# HOPE FOR DEPRESSION

## Recent innovations and future prospects

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Volume II: *Ten Year Final Report of the Global Business and Economic Roundtable on Addiction and Mental Health*

# i5 Research

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# Preface

This independent environmental scan of published material, proceedings, blog posts, videos and other sources was commissioned by Bill Wilkerson as Volume II of the *Ten Year Final Report of the Global Business and Economic Roundtable on Addiction and Mental Health*. Thank you, Bill, for including us in your project. The project was funded by Bell Canada and the Homewood Health Centre. We thank them all for their confidence in our ability to uncover innovations and future trends in the treatment of depression.

The purpose of the environmental scan was to uncover recent innovations by searching more hidden and obscure sources of information than what can be found in a standard "review of the literature". Our approach to innovation analysis and trend forecasting is based on Ulf Pillkahn's 2008 book *Using Trends and Scenarios as Tools for Strategy Development: Shaping the Future of Your Enterprise*. There are four distinct stages to Pillkahn's approach:

- Stage I – Detection
- Stage II – Reflection
- Stage III – Understanding
- Stage IV – Visualization and Reporting

In Stage I, a thorough search of many different sources is undertaken in order to detect all of the trends and signals indicating possible futures of the treatment of depression. This is much more than a "literature review" of scholarly books and articles; rather, it includes a thorough search for "weak signals" that may be hidden in conference presentations, dissertations, press releases, blogs, magazine articles, patents, and other more ephemeral documents. By the time a topic is the subject of a book or even a refereed article, it has already been in development for many years.

Information for this report was gathered from many different sources, including:

- Newspapers and magazines
- Professional journals
- Analyses, studies, reports
- Conference programs, proceedings and presentations
- Patent searches
- Published and unpublished academic papers
- Books
- Press releases and other sources of information from companies
- Blogs
- Experts
- Internet searches
- Descriptions and white papers from vendors of treatments of depression and related services

The amount of scientific literature on depression is immense! The *Proceedings of the National Academy of Sciences* in the U.S. lists over 3,000 articles about depression alone. In our search for academic articles, we looked for recent "meta-analyses" on each major type of treatment. These articles surveyed hundreds of publications and summarized their conclusions. By the end of this process, documentation from over 750 researchers in 30 countries was gathered, hundreds of conference programs and proceedings were examined, and several thousand online posts and documents were reviewed.

In Stage II, the initial reading of the gathered documentation allowed for the building of a preliminary table of contents as a framework around which to organize this report. It quickly became clear that in the past 10 years there has been an explosion of new discoveries in the fields of genetics and neuroscience, which are directly linked to new innovations in the treatment of depression. However, not all innovations in the treatment of depression are linked to scientific methods. Some are the results of accidental discoveries while researchers are looking for something else; others are simply proposals for treatments that have been made by people usually without a traditional medical or psychotherapy background. These proposals are classified in this report under the heading of Complementary and Alternative Medicine (CAM). We have listed every proposal for treating depression that we could find that has been the subject of at least one research study, without prejudging their worthiness in terms of scientific methods.

In Stage III, we were able to sort out and analyze what treatments are available today that were not well-known five or 10 years ago. This project has allowed us to understand the current state of knowledge about depression as well as see many of the issues that are raised by contemporary approaches. As well, the documentation shows many links to other diseases and conditions. This does not necessarily mean that there is a *causal* link between depression and other co-morbid conditions, but rather that there is a correlational link that may or may not be causal. Finally, we have listed a number of significant developments for the future treatment of depression which are not yet ready for controlled trials, but are based on new technologies that indicate trends in the treatment of depression that we may very well see in the near future.

In Stage IV, we synthesized the findings into this report with its accompanying visualizations. It is our hope that this environmental scan of research and innovations can form the basis for a discussion of the best avenues to treating depression moving forward.

Bill Wilkerson, Co-founder and CEO of the Global Business and Economic Roundtable on Addiction and Mental Health, and Kim Sunderland, Project Director for the *Ten Year Report*, both supplied detailed editing of several drafts of this report, for which we thank them. Thank you to both Erin Azzopardi and Anna Coventry for providing capable web research skills. Thanks to Ericka Little, our copy editor, who thoroughly edited the final manuscript, and to artist and designer San Murata who generously designed the cover of the report. We hope that these collective efforts produce new ideas and directions in the treatment of depression, and encourage collaboration among the research community working on this problem.

# Part 1 - Introduction

Depression, or "melancholy", has been written about since at least the time of Aristotle, who believed that it could be of great value because of the insights it could bring. While many see depression as something to be avoided, others argue that depression has an evolutionary function – that it is not a problem to be avoided, but a defence mechanism that in its mild and moderate forms can be "good for you" (Goeghegan, 2008). But, severe depression, now known as Major Depressive Disorder (MDD), is another matter. The suffering of people with MDD is obvious, and its debilitating effects often overwhelming. This has motivated professionals to search for effective treatments for severe depression, hopefully finding a cure.

Most of the major treatments that have been developed over the past 100 years, and which have had a positive impact for a significant portion of people with depression, are still in use today. But, there are many severely depressed people (maybe even the majority of them) who are not helped by current treatments, and remain depressed year after year. This report is a brief review of current treatments for depression, and surveys recent innovations in both understanding and treating depression that give hope that effective treatments of depression are in the process of development.

In response to a request to research some aspects of depression, neurobiologist Robert Dantzer of France's national medical research agency INSERM at the University of Bordeaux 2, replied, "At the beginning I was very reluctant to get into this question because depression is such a can of worms" (quoted in Brown, 2001). When asked to produce a report on recent innovations and future prospects for the treatment of depression, we had a similar feeling about the subject. We realized that to try to sort out the many studies on the topic of the treatment of depression would require a new approach to uncovering innovation, and a big picture view of the field.

i5 Research has developed an approach to predicting the near future (up to 10 years out) of various technologies, based on information about innovations that have already occurred but that are generally not well known (see the Preface for a more thorough discussion of our methodology). This requires a broad survey of not only books and articles, but a wide range of knowledge-based documents that produce both strong and weak signals of the possible direction(s) of a particular field of study. The production of knowledge follows a course from the birth of an idea or innovation, through its "mashup" with many other ideas, to its formulation as a distinct concept, its application to the world around us, and its usefulness (or not) in being turned into a product, process or promise of something genuinely new. To assess any current

innovation, it is necessary to plot its place on the arc of a developmental path as it is passed on from person to person. Information, in other words, has a "social life" (Brown and Duguid, 2000).

This is the approach we have taken in assessing recent innovations and future prospects for the treatment of depression. We introduce the topic by briefly discussing its definitions, basic facts, and traditional treatments, as a background to what has occurred in the past 10 years in terms of innovations, fresh ideas, and suggested courses of action. Most technologies (treatments of depression are technologies in the broadest sense of the term) take at least 10 years to go from conception to commercialization, and in many cases, take much longer than that. Technologies are first envisioned, and then invented, well before their widespread adoption throughout society. As the novelist William Gibson (originator of the term "cyberspace") said in an interview on NPR Radio in 1993, "The future is already here – it's just not very evenly distributed."

In addition to invention and innovation, the history of the treatment of depression is curiously one of several significant instances of *serendipity*. Significant events range from the railway spike exploding through the skull of Phineas Gage on September 13, 1848, which led to the confirmation of brain localization, to Freud's discovery of the "talking cure" through his use of hypnosis, to the accidental discovery of a class of drugs (monoamine oxidase inhibitors) for the treatment of depression in the late 1950s. But, what appears to be an original discovery is often the product of the work of many different individuals, often isolated from each other, whose work comes together in complex ways over an extended period of time. Many "overnight successes" are, in reality, the results of decades of hidden work. This pattern holds true for new developments in the treatment of depression.

## Understanding Depression

What is depression? For the most part, it is defined as a cluster of specific symptoms, which vary from person to person:

> Depression is a chronic, recurring and potentially life-threatening illness that affects up to 20% of the population across the globe… Most experts agree that depression should be viewed as a syndrome, not a disease. Therefore, the highly variable compilation of symptoms that is used to define depression, and the highly variable course of the illness and its response to various treatments, indicate that depression subsumes numerous disease states of distinct aetiology, and perhaps distinct pathophysiology. In fact, the lack of bona fide objective diagnostic tests for depression, beyond a compilation of symptoms, means that the diagnosis of the syndrome is quite variable, with no clear line

distinguishing people who have mild clinical depression from those who are simply having a tough time in the course of normal life (Berton and Nestler, 2006, p. 137).

The American Psychiatric Association sees major depressive disorder (MDD) as a mental disorder characterized by an all-encompassing low mood accompanied by low self-esteem, and by loss of interest or pleasure in normally enjoyable activities. A distinction is made in the literature between mild depression and MDD. Yet, there are no distinct lines between the two. The diagnosis of MDD depends on the recognition of the cluster of signs and symptoms that includes "depressed mood, and or lack of interest or pleasure, and at least four symptoms from a list that includes: weight or appetite changes; sleep changes; observable changes in psychomotor activity; feelings of worthlessness or guilt; poor ability to think or concentrate, or make decisions; and recurrent thoughts of death or suicide" (Britton, 2006). But, "many more patients are diagnosed with depressive illness (i.e. depression), but not specifically MDD because they do not meet the criteria as listed above for MDD" (Bair, Robinson, Katon, and Kroenke, 2003, pp. 5-6).

The bible of the psychiatric profession, the DSM-IV-TR, lists various depressive disorders such as major depressive disorder (MDD), minor depressive disorder, recurrent brief depressive disorder, and premenstrual dysphoric disorder. MDD is also called by other names including recurrent depressive disorder, clinical depression, major depression, unipolar depression, or unipolar disorder. The clinical status of patients with depression may also be described by severity, length of time, and frequency of recurrence. Adjectives that can be added to a diagnosis of depression include *psychotic, melancholic, atypical, catatonic,* or *postpartum onset.* All of these distinctions make it uncertain that any given research study can be compared to any other study, as most research studies do not classify their participants into the above clinical subcategories (Ibid).

The consensus among researchers is that depression is not a single entity with a single cause. Fasick (2010) says, "It is unlikely that depression is caused by a defect in a single neurotransmitter (NT) pathway, but by a combination of genetic, biochemical, socio-economic, psychological, environmental, and life-experience factors, with the biggest risk factor being chronic stress." Certainly, this view is born out by the results of this comprehensive search of the documentation on the treatment of depression.

In addition to the difficulties in describing depression, there are problems deciding when a treatment has been effective. A task force within the American College of Neuropsychopharmacology (ACNP) has been studying the concepts of recovery,

relapse, recurrence, and response as used by clinical investigators and practicing clinicians. They have come up with the following:

> Given the strong implications of remission for better function and a better prognosis, remission is a valid, clinically relevant end point for both practitioners and investigators. Not all depressed patients, however, will reach remission. Response is a less desirable primary outcome in trials because it depends highly on the initial (often single) baseline measure of symptom severity. It is recommended that remission be ascribed after 3 consecutive weeks during which minimal symptom status (absence of both sadness and reduced interest/pleasure along with the presence of fewer than three of the remaining seven DSM-IV-TR diagnostic criterion symptoms) is maintained. Once achieved, remission can only be lost if followed by a relapse. Recovery is ascribed after at least 4 months following the onset of remission, during which a relapse has not occurred. Recovery, once achieved, can only be lost if followed by a recurrence. (Rush et al., 2006).

It is clear that views and concepts of depression are not very coherent, and new understandings of this condition are needed.

## Prevalence and Impact of Depression

In spite of the difficulties of defining depression, the diagnosis of major depressive disorder (MDD) and its variants is very common. The diagnosis of MDD is based on the self-reporting of a patient's experiences, behaviours reported by relatives or friends, and/or diagnostic tests for depression. Based on the occurrence of a diagnosis of depression, a variety of statistics on depression are regularly cited in the literature. For example:

- Major depressive disorder (MDD) affects approximately 14.8 million American adults, or about 6.7 percent of the U.S. population age 18 and older in a given year (Kessler, Chiu, Demler, & Walters, 2005). (From Price, 2009)
- Major depressive disorder (MDD) affects approximately 7% of the general population in a given year and is the most common cause of disability in the United States. The disorder is costly, with over $44 billion a year in direct and indirect costs in this country alone. (Cross, 2007)
- Mood disorders are one of the most prevalent forms of mental illness. According to the DSM-IV, the lifetime risk for major depressive disorder

is between 10 and 25% for women and between 5 and 12% for men. (Jans et al., 2007)

- Major depression is a debilitating mood disorder that affects almost 19 million adults in the U.S at any given time and almost 20% of the U.S. population over a lifetime. (Britton, 2006)

- In the year 2020, depression is predicted to be the largest cause of disease burden in women and the second largest cause of disability adjusted life years worldwide, second only to… heart disease. (Britton, 2006)

- The most common time of onset of depression is between the ages of 20 and 30 years, with a later peak between 30 and 40 years.

So, while the definitions of depression are complex and varied, and the statistics cited are not in complete agreement, it is generally agreed that severe depression is a major problem that needs a deeper understanding, and to the extent possible, a solution. The impact of depression is well-known. "In the U.S., the economic burden of depression has gone up from $43.7 billion in 1990 to almost $53 billion in 2000. Indirect consequences of depression are troublesome as well, and include increased failure to finish high school, likelihood of divorce, and substance abuse" (Britton, 2006, p.15). Depression can lead to impaired concentration, memory, and attention, and a variety of structural brain abnormalities. Clearly it is not a condition from which we can walk away (Delgado and Schillerstrom, 2009).

This report is a snapshot of the ongoing work to further the understanding of depression by researchers worldwide. Before looking at the latest innovations and future prospects for depression, a brief review of the current mainstream treatments of depression is in order.

For the past 50 years or more, three treatments have commonly been available for depression. The most common treatment is the use of anti-depressant medications. This is followed by the use of psychotherapy and education, often in combination with medications. Electroconvulsive therapy is a third option, although its use has greatly declined with the advent of drug therapies. Finally, there are combinations of the above treatments in use today. This section of the report will briefly describe each of the above treatments, as well as some of the issues that have been raised by their use.

Patient care for depression is usually given on an outpatient basis unless there is a significant risk to self or others. It should be noted that this discussion of treatments applies mostly to developed countries. Treatment options are very limited in developing countries where there is often little access to professionals, medications or therapy.

# Current Treatment 1: Anti-depressants

In his 1993 book, *Good Mood: The New Psychology of Overcoming Depression*, Julian Simon refers to the use of drugs as "the gold standard for treating depression." Previous to the 1950s, psychotherapy (usually in the form of psychoanalysis) and several relatively crude interventions in the brain, such as convulsive therapy (using drugs), electroconvulsive therapy and lobotomies, were available for treating depression. Chemicals such as lithium and a variety of opiates were used for many years to treat depression, but were addictive, had tolerance buildup issues, and exhibited many undesirable side-effects. These chemicals were mostly dropped as a treatment as new anti-depressants became available in the late 1950s. However, the opiate Buprenorphine was used in a small clinical trial at Harvard Medical School in the 1990s, and a 2006 follow-up paper in the *Journal of European Neuropsychopharmacology* reported that eleven severely depressed patients found this compound "of significant benefit" (Nyhuis, Specka and Gastpar, 2006).

In 1952, Abbott Pharmaceuticals synthesized a compound it called 5-hydroxytryptamine (5-HT), which is found naturally in the guts of squid and octopi, and in human blood. Abbott sent in samples of this new compound to leading scientists around the United States to see if they could identify how this new molecule could be used. One person who received a sample was 25-year-old Betty Twarog, who had just graduated with a PhD from Harvard. At the time, she was working on discovering the chemical that mussels used to lock and unlock their shells. The new compound, which biologists had started to call *serotonin*, proved to be the neurotransmitter that mussels used to signal when their shells would open or close.  Working at the Cleveland Clinic, Dr. Twarog demonstrated the presence of serotonin in the brains of rats, dogs, and monkeys. However, given the times in which she lived, her first paper on serotonin was not published in a scientific journal until more prominent male scientists had verified it and published about it first (Greenberg, 2010).

Neurotransmitters were discovered in 1921 by the German scientist Otto Loewi. At first, there were thought to be only two neurotransmitters in the body – acetylcholine and epinephrine (aka adrenaline). With Betty Twarog's discovery, there were now three known neurotransmitters. Gary Greenberg (2010) describes what happened next:

> None of these discoveries would be of much interest outside the lab were it not for some chance observations made in the early 1950s - that, for instance, an antitubercular drug that had induced an unexpected (though not unwelcome) euphoria inhibited an enzyme that breaks down serotonin, or that lysergic acid diethylamide (LSD), already famous for its profound effects on consciousness, has a chemical structure similar to

serotonin. Out of these and other findings, scientists began to cobble together a theory: that mental illness in general and depression in particular are caused by imbalances in neurotransmitters, and especially in serotonin. (p. 5-6)

This theory led pharmaceutical companies to develop drugs that would fix these supposed imbalances. By 1958, anti-depressant drugs were available, and in 1988, Prozac was introduced. By 2005, 27 million Americans (10% of the adult population) were taking anti-depressants at an annual cost of more than $10 billion (Greenberg, 2010).

In 1993 Pinder and Wieringa identified three generations of anti-depressants, up to that year. The first generation are called monoamine oxidase inhibitors (MAOI). A monoamine is a class of neurotransmitters that contain one amino group; monoamines that are important for understanding depression include serotonin, dopamine, norepinephrine (also called noradrenaline), epinephrine (also called adrenaline), and melatonin (which regulates your circadian rhythm). However, the use of MAOIs declined "as physicians became aware of their propensity for causing hypertensive crises because of their potentially fatal interaction with compounds, particularly common foodstuffs such as cheese, containing tyramine" (p. 259). Second generation drugs proved to be not much better:

…They are slow to take effect and leave a substantial proportion of patients unaffected. They are not entirely without side effects, and two of them, zimeldine and nomifensin, were withdrawn because of severe neurological and haematological reactions, respectively. Blood dyscrasias have also been associated with mianserin, and seizures with amoxapine, bupropion, and maprotiline. Most…are at least as toxic in overdosage as their predecessors, amoxapine more so, and, in contrast to the atypical antidepressants, offer little advantage in terms of reduced anticholinergic or cardiovascular effects. (Ibid, p. 260)

The newest second-generation drugs in the 1990s were the selective serotonin reuptake inhibitors (SSRIs), such as Prozac. While improved, they continued to have disappointing results; though they worked for many people, they continued to be slow to act, and ineffective for about half of the population of people suffering from severe depression. In 2006, Willoughby Britton summarized the situation:

While antidepressant medication is the most popular treatment for depression, large meta-analytic studies report an intent-to-treat analysis response rate of approximately 55% and about 70% for study completers. Furthermore, patients who meet response criteria may remain partly symptomatic, disabled, and at higher risk of relapse. When the more

stringent outcome criteria are utilized, remission rates reportedly vary from 35 to 45%. (p.16)

These results may, in fact, be overly optimistic in terms of the efficacy of anti-depressants. A study in 2006 of 4,000 patients found that treatment with a standard anti-depressant helped only 30 per cent of the group, although a few more were helped by the addition of an additional drug (Trivedi et al, 2006). Moreover, a study of 718 depressed patients by psychologists in the United States found that anti-depressant drugs are not much more effective than *placebos* in cases of mild or moderate depression (Langreth, 2010). A similar study in 2008 in the UK that looked at 35 trials of four different anti-depressants (including Prozac) and found "virtually no difference" between drugs and placebos for patients who were moderately depressed, and "only a relatively small difference even in the very severely depressed." (Ibid)

## Current Treatment 2: Psychotherapy and Education

Psychotherapeutic approaches to the treatment of depression have a long history, going back at least to Freud and his theories of the unconscious. Freud thought that there was a similarity between depression and the response to the death of a loved one. In his 1917 book *Mourning and Melancholia*, Freud distinguishes between mourning – which is caused by a conscious loss, and melancholia – which is caused by an unconscious loss and the lowering of self-esteem (Gilbert, 1992).

Of course, the essence of Freudian therapy is the "talking cure" – lying on a couch and talking about the interpretations of dreams and associations. Psychoanalysis has evolved into a variety of schools of psychotherapy, most of which depend on the patient talking and working through issues as the main form of treatment.

More recently, the dominant form of psychotherapy for depression is known as Cognitive Behavioural Therapy (CBT), an approach that sees psychological problems as an irrational way of thinking. CBT teaches clients to challenge self-defeating but enduring ways of thinking (cognitions), and to change counter-productive behaviours. Studies have suggested that CBT performs as well or better than anti-depressants for patients with moderate to severe depression (Klein, 2008).

A milder and less rigorous form of psychotherapy is empathic non-directive counselling (Gerrard et al., 1993). As a treatment for depression, this often takes the form of telephone counselling or an online chat. There are lots of examples of this approach to treating depression and prevention of suicide. Dr. Cynthia Lee Dennis, an Associate Professor of Nursing at the University of Toronto has studied the effect of telephone counselling on women with postpartum depression. She says, "Telecare

provides additional support to people and can help them feel included and part of something…It can even help some people to speak more freely and feel more comfortable than they would in a normal face-to-face situation" (quoted in Schiewe, 2010). A recent study on telephone counselling of cancer patients by a nurse found that "centralized telecare management coupled with automated symptom monitoring resulted in improved pain and depression outcomes in cancer patients receiving care in geographically dispersed urban and rural oncology practices" (Kroenke et al., 2010).

Educational approaches to the treatment of depression are supplemental efforts to help patients understand their condition. These include courses specifically developed for patients to learn how to "cope with depression", and information packages that are made available to patients in professional offices or online.

Cuijpers et al. (2009) report that the "Coping with Depression" course (CWD), in use for over 30 years, "is by the far the best studied psycho-educational intervention for the treatment and prevention of depression, and is used in routine practice in several countries." In their meta-analysis of studies of the effectiveness of the CWD course, the Cuijpers team found that it was as effective as many methods of psychotherapy. They concluded that the CWD course is "a flexible treatment which can easily be adapted…The CWD has contributed considerably to the development and innovation of prevention of and treatment of depression in many target populations" (p. 449).

More recently, with the advent of the Internet, various groups have placed educational materials about coping with depression on their websites. Examples include:

- The Clinical Research Unit for Anxiety and Depression (CRUfAD) at St Vincent's Hospital, Sydney, Australia: http://www.crufadclinic.org
- Minding Your Head – an online site in Ireland: http://www.mindingyourhead.info
- Royal College of Psychiatrists (UK): http://www.rcpsych.ac.uk/mentalhealthinformation.aspx
- Depression Canada: http://www.depression-understood.org/information.htm

Education will continue to be part of the mix of treatments of depression, but, other than using the Internet as a new distribution platform, there has not been a lot of innovation in this area over the past decade.

# Current Treatment 3: Electroconvulsive Therapy

Electroconvulsive Therapy (ECT) is another treatment for depression that has been around for a relatively long time. It is a procedure where pulses of electricity are sent through the brain through two electrodes in order to induce a seizure in the patient. It is a controversial treatment, but those who use it contend that it works. Dr. Raphael Fraser (2009), writing in *New Scientist*, says:

> ECT has long been controversial. As a psychiatrist I can attest that its benefits are not "occasional": ECT is the most effective antidepressant treatment we know. The response rate is as high as 80 per cent, and it is most effective for severe depression. Numerous studies have been done comparing the effects of ECT with general anaesthetic alone, where the patient undergoes the same preparation but does not receive the treatment. ECT was undoubtedly effective. (p. 25)

Because ECT is controversial, it is often used as a treatment of "last resort" in cases of severe depression. However, a 2004 study of the effectiveness of ECT in community practice in the 65 years of its use found much lower remission rates than in prior research, and most of those who had received ECT treatment had relapsed (Prudic et al., 2004). For a history of ECT, and a moving personal account of going through it, watch the TED conference video presentation by Sherwin Nuland (2001) – see http://blog.ted.com/2007/10/30/sherwin_nuland.

# Current Treatment 4: Combination Therapies

Therapies that combine two or more treatment approaches are increasingly common. For example, in 2002, a large community study of 244,859 depressed veterans found that 22% of the participants were on a second anti-depressant (Valenstein et al., 2006). Often, there is a main treatment, augmented by another to support changes and prevent remission. In their 1993 article on "third generation antidepressants," Pinder and Wieringa write, "It is possible to improve the efficacy of traditionally based antidepressants, old or new, by judicious use of combination therapy." They add:

> There are now well-established strategies for dealing with refractory or resistant depression, which include the addition of lithium to full doses of other antidepressants. Other useful combinations in such patients include TCAs with MAOIs, the addition of tryptophan to a regimen of lithium with MAOIs or clomipramine, or the addition of triiodothyronine. (p. 262)

But, Trivedi et al. (2007) critically observe, "Although clinicians frequently add a second medication to an initial, ineffective antidepressant drug, no randomized controlled trial has compared the efficacy of this approach." A meta-analysis of studies on combining the effects of two types of drugs to treat depression (serotonergic and noradrenergic) failed to show a significant advantage to this particular combination (Papakostas et al., 2007).  However, a very recent randomized double-blind study of 105 patients with MDD showed statistically significantly greater reductions in ratings of depression symptoms for patients on several combinations of two drugs (fluoxetine + mirtazapine, venlafaxine + mirtazapine, and bupropion+ mirtazapine) compared with a fluoxetine (Prozac) by itself. (Blier, 2010)

In addition to drug combinations, several studies point to the combination of psychotherapy and medication as the most effective treatment of depression, especially for adolescents (Van Voorhees et al., 2008).

## Co-morbidity of Depression with Other Conditions

Depression is linked with many other diseases and social conditions. But an association does not prove a cause, merely a relationship. That is, depression may be the cause of some conditions, or some conditions may be the cause of depression, or both may be the result of a third factor.

While there are a great variety of conditions associated with depression, it is particularly prevalent among those with obstructive sleep apnea (OSA) and heart failure (HF) (Cross, 2007). Oetweiler-Bedell et al. (2008) state that, "research suggests that treatments for depression among individuals with chronic physical disease do not improve disease outcomes significantly, and chronic disease management programs do not necessarily improve mood." Obviously it is hard to live with both depression and chronic physical disease, which places a great burden on meeting the needs of a depressed person, especially if disease management and depression management are not integrated. Oetweiler-Bedell et al. offer a framework in which the management of the two conditions together is considered along with the management of either condition on its own.

It is beyond the scope of this report to investigate in-depth all of the links between depression and other diseases and conditions. In the listing below, a paragraph or two is provided that makes the connection(s), and points readers to further sources.

## *Alcoholism*

Alcoholism and depression are strongly linked. A recent study by Stevenson et al. (2009), using mice, found that "depression that emerges during abstinence from chronic alcohol use has a greater negative impact on relapse than pre-existing depression." In addition, the team also noticed a 40% drop in the number of neurons in the hippocampi of alcoholics, a finding which is often correlated with a diagnosis of depression.

## *Anxiety*

According to the National Institute of Mental Health in the United States, anxiety disorders, such as post-traumatic stress disorder (PTSD), obsessive-compulsive disorder, panic disorder, social phobia and generalized anxiety disorder, often accompany depression (NIMH, 2008). The 1992 *National Comorbidity Survey* in the U.S. reports that 51% of those with major depression disorder also suffer from a lifetime of anxiety (Harvard University, 1992). A review of 20 years of references on Medline on anxiety showed that "between 10% and 20% of adults in any given 12-month period will visit their primary care physician during an anxiety or depressive disorder episode (although typically for a nonpsychiatric complaint); more than 50% of these patients suffer from a co-morbid second depressive or anxiety disorder" (Hirschfeld, 2001).

## *Arthritis*

Lin (2008) writes, "Depression is significant among patients with arthritis and musculoskeletal illnesses." She continues,

> Results from a large clinical trial of depressed older patients with arthritis showed that a focused, collaborative depression care intervention not only decreased depression but also improved arthritis-associated outcomes, such as pain severity and arthritis-related limitations in daily activities. Relative to patients given usual care, patients receiving intervention also reported better health status and higher quality of life. Analyses of the depression interventions uncovered a reciprocal interrelation between depression and pain. Higher severity of either depression or pain decreased the benefits of systematic depression treatment and was associated with worse pain and depression outcomes. (Ibid)

Arthritis is also linked to rejection by others and low social status which in turn are also connected to depression (Slavich et al., 2010).

### *Asthma*

Asthma and depression have been linked in the research, but this might be a case of each being associated with a third variable – pollution. Aldhous (2010) reports on a new study in seven cities across South Korea that uncovered a clear association between suicide and spikes of particulate pollution. He adds, "Meanwhile, researchers who in the 1990s linked air pollution to asthma in a large group of Taiwanese children have now found that those with the condition were subsequently more likely to have killed themselves."

There may be a genetic connection between asthma and depression. Mothers who suffer from major depression or anxiety disorders are more likely to have children with asthma and other allergy-based conditions. The fact that the association was only found for biological children supports a "shared genetic liability" theory (Vince, 2005).

### *Cancer*

Williams and Dale (2006) state that, "depression is common in cancer patients, and this often remains undetected and untreated. Depression has been associated with poorer quality of life, in addition to increased impairment of immune response and poorer survival in cancer patients" (p. 372). Massie (2004) reports that up to 58% of cancer patients have depressive symptoms, and up to 38% have major depressive disorder. Jacobsen and Jim (2008) recently reviewed over a dozen studies of useful psychosocial interventions for patients with cancer, in order to derive evidence-based treatments for depression in cancer patients.

### *Chronic Pain*

Chronic pain and depression commonly occur together. In the United States, approximately 32 million people suffer from chronic pain and about 25-50% of these patients are also depressed (Fasick, 2009). This is not surprising, in that it obviously can be depressing to be in chronic pain. The co-existence of chronic pain and depression fits with Seligman's theory of "learned helplessness" (Seligman and Maier, 1967). Bair et al. (2003) observe, "Depression and pain share biological pathways and neurotransmitters, which has implications for the treatment of both concurrently."

### *Diabetes*

A comprehensive review of medical literature between 1966 and 2009 found that "coexisting depression in people with diabetes is associated with decreased

adherence to treatment, or metabolic control, higher complication rates, decreased quality of life, increased health care use and cost, increased disability and lost productivity, and increased risk of death" (Egde and Ellis, 2010). A recent study that looked at 1,433 healthy people over the age of 65 living in the south of France found that preventing type II diabetes and depression and an improved diet could reduce rates of dementia late in life. Eliminating depression and diabetes and increasing fruit and vegetable consumption would lead to an overall 21% reduction in new cases of dementia, the study concluded (CBC, 2010b).

### *Epilepsy*

Mazarati et al. (2010) report that depression frequently co-occurs with temporal lobe epilepsy (TLE). It is thought that augmentation of hippocampal interleukin-1â (IL-1â) signaling may be a mechanistic factor in both TLE and clinical depression. Research conducted with rats showed that blocking hippocampal interleukin-1 receptors has anti-depressant effects without changing the frequency of epileptic seizures. As we will see later, the hippocampus seems to play a critical role in producing and relieving depression.

### *Heart Disease*

One of the strongest links between depression and another disease is depression's association with heart disease. Schulman and Shapiro (2008) found that depression is "associated with a 3- to 4-fold increase in the risk of recurrent cardiac events and death in patients with coronary artery disease." They explain how the two conditions are connected:

> Increased platelet reactivity that causes increased platelet aggregation and thrombus formation may play a strong role in linking depression and coronary heart disease. Inflammatory markers that are increased in patients with depression have also been linked to congestive heart failure, atherosclerosis, myocardial infarction, and stroke…Depression is a risk factor for cardiovascular disease and death in many ways, directly and indirectly. It is independently linked to smoking, diabetes, and obesity—all of which are risk factors for coronary heart disease (CHD). Depressed patients are more likely to be noncompliant with treatment recommendations, including diet, medications, and keeping appointments, and are more likely to delay presentation for treatment with an acute coronary event.

Detweiler-Bedell et al. (2008) suggest that there is a direct physiological link by which depression and heart disease may cause and exacerbate the other. "For example, depression is associated with reduced heart rate variability, increased

sympathetic nervous system activity, and platelet aggregation, all of which are risk factors for cardiovascular disease and conversely, cardiovascular disease may be associated with the elevation of pro-inflammatory cytokines that perpetuate depression."

In spite of the elevated risks, people with major depression are less likely to follow medical recommendations for treating cardiovascular disorders, and cardiologists may not recognize underlying depression that complicates a cardiovascular problem in one of their patients. (Ibid)

### *Inflammation*

Phyillida Brown (2001) reports in *New Scientist* that doctors have often noticed that giving patients immune system boosting drugs for such conditions as hepatitis C and cancer can lead to severe depression and suicidal thoughts. This has led to a new way of thinking about the connection between depression and the immune system:

> Most of us associate depression with being run down and having poor immunity to infections. The startling side effects of the immune-boosting drugs turn that notion on its head. They suggest that some people who are depressed may actually be suffering from an over-heated immune system, and that damping down inflammation could offer a brand new way to treat routine clinical depression—while making billions for the pharmaceuticals industry into the bargain. It's a theory that recasts depression—one of the great plagues of our time—as a chronic inflammatory disease like rheumatoid arthritis. (Ibid)

> In an inflammatory attack, immune cells rev each other up by pumping out substances known as inflammatory cytokines. Drugs like interferon are simply artificial versions of these substances. That's why they boost immunity so well and why, according to the new "immune theory" of depression, they also induce such dark moods in some patients. If the body's own supplies of cytokines stay too high for too long, maybe they too become toxic to mood and trigger depression. (Ibid)

Several researchers have noted that inflammation is present in both heart failure and depression, and both conditions show the presence of the same three "inflammatory markers," indicating a possible relationship between inflammation, depression, and heart failure. "This relationship remains even when controlling for age, gender, body mass index, and medication use" (Cross, 2007).

The evidence that inflammation may be involved in depression is also found when it occurs with other diseases besides heart problems. Fasick (2010) notes that elevated "pro-inflammatory cytokines are routinely found in patients suffering from

depression and chronic pain...These cytokines also play a role in the turnover of monoamines within the hippocampus." Researchers at Yale University studied NF-êB in rats, a cytokine that is known to control a host of immune responses, to see whether its release might be decreasing neurogenesis – the creation of new neurons. Their hypothesis was confirmed, and when the team gave the rats an NF-êB inhibitor before stressing them, the birth of new neurons continued at a normal rate (Hamzelou, 2010).

### Obesity

A headline on the Reuters website reads, "Obesity and depression are a two-way street" (Brooks, 2010). The article describes the work of Floriana Luppino and colleagues at the Leiden University Medical Center in the Netherlands, who found that obesity "increases the risk of depression in initially non-depressed individuals by 55 percent and depression increases the risk of obesity in initially normal-weight individuals by 58 percent." Evan Atlantis from the University of Adelaide's School of Medicine commented, "Obese people - especially those who perceive themselves as being overweight - often experience weight-related stigma and discrimination, and consequently present with symptoms of low self esteem, low self worth, and guilt. Obesity is associated with socioeconomic disadvantage and low levels of physical activity, both of which are strong predictors of depression" (Atlantis et al., 2009).

### Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) affects more than 12 million adults in the United States, and has been strongly linked to depression. In her 2007 doctoral dissertation, Rebecca Cross reviews the literature on the link between depression and obstructive sleep apnea. She writes, "The results indicate that obstructive sleep apnea patients with depressive symptoms exhibit brain injury in a number of regions compared to obstructive sleep apnea control subjects without depressive symptoms. The brain regions affected include the anterior and mid-cingulate, caudate, hippocampus, insula, medial prefrontal cortex, parietal and temporal cortices, pons and cerebellum" (Cross, 2007, pp. 4-5).

### Stroke

Stroke has been defined by the World Health Organization as "a syndrome of rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin" (Moreno, 2004). Essentially, stroke is seen as the clinical

manifestation of a lack of blood supply in the brain. José Moreno's 2004 doctoral dissertation explored the links between stroke and depression. He says,

> The meta-analysis demonstrated a positive association between depression and stroke. The change in depression over time is a strong predictor of stroke even after adjusting for depression at baseline. Inflammation was not a mediator in the association between depression and stroke. There was some evidence that inflammation acted as a moderator for this relationship…We found that inflammation was not in the causal pathway in the relationship between depression and stroke.

This work is a good example of showing how two conditions can exist together, although neither one causes the other.

### Suicide

The link between suicide and depression is well-known. Even though depression and suicide are often related, not all depressed people are suicidal and not all suicidal people are depressed. Up to 15% of those who are clinically depressed die by suicide. But, "severely depressed people often do not have the energy to harm themselves, but it is when their depression lifts and they gain increased energy that they may be more likely to attempt suicide" (www.AllAboutDepression.com). The risk of suicide for depressed patients increases when accompanied by anxiety disorders (Pfeiffer et al., 2009).

While the relationship between suicide and depression is often mentioned in the literature, Bradvick and Berglund (2006) note in their review of the literature, "Individual studies, meta-analyses, and reviews have failed to show any significant difference in favor of anti-depressant medication relative to suicidal acts. In fact, several studies have shown that the risk of suicide increases for patients taking specific anti-depressants" (Ibid). A "black box warning" was introduced in the United States in 2007 on SSRIs (selective serotonin reuptake inhibitors) and other anti-depressant medications due to increased risk of suicide in patients younger than 24 years old (FDA, 2007).

However, there are problems in trying to determine a link between taking any specific drug and increased risk of suicide. Ludwig, Marcotte and Norberg (2009) explain, "It is unlikely that randomized clinical trials (RCTs) will ever be able to identify the effects of SSRIs [selective serotonin reuptake inhibitors] on suicide mortality, both because of small samples and because these samples exclude those at highest risk for suicide." Instead, these researchers used population-based observational studies in 26 countries to identify the effects of SSRIs on suicide completion rates, and

found that "the net effect of the introduction and subsequent sales of SSRIs is to reduce death by suicide." This is clearly an area that needs further study.

Most interesting for the purposes of this report are the similarities in the neurobiology of suicide and depression. Both can be linked to brain injuries (Simpson and Tate, 2007), and to the flow of serotonin in the brain. Dwivedi et al. (2010) have recently demonstrated that the brains of those thinking of suicide are associated with decreased activation and expression of selective catalytic and regulatory subunits of PI3-K, a chemical in the brain that plays a crucial role in neuronal growth and plasticity.

## Issues with Current Treatments of Depression

The above conditions that can be co-morbid with depression can also be found in more complex combinations than just a one-to-one relationship. For example, heart disease is also linked with obstructive sleep apnea and obesity, and all three can be present with depression. Researchers are now exploring the connections among the various conditions listed above.

As noted above, none of the four traditional treatments of depression are particularly effective. This does not mean that we should not keep using them, but it highlights the fact that new research and new insights into the treatment of depression are needed. Treatment efficacy for anti-depressants is relatively low with only about 30% of patients experiencing remission, and 30 to 40% of patients not showing any significant response. Moreover, anti-depressants, when they work, take several weeks or months before there is *any* response (Kato and Serretti, 2010; Berton and Nestler, 2006). Education and psychotherapy are considered useful for mild to moderate depression, but they are time-consuming and no more effective than anti-depressants. Electroconvulsive therapy is considered a treatment of last resort.

The failure of traditional treatments for depression to demonstrate their effectiveness means that there is room in this field for innovation and fresh ideas. At the same time, it is important to review the research methodologies used for recent studies, in order to make sure that new approaches to the treatment of depression are based on solid methodological standards.

Many anti-depressants have serious side effects that include sexual dysfunction, increased urinary frequency, nausea, anxiety, agitation, insomnia, sadness and suicidal feelings (Deakin, 2009). With such a dismal record, we can rightly ask why billions of dollars of anti-depressants have been prescribed and purchased. Why isn't

there research on other approaches to the treatment of depression? The answer is a complex one.

With the discovery of the effects of serotonin on the brain, a dominant theory of depression (the "monoamine theory") took hold that is difficult to question or displace. Berton and Nestler (2006) explain why:

> …There has been an impressive accumulation of knowledge about non-monoamine systems that might contribute to the pathophysiology of depression in animal models, and some human evidence is also available. However, none of these discoveries has so far been translated into a new bona fide treatment for depression. There are several reasons for this. First, it is not known whether the animal models that have been used to accurately predict the antidepressant action of serotonin- and noradrenaline-acting drugs can detect antidepressants that act through non-monoamine-based mechanisms. This is partly due to the fact that we have no bona fide non-monoamine-based antidepressants that have been adequately validated in humans. This is, therefore, a catch-22 situation (that is, one that cannot be resolved as it involves mutually conflicting or dependent conditions). Second, antidepressant efficacy studies are extremely expensive (they involve chronic treatment of at least hundreds of patients) and are notoriously risky (large placebo responses cause many trials to fail). This increases the threshold for a pharmaceutical or biotechnology company to embark on a trial of any antidepressant, especially one with a non-monoamine-based (and therefore riskier) mechanism. Third, to increase their confidence level in a non-monoamine-based drug, many groups have looked for effects of such drugs on the serotonin and noradrenaline systems. According to this view, if it can be shown that a non-monoamine-based drug enhances, for example, serotonergic transmission in some brain region, this increases the cache of that drug. However, this is another catch-22, as it does not lead us to create drugs with truly novel mechanisms of action. Finally, profits from monoamine-based drugs (SSRIs and SNRIs) have been extremely high, and this has removed the financial incentive to take the risks involved in developing drugs with non-monoamine-based actions. (p. 138-139)

Being stuck with a particular theory of depression is not the only problem that keeps progress from happening. Much of the research on depression is conducted using "animal models" that may or may not replicate human neurological conditions. For example, we know that there is a genetic component in major depressive disorders that cannot be replicated in animal models. As well, environmental conditions for human beings are vastly different than those of laboratory rats. This means studies of the effects of anti-depressants on stress-induced behavioural abnormalities in animal models may not be generalizable to human beings.

Overreliance on one theory of depression is like having a dominant paradigm in science (Kuhn, 1962). Most studies are a variation of the same theme, and it is very difficult to shift thinking towards a different theory of depression. In addition to these problems, the quality of much of the research has come into question. In 2008, Erick Turner and his colleagues studied 74 FDA-registered drug trials in the U.S. between 1987 and 2004, and found that 23 of these studies were never published in a journal. All but one of the unpublished studies concluded that the effects of the drugs were negative or questionable. This is known as the "file drawer problem" where results of studies that don't show a positive effect are filed away and never published.

There are many other problems with anti-depressant research. These include rater bias, where raters often want to please a drug company, prove their chosen treatment is effective, and/or achieve status by being published (Wagner, 2004). Wagner concludes that "there remains contradictory information pertaining to the effectiveness of SSRIs, cognitive behavioral therapy, and placebo. In the literature review, evidence was cited suggesting that each of the three treatments was superior to each other, generally effective, and generally ineffective. This explains why the mental health community as well as the general public continues to debate whether or not these treatments work." (p. 69)

At the same time, we think that the scientific community is getting closer to a deep understanding of depression, allowing new treatments to be devised. Using the methods described in the beginning of this report, we undertook a search of recent innovations (in the past 10 years) that are available now but are not well-known, and developments that can predict a more hopeful picture for treating depression over the next 10 years.

# Part 2 – What Has Changed: New Scientific Discoveries about Depression

The past 10 years have seen startling advances in technologies for genetics and neurology, as well as many new discoveries and inventions in the fields of molecular biology, nanotechnology, and medical imaging. The result has allowed scientists to develop a much closer look at the brain and its processes. While the puzzle of depression has not been solved, these advances have moved us much closer.

## Genes Influencing Depression

Berton and Nestler (2006) contend that depression "is highly heritable, with roughly 40 – 50% of the risk for depression being genetic, although the specific genes that underlie this risk have not yet been identified. There was a study in 1998 that hypothesized that one in four patients treated in hospital for attempting suicide *could* have a "death wish gene," a condition known as Wolfram Syndrome. The gene responsible for this condition has since been identified and is known as WFS1 (Wolfram Syndrome 1). The syndrome has also been linked to diabetes, optic atrophy, and deafness, but is not a strong predictor of depression (Cohen, 1998).

It is difficult to study human gene defects in depressed patients, so animal models have been used to replicate severe depression in mice. By creating genetic defects in the mice, various conditions that might cause severe depression can be simulated. For example, a team at Penn State University has bred mice with a gene defect that results in behavioural, hormonal, and neurochemical characteristics that are similar to those of human patients with drug-resistant forms of depression (Penn State, 2010). Based on this model, various anti-depressants can be tested to see if they relieve the state of depression.

By paying attention to patients' genetic makeup, a more targeted approach to anti-depressant medication can be taken. This tailored approach will reduce the guesswork involved in treating people with depression, which is an improvement over the mixed results of the current trial-and-error process. For example, Francis Lee and colleagues at Cornell University in the United States investigated a gene mutation that occurs in 20 to 30% of Caucasians. People with this gene do not respond to Prozac,

which means that another prescription can be given instead for these patients (Khamsi, 2006).

In another study, Bernard Carroll and his colleagues at the Pacific Behavioral Research Foundation in California researched 241 Korean patients with depression and found that people with two copies of a specific gene mutation had more than an 80% likelihood of responding to a class of anti-depressants known as norepinephrine reuptake inhibitors (NRIs) (Ibid). The result of this research is that, in the near future, a physician will be able to prescribe the drug most likely to work first, rather than trying a number of drugs and waiting for each one to take effect.

Nicholas Barden at the Centre Hospitalier de l'Université Laval in Quebec leads a group that has discovered a gene that makes people susceptible to depression; they identified the faulty version of the gene P2XR7 in a family from a region of Quebec in which the depression rate is particularly high. Covington et al. (2010) suggest that we should examine the gene-environment interactions to look for "susceptibility" genes that may indicate a higher risk for major depressive disorder or resistance to treatment. Kato and Serretti (2010) summarized 90 studies and found five variants within four genes (SLC6A4, HTR1A, HTR2A, TPH1 and BDNF) that may contribute to treatment response and/or intolerance for anti-depressants. Our final example is from Daniel Weinberger at the National Institute of Mental Health in Bethesda, Maryland. His team showed that a short variant of the 5-HTT gene causes people to have less grey matter in both the amygdala, which regulates fear responses, and the perigenual cingulate, an area that helps make sense of emotions.

So, while we have made progress in the field of genetics and depression we are not there yet. Peter Aldhous, in a 2007 article in *New Scientist,* asked the question, "Why the long wait for gene-specific drugs?" His answer:

> People with hard-to-treat diseases like depression are still being prescribed drugs by trial and error. Adverse drug reactions are still one of the leading causes of death in the developed world…In part, the blame lies with pharmaceutical companies. They are still dominated by a one-size-fits-all mindset: trying to sell blockbuster drugs to as many patients as possible, regardless of their genetic make-up. Pharmacogeneticists have also realised that biological sophistication alone will not win the healthcare industry over. If they are to move the idea of personalised medicine into the clinic they must also prove that genetically targeted drugs can lead to better and cheaper healthcare.

Factors outside the science of depression, including the economics of making anti-depressants, clearly have an effect on the rate of adoption of innovations in this field.

## Epigenetic Changes and Depression

While much work is being carried out on the genetics of depression, the *epigenetics* of depression has been relatively ignored. Epigenetic changes are modifications in the *expression* of a person's genes, rather than an alteration in the actual genetic code. A variety of environmental effects can change the expression of genes, and in some cases, can create mutations that are then passed on to offspring. Examples include maternal effects while a baby is in the womb, drugs that block or trigger specific gene expression, and effects of poor nutrition. Tsankova et al. (2006) explain how this may apply to people with depression:

> Many neurological and most psychiatric disorders are not due to mutations in a single gene; rather, they involve molecular disturbances entailing multiple genes and signals that control their expression. Recent research has demonstrated that complex 'epigenetic' mechanisms, which regulate gene activity without altering the DNA code, have long-lasting effects within mature neurons. [There is] recent evidence for the existence of sustained epigenetic mechanisms of gene regulation in neurons that have been implicated in the regulation of complex behaviour, including abnormalities in several psychiatric disorders such as depression, drug addiction and schizophrenia.

> …While all available antidepressant medications rapidly increase the activity of monoaminergic systems in brain, the mood enhancing effects of these compounds require weeks of administration. Thus, the nature of drug-induced neural plasticity underlying the clinical actions of classical antidepressants has recently highlighted chromatin remodeling mechanisms as an essential process in these drugs' progressive therapeutic effects. Such *epigenetic* modifications can alter gene transcription in neurons in several ways, including covalent changes to DNA (e.g., DNA methylation) and to histone N-terminal tails (e.g., acetylation, methylation, phosphorylation, among many others). Environmental experiences that modify gene function through epigenetic mechanisms do so in the absence of altering the sequence of DNA, thereby providing a strong rationale for studying epigenetic changes in depression, which is particularly evident when considering the large number of inconsistent genetic association studies. In addition, chronic exposure to stress or antidepressant drugs influences histone acetylation and methylation in brain areas important for emotional processing.

Inui (2010) reports on recent work on the relationship of the dysregulation of the fibroblast growth factor (FGF) in the brain on mood disorders. She writes, "While FGF2 gene expression was consistently downregulated in a number of brain regions in MDD, FGF9 gene expression was consistently upregulated in MDD" (pp. vii-viii). Her results indicate that "the hypothesis that dysregulation of fibroblast growth factor system gene expression may cause a disruption in circadian rhythms that underlie sleep/wake cycles" (Ibid). Other research has shown that sleep disturbances are sometimes implicated in the onset of depression.

In regards to effects from prenatal actions or condition of a mother, there is evidence that this can be a factor in the later occurrence of depression, sleep disturbances, or behaviour problems in her children. Both use of cocaine and smoking cigarettes by mothers during pregnancy can lead to sleep disturbances in their young children (Stone et al., 2009). Smoking during pregnancy has been linked to anti-social behaviour in children (Wakschlag et al., 2002). Prenatal stress can disrupt reproductive behaviour and physiology in animals and humans (Herrenkohl, 1986). Lehrer (2010) writes, "… if a pregnant rhesus monkey is forced to endure stressful conditions, like being startled by a blaring horn, her offspring are born with reduced neurogenesis, even if they never actually experience stress after birth."

Epigenetic changes to DNA are very stable, which could explain why depression can persist and anti-depressants can take so long to work (Berton et al., 2006). Much more work needs to be done in this area, as it is obvious that having a gene that makes one susceptible to depression may or may not be expressed, based on the presence of specific environmental conditions.

## The Neurobiology of Depression

Most neurological theories of depression focus on a group of neurotransmitters called monoamines such as serotonin, norepinephrine and dopamine, which are naturally present in the brain and assist communication between nerve cells. New techniques and technologies in the past ten years have given us much richer insights into how these chemicals work in the brain. Much remains to be learned, however, because the causes of depression are complex, with multiple areas of the brain involved. Depending on the technologies used, different areas of the brain are found to be involved in depression:

A large body of post-mortem and neuro-imaging studies of depressed patients have reported reductions in grey-matter volume and glial density in the prefrontal cortex and the hippocampus, regions thought to mediate the cognitive aspects of depression, such as feelings of worthlessness and guilt. However, the published findings are not consistent and are often complicated by co-morbid diagnoses and medication history, and there has been limited success in demonstrating any clear cause–effect relationships of these pathological changes.

In contrast to structural studies, experiments assessing brain function, such as functional magnetic resonance imaging (fMRI) or positron emission tomography (PET), show that activity within the amygdala and subgenual cingulate cortex (Cg25, a subregion of prefrontal cortex) is strongly correlated with dysphoric emotions: indices of neuronal activity within these regions are increased by transient sadness in healthy volunteers and are chronically increased in depressed individuals, reverting to normal levels with successful treatment. (Krishnan and Nestler, 2008)

The theory of how monoamines such as serotonin work is based on our knowledge of how messages are sent among and through neurons. While the average layperson tends to think of the brain as composed of lots of "wires" and switches, and powered by electricity, the brain is, in fact, an electrical-chemical system.
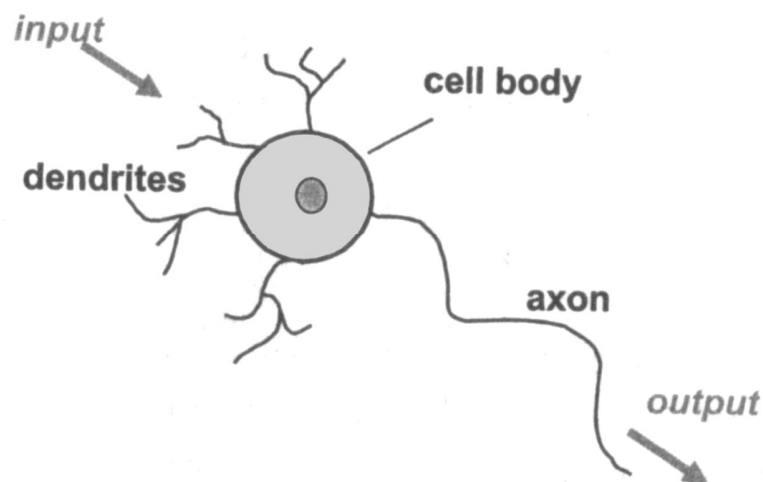


**Figure 1-** Components of a neuron. Image from LeDoux (2002).

The brain is composed of billions of cells called neurons that both transmit messages and act as switches. Each neuron has a cell body, and two kinds of nerve fibers – axons and dendrites. Dendrites receive messages while axons send messages to the next neuron (See Figure 1).  But, the flow of messages in the brain is through the movement of an electrical impulse through the neuron, followed by the movement of chemical neurotransmitters from one neuron to another across a gap called a *synapse*. The electrical impulse is called an *action potential*, triggered by incoming messages from other neurons.

Communication across a synapse is only in one direction. The synapse acts like a valve, preventing the electrical-chemical impulse from going backwards. Joseph LeDoux (2002) explains:

> …One-way conduction between neurons is due to the fact that synaptic transmission involves the release of chemicals from storage sites in the presynaptic axon terminal. These molecules are released when the action potentials propagated from the cell body reach the terminal. The released chemicals then drift across the liquid-filled synaptic space and come in contact with spines or other portions of the postsynaptic cell. Because the chemical storage sites usually are present in the presynaptic terminal and not in the postsynaptic dendrite, transmission only occurs in one direction. These chemicals are called neurotransmitters, since they allow neurons to communicate across the synaptic gap – they transmit between neurons. (p. 45)

There are several chemicals involved in transmitting signals from a presynaptic neuron to a postsynaptic neuron. Glutamates are the chemicals that transmit a signal to the next neuron, but they can be stopped by an inhibiting chemical called GABA (gamma-amniobutyric-acid). Whether or not a signal from one neuron is transmitted to another neuron depends on the balance between these two chemicals, as well as the presence of other chemicals which act as modulators. There are three classes of modulators: peptides, amines and hormones.

Depression seems to involve neuroactive peptides that act on the nervous system. In particular, depression is related to a class of peptides called monoamines, which includes serotonin, dopamine, epinephrine, and norepinephrine. Monoamines are mostly produced in the brainstem, but axons of the cells that produce them extend into many other areas of the brain.

The arrival of a single instance of a neurotransmitter is typically not sufficient to produce an electrical impulse in a postsynaptic cell. Only if the postsynaptic cell receives many messages at the same time from multiple neurons will it trigger an action

potential that can then be passed on to the next neuron. This means that the *levels* of neurotransmitters that are available in the brain have a profound impact on what happens in terms of the transmission of messages. Therefore much of the treatment of depression using drugs is based on increasing or decreasing the supply of neurotransmitters, or making the receiving spines (receptors) more or less receptive to a specific neurotransmitter (See Figure 2).
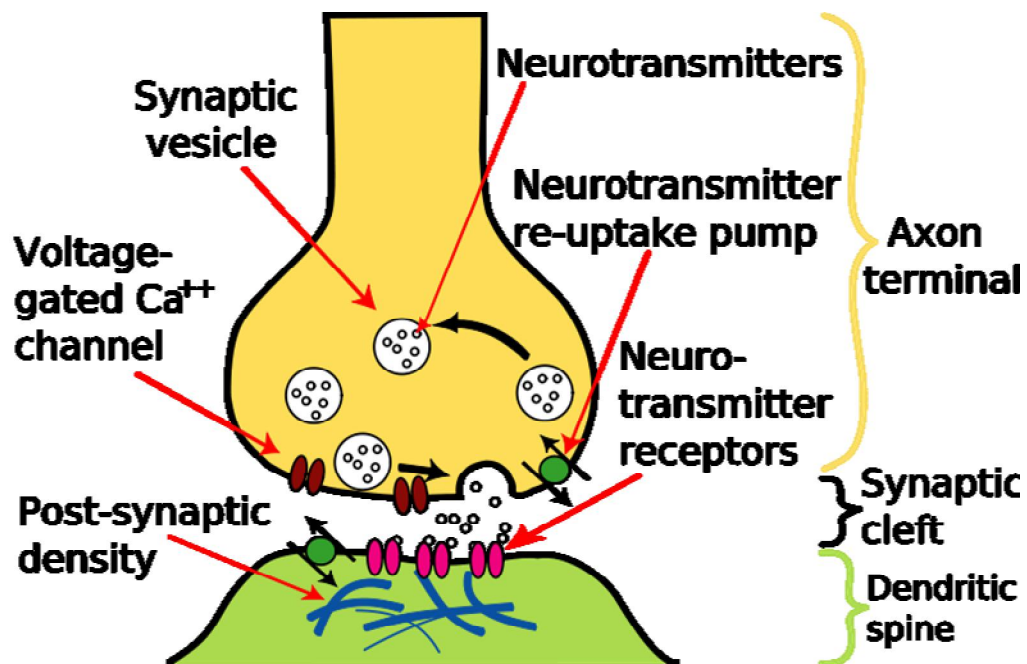


**Figure 2 -** A model of how neurotransmitters work in the brain. (Source: Wikipedia)

As noted above, a neuron rarely responds to a single instance of the arrival of a neurotransmitter at one of its dendrites. Rather, it takes many simultaneous messages to reach the cell body of a neuron before it builds up enough messages to trigger a new action potential to send on to the next neuron or set of neurons.

Understanding how the brain accomplishes tasks has moved from the individual *cell* level, to the *circuit* and *system* levels. A circuit is a collection of interconnected neurons that work together. A system is a complex circuit that performs a specific function such as hearing or seeing (LeDoux, 2002). In such a complicated arrangement of signalling, there are many things that can go wrong:

- There may not be enough neurons in a critical area to generate sufficient neurotransmitters. The process of growing new neurons is called neurogenesis, and it takes place throughout one's life (contrary to a popular myth about having all of your brain cells in place by adolescence or younger).
- The neurotransmitters can break down too quickly, before they have had an effect on their receptors.
- There can be problems with receptors on the post-synaptic neurons, or too few receptors to pick up the signal being transmitted.
- Other chemicals can be present that block the signalling of neurotransmitters.

Research continues on specific chemicals that may have an effect on how well neuronal receptors work in detecting serotonin. For example, a recent study found that a protein named p11 was necessary for receptors for serotonin to pop out on the surface of an axon and start working (Alexander, 2010). Savitz, Lucki and Drevets (2009) state that a dysfunction of the serotonin 1A receptor ($5-HT_{1A}$) may play a role in the genesis of major depressive disorder (MDD). Stockmeier et al. (2009) report that, "agonist binding [excitatory] to serotonin-1A receptors is reportedly increased or unchanged in depression or suicide, while neuroimaging studies report a decrease in antagonist binding [inhibitory] to these receptors in subjects with depression." In addition to receptor problems, shrinkage of the number of neurons and connections in the brain, especially the hippocampus, can also reduce levels of neurotransmitters.

## Neurogenesis and Depression

One factor that seems to affect the level of neurotransmitters is the sheer number of neurons available in the hippocampus to send messages. The hippocampus is a critical part of the brain involved in learning, memory, and feelings. When it grows a sufficient number of neurons (a process called *neurogenesis*), then there are relatively more neurotransmitters available to send messages. The process of neurogenesis seems critical for any understanding of the neurobiology of depression.

In the late 1990s, early work on measuring the size of the hippocampus by psychiatrist Yvette Sheline at Washington University in St. Louis led the way in pointing to neurogenesis as a major factor in the cause of depression. She scanned the brains of 10 women who had suffered recurrent bouts of major depression and 10 closely matched controls. "To everyone's amazement, a brain region buried deep beneath the cerebral hemispheres, the hippocampus, was up to 15 per cent smaller in the

women with depression. And the longer each woman had been depressed, the smaller her hippocampus" (Farley, 2004).

The reason that this was seen as amazing is that at the time, it was thought that new neurons could not be created in adults. However, all of that changed in the year 2000 when Fred Gage of the Salk Institute in San Diego, California and Elizabeth Gould of Princeton University showed that the adult hippocampus can, in fact, make new brain cells. "The brain damage seen in depression might not just be a result of cells dying, but also a lack of cells being born - a process called neurogenesis. And, on a more practical note, perhaps the condition might be reversible" (Ibid).

There are many factors that affect the process of neurogenesis in the hippocampus and other parts of the brain. Understanding these factors may help us to distinguish among different causes of depression, and to make better decisions on treatment. Robert Sapolsky of Stanford University in California and Bruce McEwen of Rockefeller University in New York, in studies conducted in the 1980s, showed that the hippocampus of animals experiencing chronic stress shrinks. The reverse is also true – a hippocampus can grow under the right conditions. For example, it has been demonstrated that the back half of the hippocampus of an average London (UK) taxi driver is usually 25% larger than normal. This is likely caused by all of the learning activities that go into acquiring "The Knowledge" – the location and directionality of every street in London within 6 miles of Charing Cross Station (Maguire et al., 2000).

The role of stress in reducing or reversing neurogenesis is particularly important, because it links molecular level views of depression with more systemic theories of why people become depressed. One dominant idea is that the hypothalamic-pituitary-adrenal axis (HPA axis), a circuit that controls the release of stress-related hormones, produces the hormone *cortisol.* Under stress, cortisol mobilizes bodily resources in the short run, which then normally returns to a balanced state. But, if stress continues for too long, the production of cortisol can destroy neurons in the hippocampus, resulting in depression.

There are many causes of stress, and more work needs to be done on why some people are more resilient than others to life's pressures and traumatic events. The mechanisms of how stress directly affects the brain are under investigation by a number of teams. One explanation comes from Sapolsky and McEwen (cited by Farly, 2004).

> In response to stress, specialised cells in the brain release a cascade of hormone signals that stimulate the adrenal glands to produce cortisol, a powerful steroid. This has survival value when triggered in acute "fight-or-flight" situations by mobilising the body's energy reserves. But according to Sapolsky and McEwen the cumulative effect of cortisol is

devastating to the body and brain. It prunes the delicate branching extensions called dendrites through which hippocampal neurons receive inputs from other cells, and it may kill off some cells completely. And because a healthy hippocampus exerts a dampening influence on cortisol secretion, once this structure has been damaged, a crucial shut-off valve is put out of action and a vicious physiological cycle is set into motion. (Farley, 2004)

There are various conditions that cause stress reactions in the brain that may induce reduction of neurons in the hippocampus. Some researchers think that patients who have experienced trauma have enlarged amygdalas (the part of the brain that creates and retains fear).

The hormone produced by the brain that triggers the release of cortisol from the adrenal glands during stress is also produced by the amygdala, where it acts as a neurotransmitter. Its work as a neurotransmitter is normally independent of the stress response, but…people prone to depression produce too much of it. If they had a genetic predisposition for an enlarged, overactive amygdala this could mimic the effects of being continuously under stress. In turn, this could begin the cycle of damage to the hippocampus and prefrontal cortex. (Farley, 2004).

Various researchers have been documenting different treatments for depression that seem to increase neurogenesis. Studies have shown that anti-depressants like Prozac, electroconvulsive therapy, and exercise all seem to promote neurogenesis in the hippocampus. It is likely that psychotherapy and stress reduction also have the same effect, as these experiences may also encourage new neurons to grow in the hippocampus. Much more work is needed in this promising area of research.

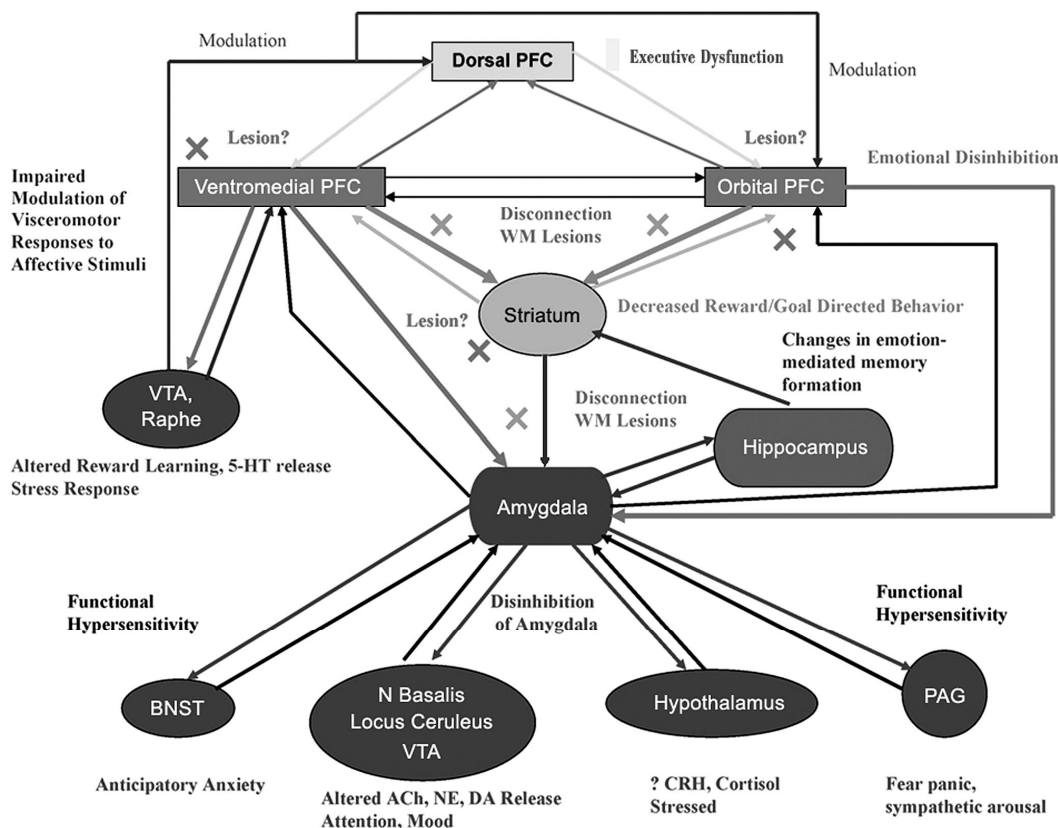## Brain Circuitry Involved in Depression

Even though it is important to understand the mechanisms of neurotransmitters at the individual synapse level, and to understand that the growth of more neurons is generally a good thing compared to the loss of neurons, there is no simple explanation that currently exists that explains depression with these mechanisms. Rather, a finding of depression implicates several different areas of the brain interacting together. In other words, the latest thinking in understanding the neurobiology of the brain is to move from a "molecular soup" view of the brain to a circuitry metaphor (LeDoux, 2002). The most recent picture looks something like this:

Observations based on neuroimaging studies with depressed patients and lesion-induced or secondary depression due to neuropathologies such as Parkinson's disease as well as studies with animal models have begun to converge on a fronto-limbic circuitry as the potential basis for mood regulation and mood disorders. The main cortical components of this circuitry include the ventromedial and dorsal prefrontal cortices (VMPFC and DPFC) and the anterior cingulated cortex. Together with these cortical structures, and forming an extensive fronto-limbic circuit are subcortical structures that include the amygdala, the hippocampus, the hypothalamus as well as the raphe nuclei, nucleus accumbens and the locus coeruleus. The basal ganglia form an integral part of the circuitry not only because of their involvement in psychomotor impairments in depression, but also because of their direct contribution to an affective-motor system. (Canbeyli, 2009)

The brain circuits that are involved in depression interconnect with each other and may be regulated overall by modulator neurotransmitters such as serotonin. However, it turns out that there are at least two different kinds of serotonin receptors in the brain, so it is not surprising to find that some studies that have shown that depression is caused by too little serotonin in some sites while other studies that have shown too much serotonin in another area of the brain.

Looking at Figure 3 from Savitz and Drevets (2009), you can see that understanding the neurological roots of depression is complicated. It is beyond the scope of this report to address the many chemical interactions that take place in all of the areas of the brain shown in the diagram. Most of the research points to the central role of the hippocampus in the causes of depression, but many other brain circuits are involved. The role of the hippocampus is not surprising given that it "expresses one third of the proteins encoding genes found in the human genome, including a wide range of receptors, such as those for steroids, immune system components, monoamines and neuromodulators, all of which play a role in the pathophysiology of chronic pain and depression" (Fasick, 2010). Neurons in the hippocampus have remarkable plasticity, and are highly susceptible to stress. This is an important fact, because many of the psychotherapeutic and alternative treatments of depression involve the reduction of stress.

**Figure 3** – Areas of the brain that have been implicated in depression support a circuitry metaphor for depression. (Adapted from Savitz and Drevets, 2009)

While the neurogenesis can occur at any age, it is also true that the process slows down with age, and the number of neurons in the hippocampus and other critical areas of the brain significantly decreases with stress. This means that treatments that may work for a young adult may not work for an older person. The life cycle of major depression and its treatment is shown in Figure 4.
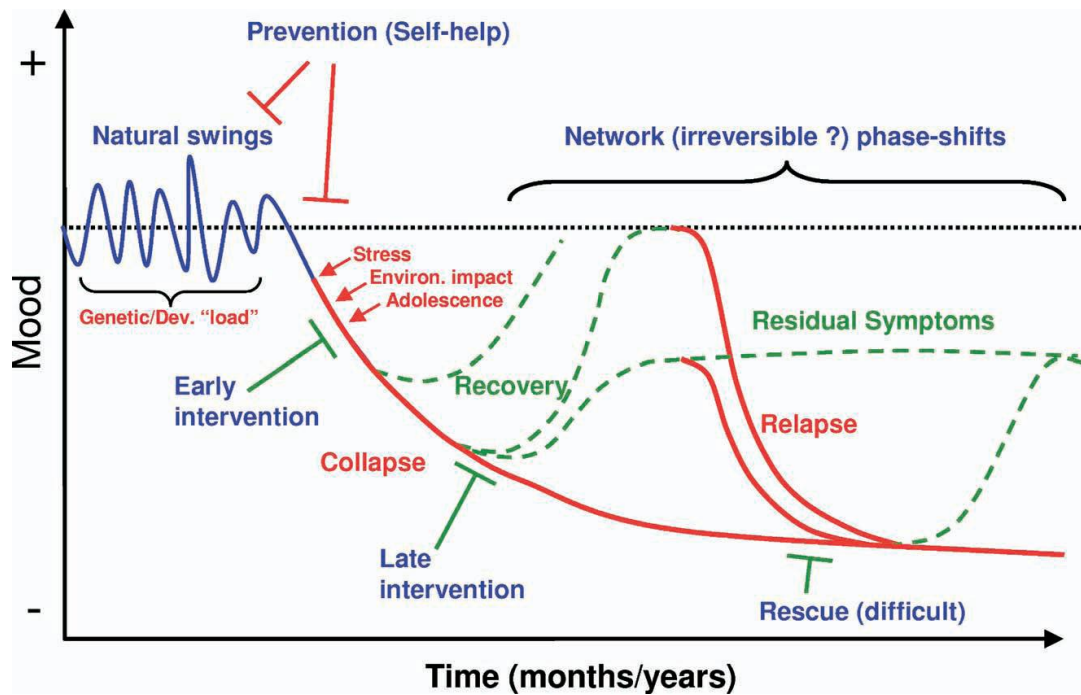
**Figure 4** – Life cycle of depression and its treatment. (From Millan, 2009)

Much has changed in the past 10 years in the treatment of depression. While many new anti-depressants are simply variants on the old monoamine-based chemicals, there are new anti-depressants that are *not* based on the effects of monoamines such as serotonin, dopamine and melatonin. There are new and innovative forms of psychotherapy now available. As well, many teams have been experimenting with brain and nerve stimulation techniques. And, a host of new treatment suggestions, most of which have not yet been thoroughly tested, fall under the category of *complementary and alternative medicine* (CAM). This section of the report reviews new treatments for depression over the last 5-10 years that have been well-researched. CAM treatments are listed and briefly reviewed in Appendix A.

## New Anti-depressants

Until recently most anti-depressants were based on modulating the action of serotonin and other neurotransmitters in the brain. Some new anti-depressants are simply more refined versions of these early discoveries. "Most of today's medications are based on the tricyclic antidepressants, which are believed to act by inhibiting the plasma membrane transporters for serotonin and/or noradrenaline. These older

medications provided a template for the development of newer classes of antidepressant, including the SSRIs (selective serotonin reuptake inhibitors), NRIs (noradrenaline reuptake inhibitors) and SNRIs (serotonin and noradrenaline reuptake inhibitors)" (Berton and Nestler, 2006, p. 137). However, a number of non-monoamine based anti-depressants are currently in clinical trials. As well, there are new insights into the nature of serotonin that indicates that its actions are more complex than previously thought.

For example, Motluk (2007) reports that for some depressed people, neurotransmitters are removed from the junction between neurons, called the synaptic cleft, too quickly. Geddes (2010) tells us that there are several kinds of serotonin neurons, and cites "mounting evidence suggesting that too much serotonin in some brain regions is to blame" for depression. Recent findings indicate that "high levels of serotonin in some brain regions like the prefrontal cortex can lead to improved mood; high serotonin in other regions could have negative effects." Our understanding of the role of serotonin needs to be expanded to account for all of its complexities.

The powerful new brain imaging techniques and experimentation with animals have provided many clues in the search for new anti-depressants. Covington et al. (2010) describe the current search for new anti-depressants:

> In clinical depression, and through the use of depression models in animals, numerous anomalies at the cellular level in distinct brain areas have indeed been revealed, which has in effect "opened the flood gates" for examining newer antidepressant targets. Also contributing to this wealth of potential new targets is the realization that the search for new antidepressants should not focus solely on mechanisms that prevent or reverse the deleterious effects of stress, but should also include mechanisms that promote resilience, continued health and well-being despite the onslaught of severe stress. Amongst such newer targets are amino acid neurotransmitter systems that are known for their dominant role in regulating neural activity and synaptic plasticity (e.g., glutamate and GABA), neurotrophic factors, molecules that are readily induced by episodes of stress, neuropeptides that maintain homeostatic energy balance (e.g., hypothalamic feeding peptides), gonadal hormones that fluctuate over time, particularly in females (e.g., estrogen), as well as the abundance of downstream cellular effectors that affect genome-wide transcriptional outcomes.

It is beyond the scope of this report to list all of the new anti-depressants that have come onto the market or which are in clinical trials in the past 10 years. However, there are many new anti-depressants which are in various stages of clinical trials (See Table 1).

Abilify (aripiprazole) - as adjunctive, or add-on, treatment
Cymbalta (duloxetine) – approved for Europe, but not U.S.
Emsam (selegiline) - transdermal patch
Ketanest  (ketamine) – for patients with bipolar disorder
Rilutek (riluzole) – normally prescribed for ALS, is now used for depression
Seroquel (quetiapine) – for patients with bipolar disorder
Valdoxan (agomelatine) – less side effects

Table 1 – Some new anti-depressants

# Brain and Nerve Stimulation Therapies

In the past 10 years, new forms of electrical stimulation of the brain have become available as treatments, in addition to electroconvulsive therapy (ECT). At least four new kinds of brain stimulation techniques and one nerve stimulation technique are now available for treatment of depression:

- Cranial Electrotherapy Stimulation
- Deep Brain Stimulation
- Magnetic Seizure Stimulation
- Transcranial Magnetic Stimulation
- Vagus Nerve Stimulation

Research on the effectiveness of these treatments range from non-existent to promising. Each type of brain or nerve stimulation is briefly reviewed below.

### Cranial Electrotherapy Stimulation

Cranial Electrotherapy Stimulation (CES) (aka "electrosleep") devices are included in this review of brain and nerve stimulation therapies because they are currently on the market in the United States. However, they have been authorized for sale by the FDA based on a "legacy waiver," because they were marketed before 1976 when new regulations requiring controlled testing were introduced. CES devices are *not recommended* because their effects on depression were either inconclusive or negative in multiple double-blind studies of psychiatric patients.

### Deep Brain Stimulation

Deep brain stimulation (DBS) has been used as a treatment in a variety of psychiatric disorders including Parkinson's disease, Tourette's syndrome, and obsessive-compulsive disorder. Deep brain stimulation for depression is based on the

fact that brain imaging studies indicated that the *subgenual cingulate* area of the brain seemed to be involved with symptoms of depression and sadness. When researchers implanted electrodes into that area in six patients, four reported feeling that "a black cloud [had] lifted". This feeling was reversed when the current was switched off (Mayberg et al., 2005).

Another study by Thomas Schlaepfer et al. (2008) showed positive results for relieving depression when DBS was applied to the *nucleus accumbens*, an area of the brain associated with pleasure and reward mechanisms. A recent review of 23 studies of DBS treatment by Lakhan and Callaway (2010) found that about half of the treated patients showed dramatic improvements, and there were few adverse reactions to the treatment.

How does DBS work? This treatment for depression is still experimental, and has not been approved for general use. Schlaepfer says that, "the brain is increasingly seen as not just a collection of regions but also as consisting of multiple networks, which can become 'misconnected' in mental illness. DBS 'retrains' these dysfunctional networks" (quoted by Callaway, 2010).

### Magnetic Seizure Stimulation

Magnetic seizure stimulation (MST) uses repetitive transcranial magnetic stimulation (rTMS) (discussed below) at higher-than-usual frequencies to induce seizures as a treatment for depression. Compared with electroconvulsive therapy (ECT), MST is a more focused tool in eliciting therapeutic seizures, with fewer side effects. Fitzsimmons (2009) describes the current research results on this treatment:

> Unlike electrical stimulation, magnetic stimulation is immune to the shunting effects of skull and scalp impedance and can therefore be used to stimulate targeted brain regions in a more controlled and focused manner. Preliminary data suggest that MST improves depression scores. However, more research will be needed to determine whether it is comparably effective to ECT. Possibly because of the suboptimal levels of stimulation that can be reached by MST devices currently in use, some research has shown it to be less effective in treating depression than ECT…Notably lacking from the literature are randomized controlled trials investigating the efficacy and side effects of MST as compared with a treatment of known efficacy. (pp. 318-319)

### Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) of the brain works by passing a magnetic field through a specific area of the brain, causing the neurons in that region to

all fire together. Although it has been used as an experimental therapy for stroke, migraines, and coma, its first approval from the FDA in the United States came as a treatment for depression for people who fail to respond to anti-depressant drugs (Trivedi, 2006). Neuronetics, a company in Pennsylvania that makes TMS devices, reports that more than half of depressed people treated showed an improvement in symptoms after receiving five 40-minute TMS sessions per week for four to six weeks. TMS is available in Canada through the MindCare clinic in Vancouver and Ottawa, and costs approximately $7,000. A 2007 review of 32 studies showed that repetitive TMS (rTMS) worked, but like other forms of treatment for depression, it was not as effective as ECT and sometimes no more so than the so-called 'placebo effect' or, in this case, 'sham rTMS' (Eranti et al., 2007). A recent clinical trial with random controls also concluded that rTMS "…could not be shown to be more effective than sham rTMS for treating depression" (Mogg et al., 2008). Clearly, more work needs to be done to prove whether or not this treatment of depression is effective.

### *Vagus Nerve Stimulation*

In 2005, an American company named Cyberonics was granted FDA approval for its Vagus Nerve Stimulator device, but not without some controversy. Similar to a pacemaker, the device stimulates nerves in the neck to alleviate symptoms of severe depression. A large double-blind study over 10 weeks was inconclusive about the effectiveness of this treatment. An article in *The New York Times* detailed the controversy with Cyberonics and its device:

> These are patients pretty much at the end of the line in terms of what treatment options are available to them," says FDA medical device chief Dr. Daniel Schultz, who said that despite initial skepticism within the FDA, he was convinced of the device's effectiveness by Cyberonics' research. Their research consisted of a study of 200 patients to see whether VNS succeeded in treating depression in patients who had not been successfully helped by other therapies. After three months of implant treatment, an FDA review last year found that there was no discernible difference in the patients' conditions, but Cyberonics says that a year later, a significant number of the test patients had realized an improvement in their depression. However, their research was not a randomized control study, and wasn't done according to standard scientific procedures, so critics questioned the validity of their results.

Along with the FDA approval came warnings of some safety issues connected with VNS implants. The primary warning stems from the fact that a significant number of the patients in the study experienced temporary alterations in their voices, including hoarseness, raspiness, or faltering speech patterns. Other complications can include difficult in breathing or swallowing. Among epilepsy patients receiving VNS implants,

there have been several deaths reported, but no deaths were reported among patients in the depression study (Feder, 2006). With these results, physicians would be wise to move with caution before recommending the Vagus Nerve Stimulator.

In summary, all of the various brain stimulation techniques need much more study before they can be declared safe and effective. Of the five treatments outlined above, the Deep Brain Stimulation technique seems to hold the most promise.

This section of the report has documented a number of new and innovative treatments for depression that have been developed in the past 10 years. Nevertheless, like current mainstream treatments of depression, these new treatments have issues that need to be discussed before they are recommended or deployed for the general public.

Research on new anti-depressants faces the same challenges to its validity and reliability as the studies on the anti-depressants that have been with us for the past 50 years. There are still enormous commercial pressures on finding a "hit" drug that will make a lot of money for whichever pharmaceutical company discovers and subsequently develops it. This is one reason that drugs undergo rigorous clinical trials before they are released to physicians.

Similarly, the various types of brain stimulation need to be assessed carefully before they become available for general use. While each claim some degree of success, there is not much understanding as to why they might work, or whether their side effects are harmful in the long run. They too are subject to regulatory scrutiny, and at this stage of development, the jury is out as to whether or not they are useful treatments for large numbers of patients with depression.

# Part 3 - Future Prospects for the Treatment of Depression

What we have described up to now are treatments that are currently either in use, or which could be tested using accepted scientific methods. In this final section of the report, we look at future developments in technology that could have an impact on the treatment of depression. All of the technologies discussed are currently under development in an early experimental phase. But, we also need to understand that depression is at the crossroads of two broad approaches to science – a modern reductionistic approach, based on controlled experimental methods, and a post-modern approach to science that is more holistic and systems-based.

## Two Broad Approaches

This review of treatments for depression reveals two broad approaches to treatment that in the literature have been referred to as "top-down" or "bottom-up". In the first approach, experts try to zero in on a single cause of depression, and then look for a specific remedy for this condition. In the second approach, depression is viewed as a complex phenomenon that is caused and supported by a host of environmental, cultural, and economic factors that interact with a depressed person's genetics, physiology, life history, family and other relationships. What seems to unite both points of view is the knowledge that stress, in its various forms, is a key player in the onset and maintenance of depression.

The top-down approach is trying to pinpoint causes and treatments of depression through a reductionistic methodology that seeks to isolate specific agents that might cause depression. It is thought that finding such agents would then lead to a "cure" for depression. It is, as Pinder and Wieringa (1993) refer to it, a "molecular mechanistic approach."

The bottom-up approach sees each depressed individual as having a *context* that is important in developing a holistic understanding of his or her depression. It sees the individual as being bombarded by stimuli from the senses that is interpreted in such

a way that depression ensues. Canbeyli (2010) explains the difference in these two approaches:

> Several lines of research on mood disorders reveal that depression involves a dysfunction in an affective fronto-limbic circuitry that involves the prefrontal cortices, the cingulate cortex, several limbic structures including the amygdala and the hippocampus, lower brainstem structures and the basal ganglia. In dealing with both depressive symptoms as well as their manifestation in the brain, clinical as well as basic research has emphasized mainly a top-down or central approach in elucidating the etiology of depression and its therapy. The present integrative review emphasizes the bottom-up or peripheral view of evaluating the impact of stimulation via sensory modalities or the motor system on the same circuitry in effecting mood regulation and possibly causing mood disorders, specifically depression.

It is clear that both approaches have merit, and that the insights of one can illuminate aspects of the other. Grobstein and Cyckowski (2006) review both the top-down "medical model" and the bottom-up "biological/neurobiological/cultural model", and call for "broader perspectives that can productively incorporate the different useful insights reached from each of a variety of different points of view." As Joseph LeDoux (2002) puts it, "…life's experiences leave lasting effects on us only by being stored as memories in synaptic circuits…Brain circuits and psychological experiences are not different things, but rather, different ways of describing the same thing" (p. 262).

As we have seen, there has been an amazing amount of progress in the past 10 years in understanding the underlying neurobiology of depression. With adequate funding, the next 10 years will advance our knowledge even further, likely at an accelerated pace.

## Future Anti-depressants

Our new knowledge of the functioning of the brain, and what can go wrong, should motivate drug companies to search for new anti-depressant chemicals. Covington et al. (2010) summarized the situation with the search for new drugs as follows:

> The need for newer compounds to treat depression is an ever-growing concern due to the enormous societal and financial ramifications of this disorder. Here, we review some of the candidate systems that could potentially be involved in depression, or an inherent resistance to depression termed resilience, and the numerous protein targets for these

systems. A substantial body of literature provides strong evidence that neurotrophic factors, glutamate receptors, hypothalamic feeding peptides, nuclear hormone receptors, and epigenetic mechanisms, among others, will make for interesting targets when examining depressive behavior or resilience in preclinical models, and eventually clinical trials. Although some of these targets for depression already appear promising, new waves of more selective compounds for any molecular system should promote a better understanding of this complex disease and perhaps improved treatments. (p. 683)

An example of research not directly involving serotonin levels is new work by Ron Duman and colleagues at Yale University who compared post-mortem brain samples from 21 people with depression with 18 non-depressed people of the same age. They found that levels of messenger RNA (mRNA) for the protein MKP-1, which is a mediator between DNA and the production of proteins, was twice as high in depressed people compared with their same age non-depressed peers. MKP-1 inhibits neural growth and development. New anti-depressants are being developed to treat this condition (Duric et al., 2010).

## Future Directions in Assessment of Depression

At the present time, a diagnosis of depression is obtained by comparing the patient's behaviors with standardized inventories of symptoms of depression. Within the next five years there will be several new technology-based assessments of depression on the market. These include:

- EEG techniques for assessing depression based on "machine learning" - a scientific method that can extract information from large data sets. Researchers at McMaster University in Hamilton, Ontario, have used machine learning to "train" computers to predict whether a patient will respond to a particular drug based on brainwave patterns recorded with EEG devices.  This innovation will lead to personalized medicine for prescribing anti-depressants, rather than the current trial and error methods (CBC, 2010a).
- Online tests are being developed to diagnose depression. Researchers at University College London have created an algorithm that can predict the risk of being diagnosed with a new episode of major depression within the coming year (Thompson, 2008).
- A content analysis of blogs can also be used to diagnose depression in the writer. Software has been developed in Israel that is capable of identifying language that can indicate a writer's psychological state, which can serve as a screening tool for depression (Kalman, 2010).

- A new kind of brain scan, called magnetoencephalography (MEG), which measures brain activity in real-time, is currently being used to pinpoint the source of an epileptic seizure. In the future, it may be used for the diagnosis and study of dementia, migraines, Parkinson's disease, traumatic brain injuries, and depression. So far, researchers at the University of Minnesota and the Minneapolis Veterans Affairs Medical Center have used MEG to look for distinct brain activity patterns among soldiers with posttraumatic stress disorder (Drummond, 2010).
- Speech recognition software has been developed by Professor Alex Pentland at MIT's Media Lab that listens to the quality of a speaker's voice on a phone for hints of depression. The software analyzes "subtle cues in speech to determine whether someone is feeling awkward, anxious, disconnected or depressed" (Chu, 2009).
- Several research teams are looking at methods of watching the brain live. These methods are farther in the future, but the vision is to be able to diagnosis depression and other brain disorders directly from brain activity. Neuroscientist and inventor Christopher deCharms uses fMRI to show brain activity - thoughts, emotions, pain - while it is happening, so you can literally see how you feel (deCharms, 2008). Professor JoAnn Kuchera-Morin at the University of California, Santa Barbara, has built a 3D simulator that allows people to walk into the middle of two 30 foot semi-spheres, and experience being inside someone's brain while they are thinking (UCSB, 2010).

These new technologies will improve both the ability to diagnose depression, and our understanding of the processes that lead to this condition.

## Future Directions in Genetics

As noted previously, Berton and Nestler (2006) contend that depression "is highly heritable, with roughly 40 – 50% of the risk for depression being genetic, although the specific genes that underlie this risk have not yet been identified." Some progress has been made in the 5 years since that quote was first submitted for publication.

For example, researchers at the University of Nice in France and McGill University in Canada have collaborated to identify the critical role of a gene named TREK-1 in the transmission of serotonin in the brain. By breeding mice without TREK-1, researchers were able to create a depression-resistant strain (Heurteaux et al., 2006).

As sequencing of individual genomes of both individuals and families becomes faster and much less expensive, expect more searches for other gene mutations that play a role in the susceptibility or onset of depression, followed by specific gene therapy to correct the problem gene (Singer, 2010). Recently, researchers at Cornell University found that the reduced presence of p11, a receptor-binding protein that mediates the effects of serotonin, is linked to depression in both mice and humans. The researchers used gene transfer into the nucleus accumbens area of the brain to treat this condition (Alexander et al., 2010).

If gene therapy is not possible, growth of new cells from "induced pluripotent stem cells" (iPS cells) may hold the key to reprogramming any part of the human body. Recently, Joseph Hanna (age 30), a fellow at the Whitehead Institute, "took skin cells from a diseased mouse and reprogrammed them to create IPS cells, which behave like embryonic stem cells, readily turning into any cell type in the body" (Subbaraman, 2010). After correcting the genetic defect, he prodded the IPS cells to develop into the type of cell that he needed. This procedure could be used to encourage neurogenesis in the hippocampus, for example.  Gene therapy for cellular problems that cause depression will likely be part of our future.


## Future Directions in Neuroscience

In order to understand brain processes more readily, a team from the Cold Spring Harbor Laboratory in New York engineered mice whose nerve cells would glow green during neurogenesis (Costandi, 2010b). This work led to a new field of study – optogenetics – where light is used to both control and visually trace brain activity. Fox (2007) comments:

> One possibility is that the technology, coupled with a method of getting light into the human skull, could create a Brave New World of neuro-modification in which conditions such as depression or Parkinson's disease are treated not with sledgehammer drugs or electrodes, but with delicate pinpricks of light. In the long term it is even possible that such treatments could be modified to enhance normal brain function, for example improving memory or alertness.

Optogenetics could also revolutionize basic neuroscience by allowing researchers to isolate and control specific brain circuits using light. New procedures using this technology can even turn a single neuron off or on (Ibid).

While there are several promising lines of research in the neuroscience of depression, many researchers have zeroed in on how to improve neurogenesis in the

hippocampus as a treatment for depression. It is already known that Prozac (fluoxetine) stimulates the growth of new neurons in the hippocampus. From the optogenetic procedures, researchers have discovered that Prozac did *not* promote neuron growth by stimulating stem cells, but did help with the division of neural progenitor cells that have already committed to becoming neurons. By isolating the specific steps in the development of neuron cells in the hippocampus, researchers hope to be able to develop specific treatments for different brain diseases, including depression.

One consequence of this new technology will be better brain implants and stimulators. As the techniques for detecting and controlling brain activities becomes much more precise, new neurostimulators will be developed that will respond directly and immediately to abnormal brain activity; at present they work on set schedules (Kleiner, 2009).

Brain stimulation technologies will continue to develop, including implants. To date, neuroscientists at the University of Southern California have developed an "artificial hippocampus" that is designed to be spliced into a patient's existing hippocampus, and communicate with the brain through two arrays of electrodes, placed on either side of the damaged area" (Carter, 2009).

In the more distant future, scientists will be able to map all of the connections in the brain and associate them with particular conditions or diseases. Just as we can now sequence the human genome, we are starting the process of mapping the human "connectome", all of the neural connections in the brain. *C. elegans*, a tiny worm about one millimetre long, has a nervous system of 302 neurons, for which all 7000+ connections were mapped in 1986. In 2009, the Human Connectome Project was announced with $40 million in funding from the National Institutes of Health in the U.S. Led by the Laboratory of Neuroimaging at the University of California, Los Angeles (UCLA), the Martinos Center, Massachusetts General Hospital, Washington University, and the University of Minnesota, its goal is to map the human brain. (See www.humanconnectome.org for details).

# Conclusions: Hope for Depression

In reviewing the published and more hidden literature on depression, and in looking at recent innovations and future prospects, several themes have emerged:

- Depression is a complex phenomenon, which likely has several different causes and many different factors influencing its course.
- The most promising lines of research that will have an impact on the treatment of depression in the next 10 years are genetic research that are looking to correct gene mutations that may cause depression, and neurobiology research that is focusing on the brain circuitry involved in depression. The importance of neurogenesis, especially in the hippocampus, seems worthy of intense research.
- Depression is linked to many other conditions, but no other disease or condition has been conclusively shown to cause depression. Similarly, depression has not been conclusively shown to be the cause of any other disease. Nevertheless, the links between the many diseases associated with depression provide valuable clues to promising directions for research and treatment.
- We will move towards better treatments for depression by understanding both the "top-down" view and the "bottom-up" view of depression. That is, new progress on the genetics and neurology of depression will yield better medical treatments, while understanding the social, cultural, familial and experiential factors that lead to depression will produce better psychotherapeutic and systemic treatments of depression. Both perspectives need to be integrated to maximize our efforts in solving the puzzle of depression.

As we look to the near future, it appears that significant progress in treating depression will occur in the next 10 years, as science zeros in on the neurobiology and genetics of depression. The future prospects for significant improvements in our ability to send depression into permanent remission look promising.

# Appendix A: Brief Reviews of Complementary and Alternative Treatments of Depression

In addition to the more conventional treatments reviewed above, there are about 24 additional treatments of depression that are mentioned in the literature, but which have not been accepted as a normal medical or psychiatric treatment in Western societies at this time. Most of these treatments fall under the category of "complementary and alternative medicine" (CAM), and each has at least some anecdotal evidence of effectiveness.

Britton (2006) reports that the use of CAM treatments for depression is on the rise. He says, "A recent national survey indicated that more than half of respondents (54%) with self-diagnosed depression indicated that they used some form of CAM therapy for their depression, while only 36% reported that they consulted a physician or other mental health professional for depression." But few CAM treatments are the subject of rigorous clinical trials that would allow them to be prescribed by trained medical and psychological practitioners. Almost none of the alternative treatments are supported by rigorous experimental or quasi-experimental research under controlled conditions. They are included here because they represent innovative thinking, and with time, some of them may prove to be useful in the treatment of depression.

Of the two-dozen treatments listed below, a few show more promise than others. In particular, we would highlight exercise, mindfulness-based psychotherapy, and the use of the herb *St John's Wort* as having stronger evidence for their efficacy compared with the other suggested treatments. Here is a brief description and the results of at least one research study on each of the CAM treatments found in the literature.

### *Acupuncture*

Acupuncture has a long history as a medical treatment in China and Japan. Long needles are inserted at specific points as a way of correcting "the imbalance of energy in the body." While there is widespread interest in acupuncture, there are only a few studies that show a positive result in the use of acupuncture for depression. For example, Cabýoglu, Ergene and Tan (2006) state, "It has been determined that

endomorphin-1, beta endorphin, encephalin, and serotonin levels increase in plasma and brain tissue through acupuncture application." However, a recent meta-review of thirty trials involving 2,812 participants found little evidence that acupuncture can assist in the treatment of depression (Smith et al., 2010). The authors conclude, "We found insufficient evidence to recommend the use of acupuncture for people with depression. The results are limited by the high risk of bias in the majority of trials meeting inclusion criteria."

### Animal Assisted Therapy

Lamb (2009) reported in *The Sunday Times* in the UK that the U.S. Army is using "exotic dogs" and other animals to "combat stress as it finds its forces increasingly stretched". There is also a group to support this treatment, called the Psychiatric Dog Society; it now has over 500 members, 150 of whom are former soldiers. Lamb says that, "David Sharpe, a sufferer from PTSD, recently set up Pets2Vets, a voluntary organisation that pairs homeless animals with traumatised service veterans in the Washington area." The results of a few research studies have supported this method of treatment (Folse et al., 1994; Barker, Pandurangi, and Best, 2003; Antonioli and Reveley, 2005).

### Ayahuasca

Ayahuasca is a tea with psychoactive properties found in the Amazon basin. It is used by native Indian and mestizo shamans in Peru, Columbia, and Ecuador. Lisa Palladino (2009) recently completed "a phenomenological study of ayahuasca and its effects on depression" as her PhD dissertation at the Pacifica Graduate Institute in California. Her study looked at the effects of ayahuasca "on six individuals suffering from chronic and/or treatment resistant depression, using a descriptive phenomenological research method. Participants were asked to describe their lived experience of depression prior to taking ayahuasca and then their experience of depression after ingesting ayahuasca. All participants were interviewed twice."

The results of her qualitative study showed all six participants reporting that their symptoms had been alleviated within a period of 10 days. No other studies of this treatment of depression were found in our environmental scan.

### Chromium picolinate

Chromium picolinate is sold as a nutritional supplement for chromium deficiency. An Internet search reveals advocacy for its use as a treatment for depression mainly by websites for vitamins and health foods. However, no one has yet identified a biochemical need for chromium in the human body. A pilot study in 2003 (Davidson et

al., 2003) suggested that chromium picolinate might be useful in treating "atypical depression"; however, a larger follow-up study by Docherty et al. in 2005 failed to show this effect.

### *Creative Arts Therapies*

Various schools of psychotherapy have promoted their efficacy over the years. However, there are very few controlled trials of different therapeutic methods, making it difficult to say if one type is more effective than another. Here are brief reviews on some of the newest approaches to psychological treatment of depression.

Starting with Freud and the invention of psychoanalysis as "the talking cure", psychotherapy is one of the oldest treatments for depression. Following Freud's lead, most psychodynamic schools of therapy use various methods to get to the unconscious and hidden memories. Creative arts therapies do this by having the patient create something to talk about, and by reducing stress and anxiety through the activity. Jennifer Price's 2009 Masters thesis reviews a number of case studies of the impact of art therapy on symptoms of depression:

- *Case Study 1 - Mandalas and Anxiety:*
  This study, conducted in 2005, examined the effectiveness of different types of art activities in the reduction of anxiety. After undergoing a brief anxiety-induction, undergraduate students were randomly assigned to color a mandala, to color a plaid form, or to color a blank piece of paper. The findings suggest that structured coloring of a reasonably complex geometric pattern may induce a meditative state that benefits individuals suffering from anxiety.

- *Case Study 2 - Painting, Depression and Anxiety:*
  Sixty cancer patients undergoing chemotherapy were included in a 2007 study to determine whether depression and anxiety symptoms improved after an art therapy intervention of painting with water-based paints. After an evaluation of the results, 58% of the patients in the intervention group improved their depression level, and anxiety levels that were scored in the normal range at baseline testing remained the same.

- *Case Study 3 - Music, Depression and Anxiety:*
  A 2008 pilot study was conducted to test whether group music therapy is effective for improving depression, anxiety, and relationships in psychiatric patients. Twenty-six patients were non-randomly allocated to either a music intervention group or a routine care group. The music intervention group received 60 minutes of music intervention for 15 sessions (one or two times weekly). After 15 sessions, the music intervention group showed significant

improvements in depression, anxiety, and relationships compared with the control group.

- *Case Study 4 - Doll Making and Depression:*
In a 2008 study conducted on the effects of art psychotherapy intervention on the levels of depression amongst black women living with HIV, the authors reported a reduction of depression symptoms in their experimental group after an all day art therapy session making dolls as compared to a control group that watched entertainment videos.

There is also research literature on the impact of music therapy on reducing symptoms of depression. Maratos et al. (2008) reviewed five studies of music therapy and found that four out of the five studies reported a greater reduction of symptoms among those randomly assigned to music therapy compared with a control group. The reviewers added the following caution about their review: "Findings from individual randomised trials suggest that music therapy is accepted by people with depression and is associated with improvements in mood. However, the small number and low methodological quality of studies mean that it is not possible to be confident about its effectiveness. High quality trials evaluating the effects of music therapy on depression are required."

### Dehydroepiandrosterone (DHEA)

Dehydroepiandrosterone (DHEA), a natural hormone produced by the adrenal glands, the gonads, and the brain, has been promoted as a treatment for depression. Two small double-blind studies have supported this contention (Wolkowitz et al., 1999; Schmidt et al., 2005), showing it to be more effective than a placebo. However, a larger placebo-controlled randomized clinical trial in 2006 found that DHEA had no benefits for elderly men and women (Nair et al., 2006).

### Exercise

One of the most promising alternative treatments for depression are the benefits of physical exercise. Tsang et al. (2008) make the distinction between "mindful exercise" such as yoga, Chi Kung (also spelled Qigong) and related martial arts such as Tai Chi, and "non-mindful exercise." They suggest that being mindful while doing exercise may be a superior way to relax and deal with stress. Nevertheless, they find that all exercise is useful in treating depression.

This result is backed up by a number of studies:

- A survey of more than 20,000 men and women in Scotland showed that 20 minutes of rigorous activity a day – anything from cleaning the house to playing sports – improved symptoms of depression (BBC News, 2008).
- In a study of 400 adults aged 55 to 85, researchers at the University of Toronto found that regular aerobic exercise in middle-age and beyond trains the body to use oxygen more effectively in generating energy, and leaves people feeling better. (Ibid)
- In a qualitative study of four depressed adolescent boys, Van Winssen (2008) concluded, "Daily 30 minute periods of moderate exercise, with social support, not only provide virtually risk free, cost-effective relief of depressive symptoms, it is relief which is both immediate and lasting."
- A 2001 study by the Duke University in North Carolina found that exercise is a more effective treatment for depression than anti-depressants, with fewer relapses and a higher recovery rate. (Reported by Armstrong, 2007)
- A 2004 study of the effectiveness of "pram-walking" for postnatal women showed that those who walked their babies in prams were significantly less depressed than those women in a social support only control group. (Armstrong and Edwards, 2004)

All of the above indicates that physical exercise programs can have a significant impact in reducing the symptoms of depression, and can make people feel better about themselves. Resit Canbeyli, in his extensive review of "sensorimotor modulation of mood and depression" summarizes the situation as "exercise improves mood and alleviates depression," and "lack of exercise or exercise withdrawal induces depressive symptoms."

### *Facial and Vocal Feedback*

One of the most unusual suggested treatments for depression is the use of botulinum toxin ("botox") to improve facial muscles. Finzi and Wasserman (2006) injected botox into the frown muscles of 10 patients, and found that 9 out of the 10 reported the absence of depression for two months, while the 10th patient reported some improvement in mood. The authors concluded that because the patients could not frown, their ability to experience sadness and depression was also diminished.

The explanation for this result is called the facial feedback hypothesis (FFH), and several studies have confirmed a correlation between facial expressions and emotional experiences (Al Abdulmohsen, 2010). Facial motion is also connected to vocal frequency, to the extent that a rise in vocal frequency "is associated with eye-

brow movement during speaking" (Ibid). Here is how this might be connected to feelings of depression:

> The accessory activities of facial muscles that accompany speech disfluencies give the appearance of "speech-related struggle" and they are most visible during the blockages. This synchrony between vocal and facial muscles during speech might mean that a disturbance of vocal function can cause a parallel disturbance of facial expressions. Theoretically, the resultant facial expression can take the form of sadness or, in other words, an increased activity of corrugator muscles. If this expression is persistent, it can virtually cause depression through facial feedback. (Ibid)

Given the role of auditory feedback in the production of speech, problems in hearing ones own voice while speaking may lead to depression. Al Abdulmohsen (2010) says, "An aberration in hearing one's own voice can cause not only stuttering but also depression." He suggests that, "using certain methods to restore the normal function of both vocal and facial muscles can hypothetically be a new treatment for depression." This suggestion is only a hypothesis at this time, but an interesting one that should be investigated nonetheless.

### *Forgiveness Education Intervention*

In 2004, Gayle Reed completed her doctoral dissertation at the University of Wisconsin. Her research compared the outcomes of a "forgiveness educational intervention" with the outcomes of several educational and psychological alternative treatments. The participants had all been divorced or separated for at least two years from psychologically abusive partners.

The forgiveness educational intervention consisted of individual weekly one-hour sessions with an intervener who was trained in the Enright Forgiveness Model, experienced in delivering forgiveness education workshops, trained as a psychiatric nurse, and had previously worked with women who had been psychologically abused. The intervener and each participant worked through a 17-unit intervention that presented all 20 steps of the Enright Forgiveness Process Model. They also received additional educational materials, heard "forgiveness stories", and participated in journaling exercises that target the particular needs of psychologically abused women.

Outcomes of this study showed that participants in the forgiveness educational intervention experienced significantly higher gains than participants in the alternative treatments, including a decrease in depression. The experimental group showed maintenance of these gains over time.

### Green Tea

Niu et al. (2009) conducted a cross-sectional study of the effects of green tea consumption on symptoms of depression in 1,058 community-dwelling elderly Japanese individuals over 70 years old. Green tea consumption was assessed by using a self-administered questionnaire, and depressive symptoms were evaluated by using the 30-item Geriatric Depression Scale. The results showed that more frequent consumption of green tea was correlated with a lower prevalence of depressive symptoms in the study's subjects. This is the only known study of the possibility of using green tea as a treatment for depression.

### Logotherapy

Robert Blair (2004) argues that youth can end up experiencing severe depression as a result of not developing a strong sense of their identity. He advocates for logotherapy, a system of counselling developed by existential psychologist Victor Frankel (1984) specifically to examine and develop a sense of identity and purpose of one's life. Logotherapy contends that "the primary motivation in human existence is a 'will to meaning,' and depression and other pathology often results when individuals are unable to identify and pursue a worthy meaning." Frankel (1967) writes that each person is responsible for the "accomplishment of concrete, personal tasks and demands, the realization of that unique and individual meaning which every one of us has to fulfill" (p. 126).

Logotherapists believe that there is meaning in suffering that needs to be discovered and used in establishing one's purpose in life. The major technique is to use Socratic dialogue to draw out and listen to stories from the person experiencing depression. The goal is "discovering meaning within depression". Blair provides several case studies of logotherapy in action, but there is little empirical research to support the efficacy of this approach.

### Low fructose diet

For some people there is poor absorption of fructose in the intestines. This condition is correlated with a higher score on depression assessment scales, such as the Beck Depression Inventory (Ledochowski et al., 1998). A diet that was low in fructose, fructans and sorbitol reduced depression scores by 65.2% after a four week trial (Ledochowski et al., 2000).

### Magnesium

Magnesium deficiency is sometimes cited as a cause of depression. This is a matter of diet, and foods such as whole grains, beans, seeds, halibut and spinach are

suggested treatments for depression caused by insufficient magnesium. Only one scientific article was found on this topic, and it emphasized that magnesium deficiency was a medical hypothesis, rather than an established fact. Eby and Eby (2006) explain how magnesium deficiency might be a cause of depression:

> Only 16% of the magnesium found in whole wheat remains in refined flour, and magnesium has been removed from most drinking water supplies, setting a stage for human magnesium deficiency. Magnesium ions regulate calcium ion flow in neuronal calcium channels, helping to regulate neuronal nitric oxide production. In magnesium deficiency, neuronal requirements for magnesium may not be met, causing neuronal damage which could manifest as depression. Magnesium treatment is hypothesized to be effective in treating major depression resulting from intraneuronal magnesium deficits. These magnesium ion neuronal deficits may be induced by stress hormones, excessive dietary calcium, as well as dietary deficiencies of magnesium.

Eby and Eby present a set of case studies that demonstrated recovery from depression in less than seven days after magnesium was added to a patient's diets. They call for further study, and fortifying refined grain and drinking water with biologically available magnesium to pre-twentieth century levels.

### *Marriage*

According to Frech and Williams (2007) one possible treatment for single people who are depressed is to get married. They studied a sample of 3,066 men and women who had been interviewed and tested for depression once in either 1987 or 1988 and then again five years later. The researchers asked them about the quality of their marriage (if they were married). Results indicated that, on average, those subjects who were depressed before marriage report larger psychological gains than those who were not depressed.

### *Mindfulness-based Cognitive Therapy*

Perhaps the most successful new psychological theory of depression is based on the Buddhist concept of "mindfulness". There are both degree programs and individual courses in mindfulness-based cognitive therapy (MBCT) in the UK and the United States. Several books have been written on this method of psychotherapy (Segal, Teasdale, and Williams, 2002; Fulton, Germer and Siegel, 2005; Williams et al., 2007), and at least two doctoral dissertations have been completed on this treatment method (Wood, 2008; Coffey, 2009).

Mindfulness, which has much in common with Buddhist traditions, advocates learning how to pay attention or concentrate with purpose in each moment and most

importantly, without judgment. (Fulton, Germer, and Siegel, 2005). Coffey (2008) says that mindfulness "may be more accurately thought of as present-centered attention, acceptance of experience, clarity about one's internal experience, and the ability to manage negative emotions" (p. iii).

MBCT started in 1979, developed by Jon Kabat Zinn at the University of Massachusetts Medical Center. A website devoted to the topic of MBCT says that it works as follows:

> 1. Mindfulness practice helps us to see more clearly the patterns of the mind and to learn how recognise when our mood is beginning to go down. This means we can 'nip it in the bud' much earlier than before.

> 2. 'Losing touch' with things can put a barrier between ourselves and the small things in life that might have once given us pleasure. Mindfulness teaches us a way in which we can get back in touch with the experience of being alive.

> 3. Low mood can bring back memories and thoughts from the past, and make us worry about the future. Mindfulness helps to halt the escalation of these negative thoughts and teaches us to focus on the present moment, rather than reliving the past or pre-living the future.

> 4. When we start to feel low, we tend to react as if our emotions were a problem to be solved: we start trying to use our critical thinking strategies. Mindfulness helps us to enter an alternative mode of mind that includes thinking but is bigger than thinking. It teaches us to shift mental gears, from the mode of mind dominated by critical thinking (likely to provoke and accelerate downward mood spirals) to another mode of mind in which we experience the world directly, non-conceptually, and non-judgementally.

> 5. When we have been depressed, we dread it coming back. Mindfulness… helps develop our willingness to experience emotions, our capacity to be open to even painful emotions.

> (Abridged from website: http://mbct.co.uk/about-mbct)

Does mindfulness-based cognitive therapy work? Damon Wood (2008) ran a study where only 5 of the 27 participants completed the research. He concluded, "Despite the small number of completers, significant findings with large effect sizes were noted for depression, mindfulness skills, and quality of life related to the perception of pain and of overall general and physical health, with most results maintained at 8-week follow-up." But such a small study should not qualify as

definitive evidence that mindfulness is effective. Another empirical study by Carmody et al. (2009) failed to support mindfulness-based therapy.

One of the problems with this treatment is that there is no clear definition of mindfulness that makes it easy to study, or to compare results of different studies. In his editorial in a special issue of the journal *Emotion* (Vol. 10, No.1), Richard Davidson (2010) says, "How the term 'mindfulness' is conceptualized and operationalized is crucial, and for progress to be made it is essential that we qualify the use of this term by reference to how it is being operationalized in each context" (p. 8). Nevertheless, he concludes that "substantial progress that has occurred in the empirical study of mindfulness and it is a harbinger of a very promising future in this area."

### *Omega-3*

In a review article on his blog, John McManamy notes, "In 1996, the *Journal of the American Medical Association* published a study comparing the prevalence of depression across 10 nations. A 1998 study published in *The Lancet* compared this data with fish consumption, finding the higher consuming populations experienced less depression." These two articles are the foundation for the suggestion that Omega-3, an unsaturated fatty acid found in certain foods, is an effective treatment for depression.

Such results are not surprising as Omega-3 fatty acids are important in the development and functioning of the central nervous system. In another review article, Logan (2004) says, "Evidence from epidemiological, laboratory and clinical studies suggest that dietary lipids and other associated nutritional factors may influence vulnerability and outcome in depressive disorders." However, a more recent review of 18 clinical trials of Omega-3 found little evidence of a beneficial effect in treating depression (Appleton et al., 2006). But just this year, in a randomized controlled trial with 432 men and women, a team at the Université de Montréal found that Omega-3 supplements can be an effective method of treating major depression in patients who do not have anxiety disorders (Lespérance et al., 2010). Clearly more research needs to be done in this area.

### *Reiki*

Reiki is a form of "energy medicine" which originated in 1922. In the UK, it has been recommended as a complementary medicine for depression by National Health Service Trusts and Princess of Wales' Foundation of Integrative Medicine. A recent review of research could find no evidence of its usefulness in the treatment of any disorder (Lee, Pittler and Ernst, 2008).

Many studies, clinical trials, books and articles have looked at the impact of religion and/or "spirituality" on depression as well as many other medical and psychiatric conditions (Koenig, 2005).

One obvious problem in conducting scientific trials is that there is little agreement on the meaning or acceptable forms of religion or spirituality, making comparisons among studies difficult. There is also controversy among the "faith community" on what constitutes acceptable evidence and methods in science.

Amy Banner completed her 2009 doctoral dissertation at the University of North Carolina titled *The Effects of Spirituality on Anxiety and Depression among Breast Cancer Patients: the moderating effects of alexithymia and mindfulness.* In the dissertation, she writes:

> Spirituality has become a topic of importance and interest in the field of counseling with both researchers and clinicians calling for its empirical examination and inclusion in the counseling process. The significance of this interest among counselors is illustrated by the development and adoption of the nine spirituality competencies for counselors developed by the Association for Spiritual, Ethical, and Religious Values in Counseling (ASERVIC) and endorsed by the American Counseling Association.

In a more recent doctoral dissertation at Walden University, Kimberly Welch-Holland (2010) notes that, "the relationship between depression and spirituality is unclear." She identifies six "spirituality mechanisms" – awareness, disappointment, realistic acceptance, grandiosity, instability, and impression management – but found that they had little value in predicting the diagnosis or outcomes for the 60 non-crisis depressed subjects in her study.

In his 1993 book, *Good Mood: the new psychology of overcoming depression,* Julian Simon states that, "religious conversion can cure depression." A recent doctoral dissertation by Damon Wood (2009) supports that contention; in his study 20 adults, who reported a "spontaneous recovery" from depression, but who also experienced a "transformational subjective experience," were recruited and interviewed. Wood concluded:

> Aftermath of the experience included rapid shift in mood, restructured personal values and beliefs, increased engagement in work and relationships, relapse prevention strategies, and a reluctance to share the experience with others for fear of ridicule or dismissal. Changes proved

stable over time, and the majority did not suffer a relapse of depression. Results indicated that the pathway of spontaneous and rapid recovery from depression could include a precipitating subjective experience followed by the attainment of a higher degree of personal wellness.

The obvious criticism of this study is that the results simply reflect a selection bias – if you select subjects who have experienced "spontaneous" recovery due to religious conversion experiences, the results will be reflective of these experiences. While there is little doubt that religious conversion experiences can have a psychological impact on people, the study says little about depression in the rest of the population.

### S-Adenosyl methionine (SAMe)

S-Adenosyl methionine (SAMe) is a "natural remedy" that is available as an over-the-counter dietary supplement in the United States and Canada, and as an anti-depressant prescription in Europe. In their review of 16 clinical trials, Mischoulon and Fava (2002) state, **"**SAMe is superior to placebo and is as effective as tricyclic antidepressants in alleviating depression… [SAMe] may have a faster onset of action than do conventional antidepressants and may potentiate the effect of tricyclic antidepressants." A more recent review of SAMe (Papakostas et al., 2010) concluded, "…Preliminary results suggest that SAMe can be an effective, well-tolerated, and safe adjunctive treatment strategy for SRI non-responders with major depressive disorder and warrant replication."

### Saffron

One study on mice reported that saffron, the flower of *Crocus sativus,* has anti-depressant properties (Hosseinzadeh, Karimi, and Niapoor, 2004). No other study was found to support this result.

### Sensory and Sensory-motor Stimulation

Professor Resit Canbeyli (2009) in Turkey has published an extensive research review of the impact of each of the senses and multi-sensory stimulation on depression. He also explains the neuroanatomy of how each sense may contribute to depression, and how depression can modify what is received by the senses. Reviewing over 350 studies, he lists the interactions between each of the senses and depression:

- Vision:
  - Light alleviates depressive symptoms
  - Inadequate light photoreception aggravates depressive symptoms
  - Emotion and mood can affect visual processing

- Audition:
  - Auditory stimulation modulates mood
  - Hearing impairment affects mood
  - Depression affects auditory processing
- Olfaction:
  - Odorants can modulate mood
  - Depression can affect the sense of smell
- Taste:
  - Tastants can modulate mood
  - Depression can affect taste and food intake

Canbeyli emphasizes "the bottom-up or peripheral view of evaluating the impact of stimulation via sensory modalities or the motor system on … depression." He shows that there is considerable data from clinical observations as well as research with animals to support activating the senses as a means of treating depression.

Perhaps the most well-known sensory stimulation strategy for depression is the use of "bright light therapy" for "seasonal affective disorder" (SAD).  However, most studies of the effects of bright light on SAD are of poor quality and tend to have a small number of subjects.  Tuunainen, Kripke, and Endo (2004) reviewed 20 studies of light therapy and concluded, "For patients suffering from non-seasonal depression, light therapy offers modest (though promising) anti-depressive efficacy, especially when administered during the first week of treatment, in the morning, and as an adjunctive treatment to sleep deprivation responders."

### St John's Wort

St John's wort, a perennial herb also known as hypericum, Tipton's Weed, Chase-devil, or Klamath weed, is seen as a treatment for depression, especially in Europe.  It is also an anti-inflammatory. A review of 29 clinical trials indicated, "The available evidence suggests that the hypericum extracts tested in the included trials: a) are superior to placebo in patients with major depression; b) are similarly effective as standard antidepressants; c) and have fewer side effects than standard antidepressants" (Linde, Berner, and Kriston, 1998).

### Vitamins

Increased intake of several vitamins has been suggested as a treatment for depression. Vitamins linked to depression include:

- *Vitamin $B_8$ (aka Inositol)* – The *Cochrane Reviews* looked at four double-blind trials of the effects of Inositol on depression, and concluded "It is

currently unclear whether or not inositol is of benefit in the treatment of depression" (Taylor et al., 2004).

- *Vitamin B$_9$ (aka Folate)* – low folate levels are thought to be one of the causes of depression, leading to poor metabolism of several neurotransmitters related to brain processes that can cause depression. Low folate levels may also be a factor in the poor response to anti-depressants shown by some patients (Coppen and Bolander-Gouaille, 2005).

- *Vitamin B$_{12}$ (aka Cobalamin)* – low blood plasma levels of Vitamin B$_{12}$ have been found in the blood of depressive patients. Low Vitamin B$_{12}$ levels may also be a factor in the poor response to anti-depressants shown by some patients (Ibid).

### Zinc

Zinc shows anti-depressant effects in animal models of depression. It is mainly found in the brain of human bodies, especially in the hippocampus and cerebral cortex. Lack of zinc in the brain can lead to problems in learning, behaviour, mood swings, and thinking. Nowack, Szewczyk, and Pilc (2005) report that, "…zinc induces brain derived neurotrophic factor (BDNF) gene expression and increases level of synaptic pool of zinc in the hippocampus." They confirmed the effectiveness of zinc supplements in treating depression in a group of patients.

\* \* \*

Much of the evidence for CAM treatments of depression are based on anecdotes and stories sometimes passed on through generations. Most of the CAM remedies have few randomized controlled trials, and those that do are usually conducted with very small samples. Professor Edzard Ernst became the UK's first Professor of Complementary Medicine and has published about 1,000 articles on the safety and efficacy of alternative medicine (interviewed by Bond, 2008). Ernst states, "Mainstream medicine is not always transparent, but complementary medicine is several degrees more murky." He calls for evidence-based treatments in his field, for which he has been severely attacked by alternative therapists. He says:

> What we've found is that about 5 per cent of alternative therapies are backed up by evidence. There is good evidence for the effectiveness of some herbal remedies, such as St John's Wort in treating mild to moderate depression, and devil's claw for musculoskeletal pain or hawthorn for heart failure.

Acupuncture works for certain things. Traditional acupuncturists will say you can use it for everything, but the evidence suggests it works only for some pain conditions and for nausea and vomiting. Other evidence-based treatments include hypnosis for pain, music therapy for anxiety, and relaxation for insomnia.

The discrepancy between experience and evidence is easy to explain. People may benefit from the encounter with the practitioner and not from the remedy; they might as well be given a placebo. That's very upsetting for a homeopath but it is nevertheless true. Many alternative practitioners develop an excellent relationship with their patients, and this helps to maximise the placebo effect of an otherwise useless treatment.

All of this does not mean that a particular CAM treatment is ineffective; it simply means that much more research needs to be done to prove the effectiveness of any specific CAM treatment before it is released for use with the general public. Freeman (2010) confirms this, and states, "At this time, several CAM treatments appear promising and deserve further study."

# Appendix B: Locations of teams working on treatments for depression

In reviewing the documentation on the treatment of depression, we were able to identify many of the researchers who are working on this topic today. Without including complementary and alternative medicine (CAM) approaches, we were able to compile a list of just over 600 people who are working on this problem worldwide. We classified the research by the following four broad treatment categories:

- Drug treatments
- Electroconvulsive therapy (ECT)
- Neurological stimulation treatments
- Psychotherapy and education treatments

Based on the number of researchers working on each treatment category, we were able to compare the relative effort being made on research for each treatment category (See Figure 5).
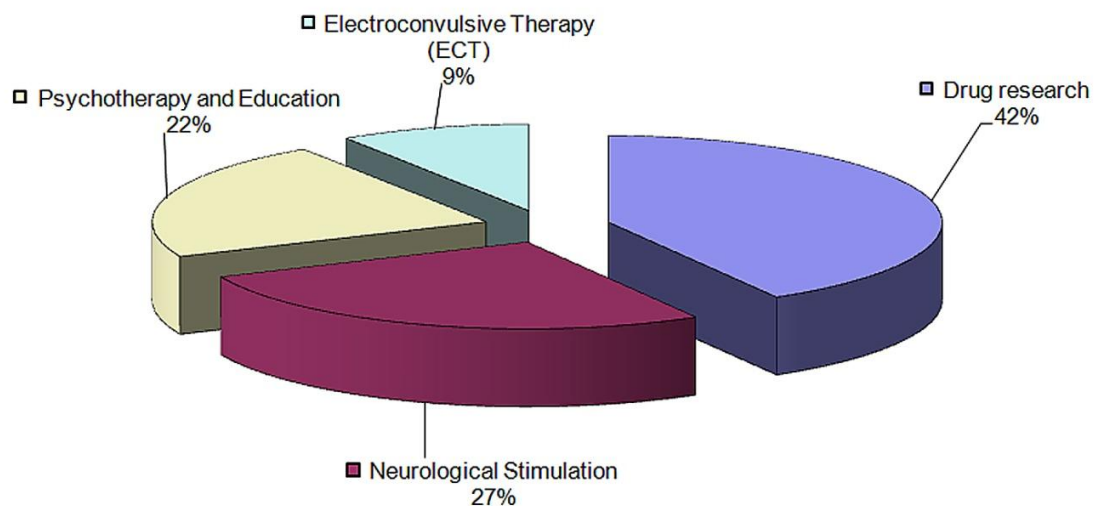


**Figure 5** – Distribution of types of treatments based on number of researchers for each treatment.

The list of researchers we have produced is by no means complete; there are literally thousands of people involved in developing treatments for depression worldwide. But, the listing we have compiled is able to give us a rough idea of which countries and institutions are most involved in this effort, and which particular treatments are the most prevalent in terms of current research.

Thirty countries were identified as having researchers on the treatment of depression. The United States is by far the biggest contributor, with over 50% of the effort worldwide (See Figure 6). This is not surprising, given that the majority of pharmaceutical companies and medical technology producers are also American. For the top 10 countries in terms of number of researchers, the United States is followed by the United Kingdom (11%), Canada (6%), Germany (5%), the Netherlands (4%), Australia (3%), France (2%), Spain (2%), China (2%), and Korea (2%). There are twenty other countries, representing 11% of the total, in which research on depression is taking place, but without large numbers of researchers.
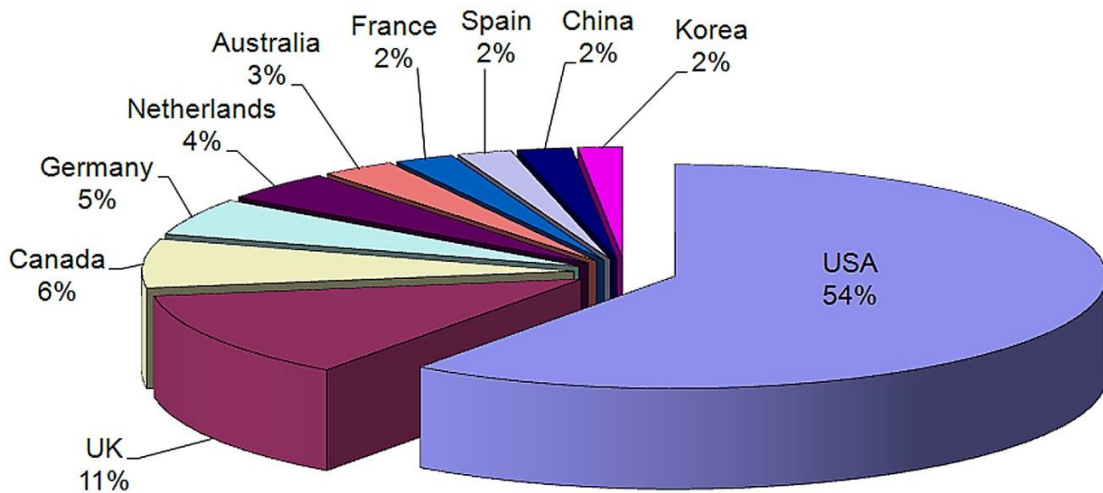


**Figure 6** – The top 10 countries in term of number of researchers on the treatment of depression mentioned in this environmental scan.

Given the predominance of the United States in research on the treatment of depression, it is not surprising that eight of the top ten institutions represented by researchers are in the United States, as shown in Figure 7.
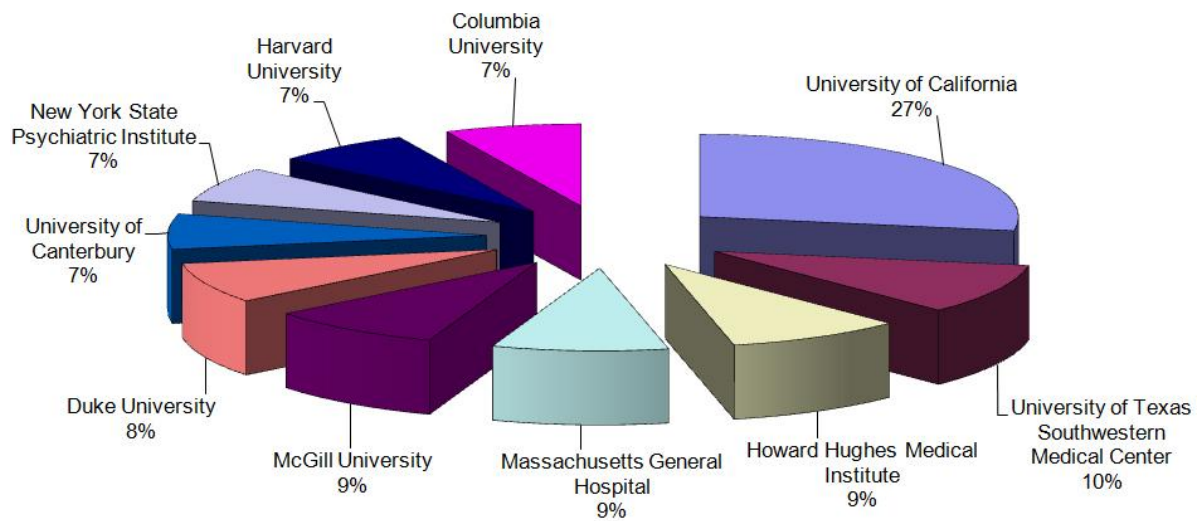
**Figure 7** – The top 10 institutions in terms of number of researchers working on the treatment of depression.

In order to see which locations outside of the U.S. are most involved with research on the treatment of depression, we calculated the top 12 *non-American* institutions by number of researchers (see Figure 8). The ranking of these institutions, with percentages of researchers out of the total pool in non-American institutions is as follows:

> 1 – McGill University, Canada (3.2%)
>
> 2 – University of Canterbury, New Zealand (2.5%)
>
> 3 – McMaster University, Canada (2.1%)
>
> 4 – University of Toronto, Canada (2.1%)
>
> 5 – Sungkyunkwan University, Korea (1.8%)
>
> 6 – Oxford University, UK (1.4%)
>
> 7 – University of Amsterdam, the Netherlands (1.4%)
>
> 8 – King's College, London (1.1%)
>
> 9 – Humboldt University, Germany (1.1%)
>
> 10 – Catholic University of the Sacred Heart, Italy (1.1%)

11 – University of London, UK (1.1%)

12 – University of British Columbia, Canada (1.1%)
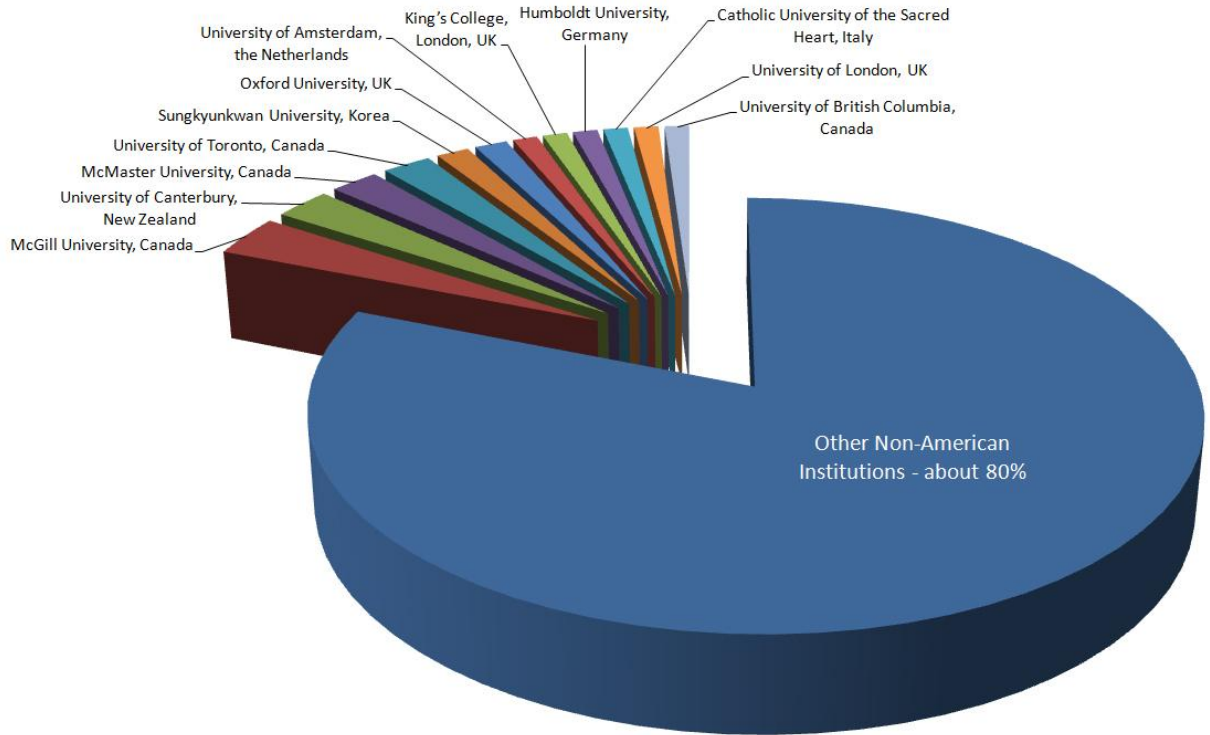


**Figure 8** – The top 12 non-American institutions by number of people researching treatment of depression based on documents in this environmental scan.

The top 12 institutions outside of the U.S. represent approximately 20% of the total of researchers in non-American research institutions, with about 80% being from other smaller research groups outside the U.S.

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**Gary Woodill** completed his doctorate in applied psychology at the University of Toronto in 1984. In 1985 he developed Ryerson University's first course on Computers in Education, and in 1993, started a multimedia company that developed over a dozen children's educational CD-ROMs that were translated into 14 languages. In 1998, he designed one of the first Canadian learning management systems (LMS) for CIBC in Toronto (now called LearnFlex, distributed by Operitel Corp., in Peterborough). While working for Operitel as Chief Learning Officer, from 2001-2006, he designed over 60 online courses for teachers, gathered requirements for clients, and wrote over a dozen white papers on emerging learning technologies.

In 2006, Gary became a full-time Senior Analyst with Brandon Hall Research, a California company with a strong reputation for producing research reports on workplace learning and learning technologies. Gary has published two books with McGraw-Hill – one co-authored book called *Training and Collaboration with Virtual Worlds* (2009), and the other titled *The Mobile Learning Edge* (2010). He is a regular speaker at conferences and webinars on emerging information technologies and social media. Gary is now the CEO of i5 Research.

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**Stephanie Wright** is a graduate from the library stream of the Masters of Information Studies degree at the University of Toronto. Her experience includes performing qualitative and quantitative research within a library environment, gaining a working knowledge of multiple library systems and public library specific software, and building IT solutions for libraries and various businesses.

Stephanie has conducted many interviews with professionals and experts in their own fields from an editorial perspective and knows how to gather information and lead a subject through a series of questions. She has also been asked to participate as an expert in a focus group.

Stephanie's web and computer knowledge is extensive. She has a working knowledge of current social media as well as experience with website planning for multiple user groups. Stephanie is also experienced in building and administering a variety of websites, and conducting research using multiple sources. Stephanie is an information analyst with i5 Research.

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