DEPRESSION MANAGEMENT - FROM NEUROBIOLOGY TO A SHARED CARE APPROACH*

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SUMMARY
The management of depression has recently been the focus of several articles, in particular regarding the efficacy of pharmacological and other treatments. In order for these to be effective as possible, correct diagnosis, consideration of the underlying neurobiology and an appropriate provision of healthcare services must be ensured.

Key words: depressive disorder – depression - antidepressive agents

INTRODUCTION
Depression is an illness that is very variable in both its presentation and its severity.

It is important to understand that patients who suffer from a depressive episode must have suffered from low mood and having little interest or pleasure in doing things for at least ten days in order to be said to be suffering from depression. Hence many patients who may present with important distress in primary care, as a result of life problems may not in fact be suffering from the illness called depression.

As a result it has been suggested that patients may often be inappropriately be treated for depression (Middleton 2011).

As a consequence of the great variation in presentation and severity of the illness, it is managed in both primary secondary care settings.

In the community, it is important that conditions that may be co-morbid with depression or may be included as part of the differential diagnosis for depression must be considered. These would include medical conditions such as hypothyroidism as well as psychiatric conditions including anxiety, bipolar disorder, PTSD, OCD and borderline personality disorder inter alia (Agius 2010).

Unfortunately, many patients with bipolar disorder, particularly bipolar II disorder, are misdiagnosed as unipolar depression (Hirschfeld 2003), and this is of great significance because treatment algorithms for unipolar and bipolar depression are different, and inappropriate treatment of bipolar illness may lead to an increase in suicidality (Agius 2010).

Furthermore, the lack of identification of co-morbidities such as Bipolar II illness, OCD , PTSD and Borderline Personality disorder (Agius 2010 ) can lead to patients appearing to have depression resistant to antidepressants.

The distinction between unipolar and bipolar illness must be made by taking a longitudinal history from every patient who is suffering from depression (Akiskal 2005), It needs to be established at what age the patient first began to suffer from depression, and whether the patient does suffer from episodes of hypomania, as well as when the first episode of mania has occurred. By definition, a full hypomanic episode is said to last for four days, while a ‘subsnydromal’ hypomanic episode may last two days (Judd 2003, Benazzi 2003). Another indicator of bipolar disorder is a family history of this condition (Akiskal 2003).

The proper identification of bipolar disorder would be important both in terms of referral to secondary care as well as the specific algorithm for the treatment of depression (Agius 2010). Indeed, many patients who may be suffering from bipolar II disorder, who are depressed for a large proportion of the time and only hypomanic for a small percentage of the time (Judd 2002), and this explains why bipolar illness may often be missed (Agius 2007, Tavormina 2007).

Thus, at primary care level it is especially important to consider this particular differential diagnosis.

* This article is based on a discussion held between Two Doctors and five Medical Students during a Tutorial in which the treatment of depression was discussed.

How this fits in:
Debate over when pharmacological therapy or other methods for the management of depressive disorders are appropriate continues. It is suggested that a fundamental change in the interaction between primary and secondary care could optimise treatment.
NEUROBIOLOGY

The key brain areas involved in regulation of mood include the Ventromedial prefrontal cortex, the Lateral orbital prefrontal cortex and the Dorsolateral prefrontal cortex (Öngür 2000, Drevets 1998, MacDonald 2000). Also involved are the Hippocampus and the Amygdala. The Hippocampus has a role in episodic, contextual learning and memory (Squire 2000, Fanselow 2000). The Amygdala: regulates cortical arousal and neuroendocrine response to surprising and ambiguous stimuli they have a role in emotional learning and memory, the activation of amygdala correlates with degree of depression (Drevets 1998) and they are implicated in the tendency to ruminate on negative memories (Drevets 1998).

The hippocampus is rich in corticosteroid receptors (Reul 1986). In this way, via these corticosteroid receptors, hippocampal dysfunction contributes to neuroendocrine dysregulation (Nestler 2002) so it is involved in regulatory feedback to hypothalamic-pituitary-adrenal axis. Hence hippocampal dysfunction may be responsible for inappropriate emotional responses.

There are neurological links between the hippocampus and the hypothalamus. The hypothalamus releases corticotrophic releasing hormone, and this stimulates the pituitary to release excessive ACTH, thus releasing corticothrophic releasing hormone, and this hippocampus and the hypothalamus. The hypothalamus Corticosteroid receptors (Reul 1986, Nestler 2002) and cell atrophy. It is likely that they do this via an increase in atrophic factors in neurons, hence causing cell atrophy. It is likely that they do this via Corticosteroid receptors (Reul 1986, Nestler 2002) and Corticotrophin releasing factor receptors (Todorovic 2005, Hauger 2006, Coste 2006, Valdez 2006, Valdez 2009).

Importantly, the underlying neurobiology of many of the disorders that form the differential diagnosis is very similar, with an intracellular balance of the neurotrophic factors and atrophic factors being disturbed.

One most important trophic factor within the neuron is BDNF- Brain-derived Neurotrophic Factor. BDNF is associated with production of new neurons and their growth and development. Both 5-HT and NE are believed to play roles in the modulation of BDNF (Duman 1997). BDNF influences regulation of mood (Shimizu 2003) BDNF is downregulated in MDD and increased with successful antidepressant treatment (Shimizu 2003).

Neurogenesis (the birth of new neurons) continues postnatally and into adulthood.

Data suggest that neurogenesis occurs in the hippocampus (Gould 1999).

BDNF is associated with production of new neurons and their growth and development (Duman 1997).

It is of great interest that there are important similarities in the neuroimaging findings of Unipolar Depression (Sheline 2002, Sheline 2003, Sheline 1996), Bipolar illness (Deicken 2003), as well as PTSD (Bossini 2008) and Borderline Personality Disorder (Driessen 2000). In all of these cases, Neuro-imaging, in particular MRI demonstrates that there is a decrease in size of the hippocampus in all of these conditions. This reflects changes in plasticity in all of these illnesses.

This suggests that it is likely that the underlying neurobiology of many of the disorders that form the differential diagnosis is very similar, and it is likely that in all cases an intracellular balance of the neurotrophic factors and atrophic factors is being disturbed.

Traditionally, the neurobiology of depression has been expressed in terms of neurotransmitters, including Serotonin and Noradrenaline. However in fact these Neurotransmitters which enable messages to be transmitted from one neuron to the next but they lead to further changes within the neurons. Thus via second messengers, including cyclic AMP (Schmidt 2010), PKA (protein Kinase A) (Pace 2009), and CREB (cAMP response element-binding protein), (Thome 2002a, Thome 2002b) within cells, the balance between trophic and atrophic factors within the neurons is affected by these neurotransmitters. There is evidence that inflammatory cytokines mediate the function of PKA, and do this through regulating function of glucocorticoid receptors (Pace 2009). Hence SSRIs and TCAs upregulate BDNF expression (Grande 2010) while lithium modulates the level of bcl-2 (Gold 2011) (Manji 2000, Chen 2000, Manji 2000). Both BDNF and bcl-2 are trophic factors within neurons. Lithium also inhibits the atrophic factor GSK-3β. Lithium also upregulates the trophic factor BAG-1, or Bcl-2 associated anathogene (Zhou 2005).

The control of neurotransmission has been shown to be important. Indeed the use of SSRIs has focussed attention on the Serotonin transporter gene (Collier 1996, Mandelli 2009, Alessandro 2008, Luddington 2009), and the way in which the variants of this gene are responsible for different responses of different persons to stress. This Serotonin transporter gene is, among others, involved in the genesis of bipolar illness as well as unipolar depression (Manchia 2010, Luddington 2009).

The pharmacological treatments reflect this similar underlying neurobiology, with drugs such as lithium, SSRIs and TCAs being found to promote neurogenesis (Santarelli 2003, Perera 2007, Wada 2009, Boku 2010, Fiorentini 2010, Kitamura 2011) and also promote an increase in the number of dendrites in neurons as a result of the changes in balance between trophic and atrophic factors. These changes, both as a result of neurogenesis and as a result of changes in the number of dendrites lead to changes in plasticity, and are reflected in the changes in hippocampal size seen on MRI scans (Stahl 2000).
Thus we appear to have demonstrated in the paragraphs above the relationship between the neurotransmitter, glucocorticoid and, neurogenesis theories of depression, so that they are all a single model of the genesis of depression, with each of these parts of the model linked by a complex signalling system of second messengers, as well as glucocorticoid receptors, which may also be modulated by inflammatory cytokines, and which overall provides effective balancing and feedback systems.

The consequence of all of this is that there is beginning to emerge a clear neuro-pathology of depression, and also of bipolar disorder and the other mental illnesses which we have mentioned before.

This is not to say that medication with Antidepressants is the only way in which depression can be treated. There is evidence that psychotherapy also can affect changes in plasticity (Zaman 2010, Zaman 2011). Hence it is reasonable that both psychotherapy and antidepressant medication should be used, preferably together, in the treatment of depression.

**CLINICAL CONSEQUENCES**

One factor which needs to be considered is that there is well documented evidence that patients with recurrent depressive disorder over time tend to develop into bipolar illness (Akiskal 1995). The cause for this change over time is unknown, however it is certainly a clinically observable fact that patients usually first present with depressive illness and only later begin to develop hypomanic episodes (Akiskal 1995).

One important consequence of the similarity in terms of pathophysiology between unipolar and bipolar depressive illness, and the development of unipolar depression into bipolar illness is the difficulty in choosing appropriate treatment.

This is because there are two different protocols for treating unipolar and bipolar illness (Agius 2010).

Unipolar illness is treated with antidepressants (SSRIs, Triciclics, or other groups) for a period of six months (Paykel 1992). Whereas Bipolar illness is treated with Mood Stabilisers (Lithium, Anti-Epileptics, or Atypical Antipsychotics) in the long term, with antidepressants only being used while a patient is depressed, and under the cover of mood stabilizers (Peet 1994, Beckford-Ball 2006, Ghaemi 2003).

At a practical level, the consequences of treating patients with bipolar II disorder with anti-depressants, either as a result of mis-diagnosis or as a result of injudicious treatment of bipolar illness with antidepressants alone, runs the risk of inducing a shift to Mania (Peet 1994), or of pushing patients into affective mixed states or rapid cycling with consequent increase in suicidality (Valtonen 2008). Hence patients who have been labelled as ‘depressed’ and continue to have instability of mood need to be urgently reassessed in order to establish whether they in fact suffer from bipolar illness.

In addition, many patients who are in fact occult bipolar patients present as patients who have resistant depression due to their resistance to common antidepressants including SSRIs (Correa 2010, Amsterdam 2009).

**HOW CAN THIS KNOWLEDGE BE APPLIED IN A PRIMARY CARE SETTING?**

Given thorough assessment of the patients to identify bipolar disorder and co-morbid conditions, the next step is to organise appropriate management. We argue that this should be carried out in a systematic fashion, following the appropriate treatment algorithms (Agius 2010). Hence, patients with unipolar depression would require treatment with anti-depressant for up to six months and would need to take their medication regularly (Paykel 1992). There is evidence that trained CMHs or practice nurses are able to monitor treatment concordance effectively by seeing patients on a monthly basis in conjunction with the GPs (Wilkinson 1993). Equally, patients with bipolar disorder will need to take mood stabilisers regularly. In patients who are on lithium therapy, regular monitoring of TFTs, U&Es, creatinine as well as lithium levels will have to be performed. These blood tests should be carried out every three months, except for TFSs which should be carried out every six months (Gerrett 2010, Paton 2010). Moreover, patients will require easy access to a doctor. Often a GP may be able to offer the treatment required. However, in light of the issues mentioned it would be pertinent for the GP to be able to have access to a consultant psychiatrist, who could supervise the service and treat difficult cases such as bipolar patient who are in mixed states or who have rapid cycling and who would also advise on co-morbid conditions including PTSD. It would be useful to have access to other health care professionals including psychologists, who may be located in primary or secondary care, depending on the complexity of the case.

Thus what we propose is that patients in primary care who suffer from depression, bipolar disorder should be treated in a systematic way, by a system of case management, and that, while the doctors should establish a clear diagnosis, especially whether the patient is suffering from unipolar depression or bipolar II or Bipolar I illness. He can then be supported by a case manager, either a practice nurse or a Community Mental Health nurse who will see patients regularly, at least monthly, perhaps alternately with the doctor, in order to ensure compliance with treatment. Simultaneously, it is appropriate that evidence based psycho-therapeutic techniques such as CBT be offered within primary care by practice counsellors and psychologists within the ‘Increasing access to Psychological Therapy’ organisation. These therapists must also be deployed within the General Practices, and collaborate with the GPs and case managers/practice nurses. The
system would be supervised by a consultant psychiatrist, who would oversee the case managers and offer support to the GPs and their teams, helping with difficult cases and identifying those who will need more specialised support and treatment within secondary care.

The consequence of the systematic approach which we have described is that within primary care, both psychological and pharmaceutical approaches to treatment of mood disorders (bipolar and unipolar) will be optimised, and thus the positive effects on both neurogenesis and neuroplasticity will be used to best effect.

What we have described above is essentially a shared care system where primary and secondary care work together. A number of studies, mostly American, but also British, have demonstrated that significantly better results can be achieved using this model (Gilbody 2006, Agius 2005, Agius 2010). Unfortunately, although there have been many calls for such a system to be set up in the UK, there is at present no contractual arrangement for such a system to be set up within the National Health Service of England, despite the contractual arrangements that presently exist in primary care to use systematic rating scales to help in diagnosis of depression and to regularly monitor lithium therapy.

It is evident that in order to develop a shared care model, appropriate training would need to be offered to both the primary and secondary care teams. They would also need to be better structurally integrated than they are at present. With such a development in care, the likely benefits would more than counter-balance the initial costs of re-designing services and training.

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