

# Depression: a Disease and Its Treatment

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## **Abstract**

“Depression” – derived from Latin “deprimere” (to press down) – designates a patient’s continued experience of sadness, frustration, and loss of interest. Historically, this state was called *melancholia* and thought to be caused by *black bile*. The modern concept of depression inherits from its ancient predecessor; and already Homer mentions the mood lifting effects of psychoactive drugs to in his *Odyssey*. Classification and treatment of depression have substantially changed since his time, however: contemporary accounts of depression are primarily given in terms of neurotransmitter imbalances treatable with pharmacological substances. Nevertheless, effective therapy today is neither restricted to antidepressant drugs nor wholly to the merit of research into depression’s neurobiological basis. The current essay offers a brief overview. A particular focus will be on the development of antidepressant medications and brain stimulation techniques. Directions for future treatment and research will be outlined in due course.

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# 1 Historical Review

Around 400 BC, Hippocrates described *melancholia* as “fears and despondencies, if they last a long time” that were caused by *black bile*, a *humor* (bodily fluid). It’s antagonist, *yellow bile*, was thought to cause *mania*, the opposite of melancholia.

Anxiety and a depressive mood are accompanied by slowed thinking and actions and withdrawal from social contact. Treatment attempted to eliminate noxious humor, e.g. *via* blood-letting, sweating, healthy diet, balanced exercise and rest, sufficient sleep, and even discussing problems with a friend. Essentially the same therapeutic rules were followed in the 16th and 17th century (e.g. Boerhaave, 1742; Burton, 1821); alternative strategies aimed to strengthen the body by excessive alcohol and opium consumption (Brown, 1788).

With progressive understanding of the nervous system, humoral explanations were replaced by electrical and mechanistic ones. By the end 18th century, melancholia – then classified as neurosis – was explained in terms of changes in the *dura mater* (Diethelm, 1972).

In the 19th century, Kraepelin referred to different types of melancholia – the ancient concept included depression, dementia, and schizophrenia – as “depressive states” (Diethelm, 1972). Subsequently, schizophrenia and dementia were singled out from depression which was still contrasted with mania (Falret, 1864).

Meyer’s (1905) *Discussion of Melancholics* favoured the use of “depression” as scientific term; its establishment is marked by the 1934 entry in the *Dictionary of Psychology* which describes “depression” as referring to “a mood of pronounced hopelessness and overwhelming feeling of inadequacy or unworthiness” (Warren, 1934). In 1953, Kleist added the distinction between unipolar

and bipolar (manic-depressive) disorders; his taxonomy survives in contemporary diagnostic manuals.

## 2 Present Classification

*Unipolar (major) depression* is a mood disorder during which the patient suffers from a severe loss interest in almost anything. Psychologically, a continued sad mood, hopelessness, feelings of worthlessness or guilt, and a negative self-concept are prominent symptoms. Biologically, these are accompanied by altered sleeping habits (insomnia, sometimes hyposomnia), psychomotor activity (agitation, retardation), appetite/weight, and loss of sexual desire. Behaviourally, sadness and hopelessness translate into reduced motivation and activity levels (tiredness, fatigue), difficulties concentrating or making decisions, hypochondriac complaints, seeking help, recurring thoughts of death and/or suicide and plans or attempts thereof (American Psychiatric Association, 2000).

To meet the criteria for a clinical diagnosis, the patient's general depressive mood must last for at least two weeks and be accompanied by at least four of the additional symptoms listed above.

*Bipolar disorders* include depression and mania, alternating in episodes. A *manic* episode is characterised by "an abnormally and persistently elevated, expansive, or irritable mood" including grandiose delusions and unwarranted optimism (American Psychiatric Association, 2000, p. 357). For a clinical diagnosis, it must extend over at least one week while three additional symptoms have to be present: inflated self-esteem or grandiosity, decreased sleeping need, pressure of speech (loud, rapid, difficult to interrupt), racing thoughts, distractability,

increased involvement in goal-directed activities or psychomotor agitation, excessive involvement in pleasurable activities with potentially painful consequences, and increased sexual drive (American Psychiatric Association, 2000).

Both depression and mania go along with impaired social and occupational functioning.<sup>1</sup> Importantly, confounding factors need to be ruled out for diagnosing purposes as e.g. drug-induced alternations of mood are classified separately.

No laboratory findings are diagnostic of depression. Yet, sleep abnormalities (especially reduced non-REM sleep), dysregulation of neurotransmitter (acetylcholine, dopamine, gamma-amino-butyric acid, norepinephrine, serotonin) systems, hormonal disturbances, decreased blood flow in limbic, paralimbic, and lateral prefrontal structures, and (especially in elderly patients) vascular changes have been suggested as indicators (American Psychiatric Association, 2000).

### **3 Treatment in the 20th & 21st century**

In the mid-20th century, chemical neurotransmitter imbalances became the prominent explanation for depression. However, depressive disorders not usually arise from a single cause (Hippus, 1972): Freud (1917) emphasised the relevance of social, cultural, and personality developmental aspects in depression while recent research indicates a role for genetics and circumscribed cortical connectivity. The current section explores a range of treatments available to date along with promising future prospects.

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<sup>1</sup>In contrast to mania, hypomania allows – despite the presence of manic symptoms – for normal or even improved functioning. Depression in combination with hypomania is thus classified as a separate type of bipolar disorder.

### 3.1 Cognitive Behavioural Therapy

In the late 1970s, Beck's cognitive behavioural therapy (CBT) became widely applied (Beck *et al.*, 1979). His approach, rooted in Freudian *psychoanalysis*, added explicit treatment strategies to Seligman's (1975) *learned helplessness* account of depression. CBT is based on the assumption that the patient's emotional disturbances (hopelessness, anxiety, tension, guilt, shame, irritability) – resulting in behaviourally observable foreground symptoms (withdrawal from social interaction, slowness, inattention, memory problems, delusions, suspiciousness, lack of interest, indecision) – are caused by distortions in thinking that need to be “met and dealt with *head on*” (Williams, 1992, p. 111).

In order to achieve this, the therapist aims to (i) elicit the patient's thoughts and interpretations of events, (ii) gather evidence – collaborating with the patient – for or against proposed interpretations, and (iii) set up little experiments testing the interpretations' validity. The patient is thereby trained to recognise and no longer commit to habitual reasoning errors such as dichotomous (black and white) thinking, overgeneralisation, arbitrary inferencing, and catastrophising.

CBT usually encompasses weekly sessions of about one hour over months or years depending on the severity of depression. It starts with an emphasis on behavioural techniques (task assignments) and progressively includes more cognitive aspects (discussing thoughts and assumptions). In both domains, therapy progresses from simple (broken-down) to complex matters.

Today's *psychotherapy* still takes this basic form. Despite the progress in pharmacotherapy (see section 3.2) CBT has been shown to be superior to placebos and equally effective as modern antidepressants in treating unipolar depres-

sion (DeRubeis, *et al.*, 2005). However, combination of antidepressants and CBT yields even better outcomes (e.g. Biggs & Rush, 1999) and lower relapse rates than either treatment alone (Young *et al.*, 2008). Nevertheless, in many countries, e.g. the US, there is a psychopharmacological treatment bias, viz. CBT is only recommended to patients not responding to medication alone (Seaman, 1999).

## 3.2 Pharmacotherapy

Until the mid-1950s, tranquilizers – e.g. *benzodiazepines* exhibiting sedative, muscle-relaxant, and anti-anxiety effects – were used to treat depressive symptoms (Page *emph et al.*, 2002). Alternatively, opiates and amphetamines were administered. How these substances worked was unclear; but despite their therapeutic effect they caused addiction and unpleasant side-effects.

### 3.2.1 Neurobiology in a Nutshell

When an electrical signal reaches a nerve terminal (synapse), neurotransmitter molecules are released into the synaptic cleft and selectively open ion channels on the post-synaptic cell. Ion influx induces excitatory or inhibitory potentials in the post-synaptic cell, depending on the polarity of the inflowing ions, which is determined by the type of channel being opened. This, in turn, depends on the kind of neurotransmitter being released.

This mechanism enables propagation of neural signals across cellular boundaries.<sup>2</sup> Neurotransmitters are effective for only a short time as they are ei-

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<sup>2</sup>This section describes *chemical* synapses only. Neural signal transmission is also achieved *via* electrical synapses, but that makes for another story.

ther taken back up by the synapse or decomposed by specialised enzymes (e.g. monoamine oxidase (MAO)).

Treatment of depression and mania typically focuses on the enhancement of excitatory neurotransmitters, i.e. those eliciting excitatory post-synaptic potentials, to counterbalance depressive symptoms. The aim of antidepressant medications thus is to selectively increase the effect of excitatory neurotransmitters (dopamine, norepinephrine, serotonin). Their existence in the synaptic cleft is thus prolonged by inhibiting their re-uptake or decomposition.<sup>3</sup>

Our understanding of (chemical) synaptic signal transmission is still incomplete to date. However, the basic mechanism had been discovered by the 1950s (cf. Bear, Connors & Paradiso, 2006).

### 3.2.2 1st Generation: Tricyclics & MAO Inhibitors

First antidepressants developed on a trial-and-error basis, initially from tuberculosis medication. In 1952, Selikoff and Robitzek reported a positive effect of *iproniazid* on depressive patients. In 1957, iproniazid was identified as a MAO inhibitor and marketed as antidepressant. Because it caused lethal liver damage, it was recalled in 1961 (López-Muñoz, 2007).

*Chlorpromazine* was used as alternative treatment. It has only recently been discovered that chlorpromazine blocks dopamine receptors causing, *via* a feedback loop, an initial increase in dopaminergic activity (Gilman *et al.*, 2001).

Trying to improve chlorpromazine, Kuhn (1957) discovered *imipramine*, the first tricyclic antidepressant (TCA). Many variants were developed in subsequent

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<sup>3</sup>This inhibition will not be absolute but relative to the dose of antidepressant medication. The higher the dose, the more re-uptake or decomposition agents will be blocked, and thus, the longer it takes until all neurotransmitter molecules are removed from the synaptic cleft.

years. Though TCAs were effective in the majority of patients, they failed in up to 30% of cases (Hippus, 1972). If so, they could be combined with MAO inhibitors but this often yielded complications. However, even in 1991, Potter *et al.* proposed MAO inhibitors as the medication of choice in severe cases of major depression.

In the 1960s, TCAs were thought to mainly inhibit norepinephrine re-uptake. It was gradually discovered that their antidepressant effects are primarily mediated through serotonin pathways, however (e.g. deMontigny & Aghajanian, 1978). This insight motivated the *serotonin hypothesis* according to which insufficient serotonin supply in the central nervous system (CNS) causes depression.

### **3.2.3 2nd Generation: Selective Re-Uptake Inhibitors**

Better understanding of neural signal transmission and the belief that serotonin is the key to treating depression provoked the design of drugs selectively targeting serotonin pathways, viz. selective serotonin re-uptake inhibitors (SSRIs). *Fluoxetine* was the first SSRI to be widely marketed from 1988. In 1999, SSRIs were considered the “treatment of choice” (Masand & Gupta, 1999) for depression as they had a better profile of side-effects, were clinically safer, and came along with better patient compliance (Fiedorowicz & Swartz, 2004).

Analogously to SSRIs, selective norepinephrine re-uptake inhibitors (NRIs) have been developed. These show particularly positive effects on concentration and motivation and are thus discussed as *cognitive enhancers* (e.g. Stahl, 2003). In severe depression, the beneficial effects of SSRIs and NRIs can be combined in serotonin-norepinephrine re-uptake inhibitors (SNRIs).

New-generation antidepressants still have disadvantages, however: first, treat-

ment effects are (as with TCAs) delayed two to six weeks to medication onset making them less suitable for severe cases that require rapid action (e.g. if patients attempt suicide); second, sudden discontinuation of the drugs may cause withdrawal symptoms (Beck & Alford, 2009); third, they still do not work for all patients.

### **3.3 Electroconvulsive Therapy**

First convulsive therapies in the 1930s used camphor and metrazol to induce seizures and thereby elicit a therapeutic effect on depression, schizophrenia, and mania (Berrios, 1997). Electricity, being more cost-effective and convenient, soon replaced these substances (Cerletti, 1956).

Classical electroconvulsive therapy (ECT) involves placing electrodes on the patient's scalp, bilaterally, through which the brain is stimulated with a strong sinusoidal current. Thus induced seizures are accompanied by brief (min. 15s) loss of consciousness (Rudorfer, Henry & Sackeim, 2003).

The use of muscle relaxants improved ECT safety from the 1950s onwards. Unilateral ECT application was found to have less side-effects – such as retrograde and anterograde amnesia – but also is less effective (Cronin *et al.*, 1970). Also reducing side effects but retaining efficacy, Blatchley replaced the sinusoidal current with brief pulse in 1976 (Rudorfer, Henry & Sackeim, 2003).

The exact working mechanisms of ECT are unclear. However, it is effective in up to 85% of patients with depression (Rudorfer, Henry & Sackeim, 2003) and still used today. On the downside, ECT may be followed by (permanent) cognitive impairments (e.g. retrograde and anterograde amnesia). Repeated ECT in rats

was found to cause brain lesions in particularly vulnerable areas associated with memory, viz. entorhinal cortex and dentate gyrus (Cardoso *et al.*, 2008).

Today, ECT is advised only as a method of last resort to achieve rapid short-term effects in patients whose current condition is life-threatening and who do not respond to other treatment (e.g. NICE, 2003).

### **3.4 TMS, tACS & Sleep**

Reviewing data from clinical repetitive transcranial magnetic stimulation (rTMS) application, Loo and Mitchell (2005) find that rTMS has positive, though limited, effects on depressed patients. Given that TMS primarily affects areas proximate to the cortical surface while neurotransmitter systems are primarily regulated by phylogenetically old deep brain structures, TMS may not be suited to treat depression. However, with future technology and a fuller understanding of how induced currents spread through the brain, TMS may bear therapeutic potential.

Another way of surface stimulation, transcranial current stimulation (tACS)<sup>4</sup>, may be even more promising to treat depression.

Research indicates a contributing role for neurotransmitters in oscillatory brain activity. For instance, dopaminergic pathways interact with mechanisms of theta-wave (4-8Hz) generation (Mesulam, 2004; Yamawaki *et al.*, 2008). Thus, selective application of tACS to manipulate brain oscillations during sleep may offer future treatment options in depression.

This idea gains support when considering that – while human *early* and *late*

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<sup>4</sup>TMS rapidly induces an electromagnetic current primarily affecting superficial cortical areas. tACS is based on the application of constantly alternating low intensity currents through electrodes on the scalp over seconds; sinusoidal stimulation at different frequencies can thereby be achieved.

*sleep* are usually dominated by slow wave sleep (SWS; <1Hz) and rapid-eye-movement (REM) sleep, respectively (Plihal & Born, 2008) – depressive patients display an overall reduction of SWS and REM sleep during the early night. These alternations in sleep patterns typically precede the onset of a depressive episode and outlast its remission (American Psychological Association, 2000). Moreover, REM suppression has been reported to mark effectiveness of pharmacological treatment (Steiger & Kimuara, 2009). Oscillatory brain activity during sleep may thus serve as (i) diagnostic tool for depression and (ii) predict the effectiveness of antidepressant medication.

Another way to treat depression *via* sleep modification is *cortisol administration*. In healthy as well as depressed individuals, cortisol has been found to suppress REM sleep and increase SWS (Schmid *et al.*, 2008) while activity of the hypothalamus-pituitary-adrenal system differentially modulated cortisol effects. The exact mechanisms linking sleep, hormones, oscillatory brain activity, and neurotransmitters remain subject to future investigation.

### **3.5 Deep Brain Stimulation**

Targeted deep brain stimulation (DBS) may be promising when non-invasive methodologies fail. A prerequisite for its application is the identification of relevant neurological circuits and their precise localisation.

In recent years, depression has become associated with altered *emotional* and *reward* processing in the brain. Functional imaging studies revealed ventro-medial frontal dysfunction in manic patients (Elliott *et al.*, 2004) as well as prefrontal and striatal dysfunction in major depressive patients (Drevets, 2001). These circuits

are thought to normally modulate emotional processing in the limbic system. The limbic system as well as basal ganglia and cortical areas provide input to the lateral habenula (LHb) – a structure in the dorsal diencephalon of vertebrates, located below the cingulate cortex. LHb has been suggested as major source of negative reward-related signals (Matsumoto & Hikosaka, 2007). It sends efferents to the serotonin, norepinephrine, and dopamine systems of vertebrate cortex (Geisler & Trimble, 2008) and controls serotonin release throughout the brain *via* feedback connections to midbrain raphe nuclei (Morris *et al.*, 1999). During depressive states (Sartorius & Henn, 2007) and selective reduction of serotonin precursors (Roiser *et al.*, 2009) LHb activity increases.

Taken together, this indicates a crucial role for LHb in major depression. In particular, its overactivation may downregulate dopamine, norepinephrine, and serotonin pathways. Therefore, selective inhibition of LHb may elicit remission from major depression. Indeed, Sartorius *et al.* (2010) report an otherwise treatment resistant major depressive patient whose symptoms markedly subsided after DBS of LHb.

This case marks significant progress in the treatment of depression. Although arguably more invasive than ECT, DBS is much more targeted. As such, it is better controlled than ECT, less hazardous, and causes less side-effects.

### **3.6 Acupuncture**

In 2003, Zhang proposed acupuncture may be employed to treat depression but its effectiveness remained unclear. A recent meta-analysis of eight studies (Wang *et al.*, 2008) indicates an overall alleviating effect on depressive symptoms despite

vastly differing acupuncture and placebo procedures across studies.

Current interpretations suggest acupuncture stimulates – via needle insertion or laser application – a group of afferent nerves and thus triggers release of neurotransmitters including serotonin, norepinephrine, dopamine, and endorphin in the CNS (Wanget *al.*, 2008). A direct, but poorly understood, influence of acupuncture on the pathology of depression has thus been suggested (Siedentopf *et al.*, 2005; Zhang *et al.*, 2006).

While acupuncture was reported to be as effective as antidepressants (Leo & Ligot, 2007; Luo *et al.*, 2003), it is associated with less adverse effects than pharmacotherapy and better patient compliance (Wang *et al.*, 2008). Acupuncture is gradually utilised by depressed patients (Tachil *et al.*, 2007).

### **3.7 Light Therapy**

Depression may be seasonal (e.g. Rosenthal *et al.*, 1984). Patients with winter depression highly benefit from exposure to very bright light: within a few days, up to 65% of patients experience remission (Terman *et al.*, 1989; Tam *et al.*, 1995). Whether or not light therapy (LT) can be used to treat non-seasonal depression remains unclear. In 2008, Even and colleagues analysed data from 15 studies using LT to treat major depression. They found a facilitating effect of light in conjunction with medication but the effects of LT alone remained inconclusive.

The working mechanisms of LT remain unclear. Even *et al.* (2008) hypothesise light may be “at least partly mediated through the serotonergic system” (pp. 15-16). Alternatively, light could exert an antidepressant effect through the circadian system. Supporting this suggestion, Bourin, Mocaër and Porsolt

(2004) found that melatonin<sup>5</sup> antagonists have antidepressant effects in rats.

LT's beneficial effects on depression, its safety, ease of application, and lack of side-effects make it a promising candidate for future treatment of major depression.

A role for circadian rhythms in depression aligns with patients' altered sleep patterns and pharmacological effects of SSRIs. The interplay between light, serotonin-derived substances and mood calls for future investigation.

## 4 Guidance for Treatment Selection

Choosing the right therapy for an individual patient is crucial for successful remission. Most importantly, the patient has to be as comfortable and compliant with the treatment as possible. Additionally, heredity factors and the patient's age and sex may be considered (Hippus, 1972; Young *et al.*, 2008).

Depression appears to be, at least partly, heritable (up to 50% in unipolar, 80% in bipolar disorder) where several genes are thought to contribute small effects that interact with environmental factors (Farmer, Elkin & McGuffin, 2007). Family history of depression and its treatment may thus be used to select treatment. Since research indicates that antidepressant medication may interact with genetic factors (e.g. Uz *et al.*, 2005), genetics may be used to identify and design tailored medications in future.

A recent study hints at a different strategy: patients' responses to treatment may be predictable based on neuroanatomical connectivity. Analysing structural

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<sup>5</sup>Melatonin is a hormone driving circadian rhythms; it is produced from serotonin in dim light conditions and thought to be contributing to winter depression as melatonin levels are elevated throughout darker as compared to lighter seasons.

data from fMRI studies, Seminowicz *et al.* (2004) developed a model able to distinguish (i) patients successfully responding to pharmacotherapy from those that did not based on limbic-cortical connections, and (ii) patients responding to CBT from those responding to antidepressants based on lateral prefrontal-hippocampal connectivity and orbito-frontal to medio-frontal connectivity. This aligns with brain activity during sleep marking depression and pharmacological treatment success (see section 3.4) and the features of emotion and reward processing described earlier (see section 3.5). Such screening methods have not yet reached clinical applicability, however.

## 5 Concluding Remarks

Treatment of depressive disorders has significantly progressed in safety and efficiency; and there are promising future prospects. This is especially evident in neurotransmitter specific pharmacology, DBS, and possibilities to analyse neural connectivity, brain oscillations, and genes for treatment selection.

It should be considered, though, that if reward and emotional processing play a key role in depression (see section 3.5) mood disorders may be viewed in a whole new light and our pharmacological accounts may be misguided: rather than altering a patient's mood directly, SSRIs may impact emotional (and likely cognitive) processing (cf. Harmer, Goodwin & Cowen, 2009) while mood effects are only secondary in nature.

In line with this *cognitive hypothesis of depression* (CH), Eshel and Roiser (in press) argue that depressed patients “over-react” to reward and punishment, which manifests in abnormal fronto-striatal function. As a result, patients cannot

use reinforcement and affective processing to guide their behaviour. Since CBT addresses exactly such deficits, its efficacy may be seen to support CH.

Despite the marked progress in depression treatment, many methodologies have been, and still are, trial-and-error based. We do not fully understand how successful and/or promising treatments achieve their effects, or what the neurobiological basis of depression is. And CBT, largely steady since the 1950s and without recourse to neurobiology, has proven equally effective as modern antidepressants. Therefore, one may argue, the effects of neurobiological research on depression treatment are rather limited.

Future research is needed to clarify the role of various neurotransmitters, brain structures and activity patterns (e.g. oscillations) before we understand what happens in depression. The process may be aided by investigating the working mechanisms of alternative treatments (e.g. LT, acupuncture).

To date though, we – similarly to Hippocrates – are largely left with smart guesses as to how to explain and treat depression; only are we ~2000 years of medical history ahead and equipped with 21st century technology.

## References

- American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text revision). Washington, DC: American Psychiatric Publishing.
- Bear, M.F., Connors, B.W., & Paradiso, M.A. (2006). *Exploring the Brain* (3rd ed.). Baltimore, MD: Lippincott Williams & Wilkins.
- Beck, A.T. & Alford, B.A. (2009). *Depression: Causes and Treatment* (2nd ed.). Philadelphia, PA: University of Pennsylvania Press.
- Beck, A.T., Rush, A.J., Shaw, B.F., & Emery, G. (1979). *Cognitive Therapy of Depression*. New York, NY: Guilford Press.
- Berrios, G.E. (1997). The scientific origins of electroconvulsive therapy. *History of Psychiatry*, 8, 105-119.
- Biggs, M.M. & Rush, A.J. (1999). Cognitive and behavioural therapies alone or combined with antidepressant medication in the treatment of depression. In D.S. Janowsky (Ed.), *Psychotherapy Indications and Outcomes* (pp. 121-172). Washington, DC: American Psychiatric Press.
- Boerhaave, H. (1742). *Boerhaave's Aphorism*. London: Innys and Hitch.
- Bourin, M., Mocaër, E., & Porsolt, R. (2004). Antidepressant-like activity of S 20098 (agomelatine) in the forced swimming test in rodents: involvement of melatonin and serotonin receptors. *Journal of Psychiatry and Neuroscience*, 29, 126-133.
- Burton, R. (1821). *The Anatomy of Melancholy*. London: J. Cuthell.
- Brown, J., (1788). *The Elements of Medicine*. London: J. Johnson.
- DeRubeis, R.J., Hollon, S.D., Amsterdam, J.D., Shelton, R.C., Young, P.R., Salomon, R.M., et al. (2005). Cognitive therapy vs. medications in the treatment of moderate to severe depression. *Archives of General Psychiatry*, 62, 409-416.
- Cardoso, A., Assunção, M., Andrade, J.P., Pereira, P.A., Madeira, M.D., Paula-Barbosa, M.M., & Lukoyanov, N.V. (2008). Loss of synapses in the entorhinal-dentate gyrus pathway following repeated induction of electroshock seizures in the rat. *Journal of Neuroscience Research*, 86, 71-83.

- Cerletti, U. (1956). Electroshock therapy. In A.M. Sackler *et al.* (Eds.) *The Great Physiodynamic Therapies in Psychiatry: an Historical Appraisal* (pp. 91-120). New York: Hoeber-Harper.
- Cronin, D., Bodley, P., Potts, L., Mather, M.D., Gardner, R.K., & Tobin, J.C. (1970). Unilateral and bilateral ECT: a study of memory disturbance and relief from depression. *Journal of Neurology, Neurosurgery, & Psychiatry*, 33, 705-713.
- deMontigny, C. & Aghajanian, G.K. (1978). Tricyclic antidepressants: long-term treatment increases responsivity of rat forebrain neurons to serotonin. *Science*, 202, 1303-1306.
- Diethelm, O. (1972). The evolution of the concept of depression. In F.F. Flach & S.D. Draghi (Eds.), *The Nature of Depression and its Treatment*. Sydney: Wiley.
- Drevets, W.C. (2001). Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. *Current Opinion in Neurobiology*, 11, 240-249.
- Elliott, R., Ogilvie, R., Rubinsztein, J.S., Calderon, G., Dolan, R.J., & Sahakian, B.J. (2004). Abnormal ventral frontal response during performance of an affective go/no go task in patients with mania. *Biological Psychiatry*, 55, 1163-1170.
- Eshel, N. & Roiser, J.P. (in press). Reward and punishment processing in depression. *Biological Psychiatry*.
- Even, C., Schröder, C.M., Friedman, S., & Rouillon, F. (2008). Efficacy of light therapy in nonseasonal depression: a systematic review. *Journal of Affective Disorders*, 108, 11-23.
- Falret, F.P. (1864). *Des Maladies Mentales*. Paris: Baillières.
- Farmer, A., Elkin, A., & McGuffin, P. (2007). The genetics of bipolar affective disorder. *Current Opinion in Psychiatry*, 20, 8-12.
- Fiedorowicz, J.G., & Swartz, K.L. (2004). The role of monoamine oxidase inhibitors in current psychiatric practice. *Journal of Psychiatric Practice*, 10, 239-248.
- Freud, S. (1917). Trauer und Melancholie. *Internationale Zeitschrift für Ärztliche Psychoanalyse*, 4, 288-301.

- Geisler, S. & Trimble, M. (2008). The lateral habenula: no longer neglected. *CNS Spectrums*, 13, 484-489.
- Gilman, A., Goodman, L.S., Hardman, J.G., & Limbird, L.E. (Eds.) (2001). Goodman & Gilman's The Pharmacological Basis of Therapeutics (10th ed.) (pp. 447-449). New York: McGraw-Hill.
- Harmer, C.J., Goodwin, G.M. & Cowen, P.J. (2009). Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action. *British Journal of Psychiatry*, 195, 102-108.
- Hippocrates (400 BC). Aphorisms. Retrieved from <http://classics.mit.edu/Hippocrates/aphorisms.html>.
- Hippus, H. (1972). The current status of treatment for depression. In P. Kielholz (Ed.), *Depressive Illness* (pp. 49-62). Bern: Hans Huber Publishers.
- Kleist, K. (1953). Die Gliederung der neuropsychischen Erkrankungen. *Monatsschrift für Psychologie und Neurologie*, 125, 526-554.
- Kuhn, R. (1957). Über die Behandlung depressiver Zustände mit einem Iminodibenzylderivat (G22355). *Schweizerische Medizinische Wochenschrift*, 87, 1135.
- Leo, R.J. & Ligot, J.S. Jr. (2007). A systematic review of randomized controlled trials of previous term acupuncture. *Journal of Affective Disorders*, 97, 13-22.
- Lewis, A.J. (1934). Melancholia: a historical review. *Journal of Mental Sciences*, 80, 1-42.
- Lool, K.L. & Mitchell, P.B. (2005). A review of the efficacy of transcranial magnetic stimulation (TMS) treatment for depression, and current and future strategies to optimize efficacy. *Journal of Affective Disorders*, 88, 255-267.
- López-Muñoz F, Alamo C, Juckel G, & Assion HJ (2007). "Half a century of antidepressant drugs: on the clinical introduction of monoamine oxidase inhibitors, tricyclics, and tetracyclics. Part II: monoamine oxidase inhibitors". *J Clin Psychopharmacol* 27 (6): 555-569.
- Luo, H.C., Ureil, H., Shen, Y.C., Meng, F.Q., Zhao, X.Y., Liang, W., Tan, C.X., Han, H., Zhou, D.F., & Deng, P. (2003). Comparative study of electroacupuncture and fluoxetine for treatment of depression. *Chinese Journal of Psychiatry*, 36, 215-219.

- Masand, P.S. & Gupta, S. (1999). Selective serotonin-reuptake inhibitors: an update. *Harvard Review of Psychiatry*, 7, 69-84.
- Matsumoto, M. & Hikosaka, O. (2007). Lateral habenula as a source of negative reward signals in dopamine neurons. *Nature*, 447, 1111-1115.
- Mesulam, M. (2004). The cholinergic lesion of Alzheimer's disease: pivotal factor or side show? *Learning and Memory*, 11, 43-49.
- Meyer, A. (1905). Discussion on the classification of the melancholics. *Journal of Nervous and Mental Disease*, 32, 114.
- Morris, J.S., Smith, K.A., Cowen, P.J., Friston, K.J., & Dolan, R.J. (1999). Co-variation of activity in habenula and dorsal raphé nuclei following tryptophan depletion. *Neuroimage*, 10, 163-172.
- NICE (2003). Guidance on the Use of Electroconvulsive Therapy. *Technology Appraisal*. London: NICE. Retrieved from <http://www.nice.org.uk/pdf/59ectfullguidance.pdf>
- Page, C., Michael, C., Sutter, M., Walker, M., & Hoffman, B.B. (2002). *Integrated Pharmacology* (2nd ed.). New York, NY: Elsevier.
- Plihal, W. & Born, J. (2008). Effects of early and late nocturnal sleep on declarative and procedural memory. *Journal of Cognitive Neuroscience*, 94, 534-547.
- Roiser, J.P., Levy, J., Fromm, S.J., Nugent, A.C., Talagala, S.L., Hasler, G., Henn, F.A., Sahakian, B.J., & Drevets, W.C. (2009). The effects of tryptophan depletion on neural responses to emotional words in remitted depression. *Biological Psychiatry*, 66, 441-450.
- Rosenthal, N.E., Sack, D.A., Gillin, J.C., Lewy, A.J., Goodwin, F.K., Davenport, Y. *et al.* (1984). Seasonal affective disorder: a description of the syndrome and preliminary finding with light therapy. *Archives of General Psychiatry*, 41, 72-80.
- Rudorfer, M.V., Henry, M.E., & Sackeim, H.A. (2003). Electroconvulsive therapy. In A. Tasman, J. Kay, J.A. Lieberman (Eds.) *Psychiatry* (2nd ed.) (pp. 1865-1901). Chichester: John Wiley.
- Sartorius, A., Kiening, K.L., Kirsch, P., von Gall, C.C., Haberkorn, U., Unterberg, A.W., Henn, F.A., Meyer-Lindenberg, A. (2010). Remission of major depression under deep brain stimulation of the lateral habenula in a therapy-refractory patient. *Biological Psychiatry*, 67, e9-e11.

- Sartorius, A & Henn, F.A. (2007). Deep brain stimulation of the lateral habenula in treatment resistant major depression. *Medical Hypotheses*, 69, 1305-1308.
- Schmid, D.A., Brunner, H., Lauer, C.J., Uhr, M., Yassouridis, A., Holsboer, F., & Friess, E. (2008). Acute cortisol administration increases sleep depth and growth hormone release in patients with major depression. *Journal of Psychiatric Research*, 42, 991-999.
- Seaman, H. (1999). Psychotherapy gets short shrift at White House WM meeting. *National Psychologist*, 8, 21. (cited in Young *et al.*, 2008)
- Seligman, M.E.P. (1975). *Helplessness: On Depression, Development, and Death*. San Francisco, CA: W.H. Freeman.
- Selikoff, I.J. & Robitzek, E.H. (1952). Tuberculosis chemotherapy with hydrazine derivatives of isonicotinic acid. *Diseases of the Chest*, 21, 385-438.
- Seminowicz, D.A., Mayberg, H.S., McIntosh, A.R., Goldapple, K., Kennedy, S., Segal, Z., & Rafi-Tarib, S. (2004). Limbic-frontal circuitry in major depression: a path modeling metanalysis. *NeuroImage*, 22, 409-418.
- Stahl, S.M. (2003). Neurotransmission of cognition: II. Selective NRIs are smart drugs: exploiting regionally selective actions on both dopamine and norepinephrine to enhance cognition. *Journal of Clinical Psychiatry*, 64, 110-111.
- Steiger, A. & Kimura, M. (2010). Wake and sleep EEG provide biomarkers in depression. *Journal of Psychiatric Research*, 44, 242-252.
- Tam, E.M., Law, R.W., & Levitt, A.J. (1995). Treatment of seasonal affective disorder: a review. *Canadian Journal of Psychiatry*, 40, 457-466.
- Terman, M., Terman, J.S., Quitkin, F.M., McGrath, P.J., Stewart, J.W., & Rafferty, B. (1989). Light therapy for seasonal affective disorder. A review of efficacy. *Neuropsychopharmacology*, 2, 1-22.
- Thachil, A.F., Mohan, R., & Bhugra, D. (2007). The evidence base of complementary and alternative therapies in depression. *Journal of Affective Disorders*, 97, 23-35.
- Uz, T., Ahmed, R., Akhisaroglu, M., Kurtuncu, M., Imbesi, M., Dirim Arslan, A., & Manev, H. (2005). Effect of fluoxetine and cocaine on the expression of clock genes in the mouse hippocampus and striatum. *Neuroscience*, 134, 1309-1316.

- Wang, H., Qi, H. Wang, B.-S., Cui, Y.-Y., Zhu, L., Rong, Z.-X., & Chen, H.-Z. (2008). Is acupuncture beneficial in depression: a meta-analysis of 8 randomized controlled trials. *Journal of Affective Disorders*, 111, 125-134.
- Warren, H.C. (Ed.) (1934). *Dictionary of psychology*. Oxford: Houghton Mifflin.
- William, J.M.G. (1992). *The Psychological Treatment of Depression* (2nd ed.). London: Routledge.
- Yamawaki, N., Stanford, I.M., Hall, S.D., & Woodhall, G.L. (2008). Pharmacological induced and stimulus evoked rhythmic neuronal oscillatory activity in the primary motor cortex (M1) in vitro. *Neuroscience*, 151, 386-395.
- Young, J.E., Rygh, J.L., Weinberger, A.D., & Beck, A.T. (2008). Cognitive therapy for depression. In D.H. Barlow (Ed.), *Clinical Handbook of Psychological Disorders* (4th ed.) (pp. 250-305). New York, NY: Guilford Press.
- Zhang, J.B., Wang, L.L., Lv, M. et al. (2006). Effects of acupuncture on serotonin and norepinephrine in hippocampus of depressed model rats. *Journal of Chinese Medicine Research*, 2006, 844-846.
- Zhang, X. (2003). *Acupuncture: Review and Analysis of Reports on Controlled Clinical Trials*. Geneva: World Health Organization.