in most countries and especially in primary care settings has therefore been on antidepressant drugs, which have become the mainstay of both acute and long-term management of depression.

There are many antidepressant drugs available, ranging from the original tricyclic antidepressants (TCAs) and their successors through the old and new monoamine oxidase inhibitors (MAOIs) to the modern Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin-Noradrenaline Reuptake Inhibitors (SNRIs), Noradrenaline Reuptake Inhibitors (NRIs), Noradrenaline and Serotonin Specific Antidepressants (NaSSAs) and others of an atypical nature.[11] At the last count, eighteen TCAs were available together with five MAOIs, six SSRIs, three SNRIs, two NRIs, one NaSSA and five others, as well as several mood stabilizers and herbal remedies. This rich panoply of drugs has not in general substantially improved upon the efficacy of the original examples of the genre, imipramine and iproniazid, although modern antidepressants lack many of the side effects and much of the toxicity of the first generation. What really distinguishes antidepressant drugs from placebo treatment, despite the relatively small effect sizes seen in short-term randomized clinical trials[12], is their ability to prevent relapse and recurrence upon longer term treatment.[13-15] Thus, many of the older TCAs and MAOIs[13] as well as all of the modern antidepressants including SSRIs, mirtazapine and nefazodone[15] have been shown to prevent relapse in placebo-controlled studies. As a general rule of thumb and despite variations in relapse rates in studies of individual antidepressants, about twice as many relapses occur on placebo as on antidepressants.[13-15] Appropriate maintenance treatment after initial recovery from the first episode of depression is essential since the probability of recurrence is high; patients who have had two episodes of major depression have a 60-90% chance of recurrence which increases to 95% in those who have had more than two episodes.[7,15]

Despite the broadly similar efficacy of different antidepressants in preventing relapse, there is growing evidence that they are not all equally effective in terms of speed of response and degree of remission.[16-23] The long-feared absolute mechanistic barrier to a fast action seems to have been a red herring, although the most widely prescribed group, the SSRIs, do have a built-in limitation because of their negative feedback action upon 5-HT autoreceptors.[11,24] Of the current antidepressants, the evidence for faster action and more remission is strongest for the two dual action agents, venlafaxine[21-23] and mirtazapine[16-20], although there is emerging data on a third such drug, duloxetine.[25] Such inferences can only be drawn when a consistent advantage is demonstrated across multiple methodologies, of which the most rigorous and sensitive appears to be survival analysis.[26,27] Multiple methodologies including survival analysis have been applied to both the venlafaxine and mirtazapine data bases although duloxetine still needs similar detailed attention. Pooled clinical trial data indicate that venlafaxine and mirtazapine are always at least a week ahead of the SSRIs in inducing response and additionally provide a greater degree of remission at the end of the studies (Table 2). In the only study comparing the two agents, performed over 8 weeks in severely ill, hospitalized depressed patients with melancholia, there were no statistically significant differences between the drugs in speed or degree or response and remission (Table 2).[28] Larger studies are needed, with sufficient statistical power to detect any differences that may exist between the two agents, before definite conclusions can be drawn about their relative efficacy.

The dual action antidepressants can provide better and faster efficacy than the SSRIs, but remission rates are still low even in the context of controlled clinical trials. Indeed, the majority of depressed patients do not experience a full return to psychosocial functioning on whatever treatment they are given, be it pharmacological, herbal, psychotherapeutic or one of the techniques for brain stimulation. Treatment outcome is still a hit-and-miss affair and requires assiduous choice and application of the many possibilities on offer. It will frequently involve switching, augmentation and combination strategies to achieve an optimal outcome. It is unclear whether our current treatment options will additionally reverse the structural brain changes that may be associated with depression.

Structural Brain Changes in Depression

Unusually high rates of depression are found in neurological diseases associated with both cortical and subcortical atrophy, including Huntingtons's disease, post-stroke syndromes, Alzheimer's disease, epilepsy and Parkinson's disease.[8] These disorders involve damage to parts of the brain associated with emotional functioning, most notably those in the neuroanatomical circuit of Nauta termed the limbic-cortical-striatal-pallidal-thalamic tract, which are also involved in major depression. Although a direct cause and effect relationship has not been established between structural impairment in neurological disease and depression, it may be that some neurological patients have an increased vulnerability to depression and that when depression occurs it may further contribute to additional structural damage.[8]

Table 2. Remission rates during clinical trials with venlafaxine, SSRIs and placebo,[23] mirtazapine and SSRIs,[20] and venlafaxine and mirtazapine[28]

After 8 Weeks of Treatment[a-d]

Venlafaxine (n=3300)	SSRIs (n=3236)	Placebo (n=927)
41%**	35%**	24%**

After 6 Weeks of Treatmenta-c,e

Mirtazapine (n=1402)	SSRIs (n=1405)
39%*	34%*

After 8 Weeks of Treatmenta

Venlafaxine (n=75)	Mirtazapine (n=77)
29% (ns)b	38% (ns)b
43% (ns)f	53% (ns)f

[a] All based upon the Intention-To-Treat population with missing data evaluated using the Last-Observation-Carried-Forward (LOCF) analysis
[b] HAM-D17 total score of 7 or less
[c] SSRIs included fluoxetine, paroxetine, sertraline, citalopram and fluvoxamine
[d] **P<0.001, venlafaxine-SSRIs, venlafaxine-placebo, SSRIs-placebo
[e] *P<0.03, mirtazapine-SSRIs
[f] MADRS total score of 12 or less

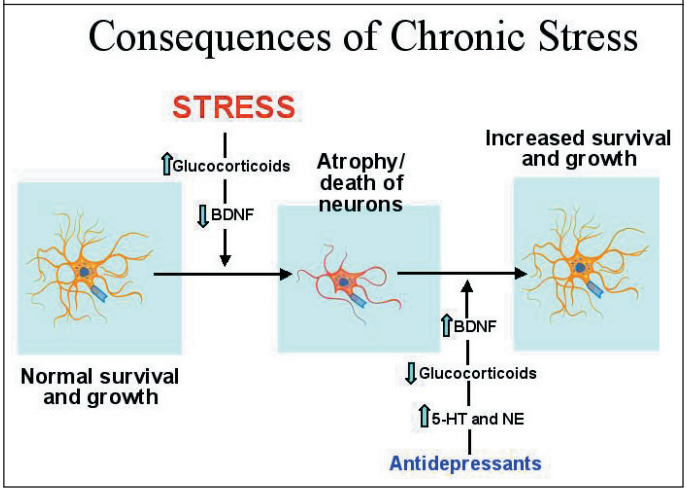
Neuroimaging studies in depressed patients have also revealed structural changes in the circuit of Nauta, but it is still unclear whether they are the cause or a consequence of the disorder.[8] Although structural changes have been reported in frontal cortex, amygdala and basal ganglia, the most consistent results have been found in the hippocampus. In general, depression seems to be associated with hippocampal volume loss ranging from 8 to 19%. Volume loss may have functional consequences, with reports of associations between acute depression and abnormalities of recollection[9] and declarative memory[29] as well as between depression in remission and impaired verbal memory.[30] Volume loss seems to be directly associated with illness duration[9,30,31] and severity of depression[32], and may be absent in remitted depression.[33] Although it is still unclear as to whether reductions in hippocampal volume antedate illness onset, volumes may decrease at their greatest rate in the early years after onset of depression and with multiple episodes.[9]

A large body of evidence in animal studies has also revealed memory deficits and hippocampal damage after exposure to stress.[34,35] Mechanisms invoked to explain these findings include glucocorticoid neurotoxicity, increased release of excitatory amino acids, inhibition of neurogenesis, loss of plasticity and decreased brain-derived neurotrophic factor (BDNF).[8] It is clear that some of the changes can be reversed by chronic antidepressant drug treatment; tianeptine can reverse stress-induced reductions in hippocampal volume and the associated neuronal atrophy in tree shrews[36], while a variety of antidepressant treatments including ECT, SSRIs, MAOIs and NRIs reversed hippocampal atrophy and promoted neurogenesis in the dentate gyrus of rat brain.[37,38] In human studies, successful treatment of depressed patients with a variety of antidepressant medications from TCAs, SSRIs and SNRIs to trazodone and mianserin restored their low serum levels of BDNF to normal.[39] In patients with post-traumatic stress disorder (PTSD), a condition also associated with hippocampal volume loss and a decline in verbal declarative memory, treatment with paroxetine restored both memory and hippocampal volume.[40] Antidepressants may have a neuroprotective effect during depression since hippocampal volume was predicted by the duration of untreated depression whereas there was no relationship between cumulative time treated with antidepressants during depression.[31]

The HPA Axis in Depression

The HPA axis and its vulnerability to stress may be the common factor in the hippocampal atrophy and associated memory deficits seen in depression and other disorders such as PTSD.[41] HPA axis hyperreactivity is common across a number of disorders and is not specific to depression. Excessive levels of glucocorticoids produced during HPA axis hyper-reactivity can lead to a state of glucocorticoid neurotoxicity and decreased levels of BDNF with neuronal atrophy in the hippocampus (Figure 1).[42] Although antidepressant treatments of many classes can indirectly up-regulate glucocorticoid receptors and restore HPA axis function[43], mirtazapine is unique in being able to inhibit cortisol secretion in depressed patients after both acute and chronic administration.[44] All other antidepressants stimulate cortisol secretion, including the other dual action antidepressant shown to produce faster and more remission, venlafaxine, although the doses used were below those needed for venlafaxine to exert its true SNRI effects. Although mirtazapine seems to exert its effects more by its influence upon 5-HT receptors than via any direct antagonism at central glucocorticoid receptors (GR), it may be the antidepressant of choice for reversing hypercortisolaemia and restoring normal HPA axis function. Studies of its influence upon hippocampal deficits in depression, both in volume and memory, are needed, especially since

Figure 1. Schematic representation of glucocorticoid neurotoxicity and its effect upon survival of hippocampal neurons (after Duman et al.42)



sustained central hypernoradrenergic activity in major depression with melancholia seems to be associated with hypercortisolaemia.[45] Mirtazapine is, above all, a central µ2-adrenoceptor antagonist.

Following the early experiments with steroid synthesis inhibitors in mood disorders the glucocorticoid receptor is now seen as a respectable therapeutic target, and direct antagonists of the receptor and of corticotropin-releasing hormone are in clinical development.[43] Early results look promising with the two leading GR antagonists, mifepristone in psychotic depression46 and ORG 34517 in dexamethasone non-suppressors.[47] It will be interesting to see whether these agents will reverse hippocampal abnormalities of volume and cognition simultaneously with their already demonstrated improvement of treatment outcome in symptomatology.

Conclusion

Remission rates are still low in depression even with the best treatments that we have available, including dual action antidepressants, ECT and CBT – a large proportion of patients are still not achieving a full response.[7] Indeed the very diversity of what we have available to treat depression speaks volumes about the heterogeneity of the diagnosis and its pathophysiology. One of the major obstacles to deciding the best approach to treating a particular patient with depression is the lack of understanding of the pathophysiology and neurobiology underlying the disorder. HPA axis hyper-reactivity and changes in hippocampal volume and function may be only the first hints of what is fundamentally wrong in the pathophysiology of depression. There is optimism and some data to suggest that we may be able to reverse both of these abnormalities with current antidepressants indirectly and possibly with new agents in a more direct fashion. There may well come a time when knowledge on the genetic vulnerability, other biological markers and the possible structural brain changes associated with depression is such that more specific therapies can be directed to a more highly selected group of patients while additionally allowing objective evaluation of treatment response. For the moment, resolution of symptoms remains the primary measure of improvement.

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Commentary

Andreas H. Schenk
Division of Psychiatry, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

Depression is a common disorder which appears to be underdiagnosed in the general population, and when diagnosed, rarely treated to remission. It is estimated that the economic costs as well as morbidity of untreated or partially treated depression are high and therefore much attention should be directed at optimal management. In order to achieve this goal a multifaceted approach is needed, including psychotherapy, pharmacotherapy, social intervention and management of comorbid conditions. It is clear that depression is a heterogenous disorder with many different causal pathways leading to depressive symptomatology. These pathways include both biological as well as environmental factors. However, polarisation of biological and psychosocial aspects of psychiatry has promoted a form of Cartesian dualism.[1] In this article by Dr Pinder, psychotherapy has been briefly mentioned in as far as its limitations are concerned and the bulk of the attention is given to biological causality and management. Although I agree with Dr. Pinder that psychotherapy use is restricted by the limitations mentioned (above all short term cost), I would argue that advances in neuroscience research have led to a more sophisticated, integrative understanding of the illness. In light of this it is of interest to note that psychotherapy has specific measurable effects on the brain independent of medication[2] and so it seems that depression can still be conceptualised as a disease of the mind as well as the brain.

Over and above the emphasis on biology evident in the article, one particular cluster of research findings has been isolated. The author has presented a well referenced review of these findings, and indeed a very compelling biological theory of depression involving structural brain changes and the HPA axis. More specifically he has elegantly linked depression induced hippocampal volume loss to hypercortisolaemia which in turn is linked to the ability of antidepressants to restore HPA axis function. Mention is also made of mirtazipine's unique ability amongst antidepressants to inhibit cortisol secretion in depressed patients.

Although it is tempting to accept these arguments given the extensive list of references, it is also important to remember that the list represents only a fraction of the total biological research done in depression. The publications are so numerous, and at times contradictory, that it is possible to preferentially select a number of them to support a specific theory or point of view. Keeping this in mind it is essential to state that the theories presented in the article are not universally agreed upon. The hippocampus is not the only area of the brain that has been focussed on in the genesis and treatment of depression. For instance axonal degeneration of noradrenergic axons has been proposed in the depression model.[3] Interestingly, it has been hypothesised that antidepressants such as desipramine may induce regeneration of noradrenergic neurons in the locus coeruleus. Even the fundamental link between depression, cortisol and neurodegeneration in the hippocampus has been questioned. The first study to investigate the postmortem anatomical consequences of glucocorticoid overexposure for neuronal viability in the hippocampus was published in 2001.[4] Interestingly, no significant structural or synaptic changes could be found in the hippocampi of 15 major depressed patients and it was concluded that hippocampal apoptosis in major depression is a minor event and absent from subareas at risk for glucocorticoid overexposure (such as CA3). It was suggested in this study that the decrease in hippocampal volume noted on MRI investigations could be due to a shift in water content.

Given our present lack of understanding and consensus into the neurobiology and pathophysiology of depression, I would strongly agree with Dr. Pinder that resolution of symptoms remains the primary measure of improvement. Treatment outcome comparing different antidepressant medications has been presented and the evidence appears to favour the dual action agents over other medication in terms of faster action and higher remission rates. It seems however unlikely that the faster response to ECT or structural brain changes with psychotherapy response adhere to the exact same biological pathways that are proposed for dual action antidepressants. This reinforces in my mind the concept of depression as a highly complex and heterogenous disorder that defies biological simplification.

Correspondence:
Dr AH Schenk, Division of Psychiatry, Faculty of Health Sciences, University of the Witwatersrand, 7 York Road, Parktown, 2193, Johannesburg, South Africa
email: andreas@yebo.co.za

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