

## INTRODUCTION

Major Depressive Disorder, or Clinical Depression as it is more colloquially known, has a prevalence rate of approximately 20% for females, and 8-12% for males (Journal of the American Medical Association, 1996). In 2015, an estimated 16.1 million adults in the USA had had at least one major depressive episode in the last 12 months (NIMH, 2015), and every year at least 1 in every 15 people suffer from a major depressive episode in Europe, and depression alone accounts for 11% of all years lived with a disability, making it the leading chronic condition in Europe. Suicide accounts for 17.6% of all deaths of young adults aged 15-29 in high-income countries, with 90% of these being linked to mental health disorders such as MDD, making it the second biggest killer of young people (WHO, 2016).

## MAJOR DEPRESSIVE DISORDER: IN HISTORY

Depression has been known, described or written about, in one form or another, throughout most of human history. It was first referred to as 'melancholia', and this term existed from the Greco-Roman era, to the early 1700s. Treatments ranged from bloodletting and a change in diet and exercise prescribed by Hippocrates, to trepanning, which was used throughout Ancient Times, to the Medieval Era, and, controversially, is still advocated, particularly online, for treatment in modern times. Emil Kraepelin, a German psychiatrist, was one of the first to describe the condition as 'depression', using it as an overarching term for a series of already identified depressive conditions, including hypochondria. He also defined all types of mood-disorder, or 'manic-depressive insanity', into two subtypes, exogenous, or externally caused, often by stress or grief, and endogenous, or internally caused by genetics or a biological imbalance.

Within the same time period, Sigmund Freud began to popularise psychoanalysis as a treatment for a wide variety of mental health conditions, including depression. Though many other doctors at this time viewed depression as a physical disease, Freud believed that depression originated from loss in a person's life; whether that be real loss, such as grief, or symbolic loss, such as a missed opportunity. The loss experienced would cause an unconscious anger within a patient, and this would result in self-hate and self-destructive behaviour. However, other doctors during this era viewed depression as a brain 'disease', something far more physical than an unconscious anger.

The treatment for depression continued to be fairly ineffective throughout the late 19<sup>th</sup> and early 20<sup>th</sup> centuries, with lobotomies and electroconvulsive therapies being considered as viable options for those with the most severe forms of the illness.

With the 1950s came the biggest turning point in the understanding of depression, with doctors and professionals recognising a classification system that divided 'types' of depression by what caused them. The DSM-I, published in 1952 contained 'depressive reaction', and the DSM-II (1968) 'depressive neurosis', both defined as depressive states that arose from an extreme reaction to negative events or stress that occurred in a patient's life. It was at this time that the antidepressant side effects of tuberculosis medication Isoniazid, and hypertension medication Reserpine were first noticed, leading psychologists to hypothesise that depression was caused by a chemical imbalance in the brain.

The final stage in the evolution of Major Depressive Disorder as it is known today was its inclusion into the DSM-III in 1980.

## DIAGNOSTIC AND STATISTICAL MANUAL

The Diagnostic and Statistical Manual (DSM), now in its fifth edition, is a diagnostic manual developed by the American Psychological Association (APA) to assist in the diagnosis of mental health conditions. It is primarily used by psychologists and psychiatrists in the USA. The diagnosis of Major Depressive Disorder can be used either to diagnose the disorder, or to diagnose a Major Depressive Episode (MDE). An MDE can last two weeks or more, and may occur after a patient experiences trauma or particular life difficulties. They may recover from this episode and be able to continue their life normally. MDD is made up of recurrent episodes of depression, that can last a patient's entire life.

The DSM-V diagnostic criteria for Major Depressive Disorder are as follows:

- A. Five (or more) of the following symptoms have been present consistently for more than two consecutive weeks, and represent a change in previous functioning:
  - i. Depressed mood, indicated either by subjective report, or from the observations reported by others. In children and adolescents, this may also present itself as irritability.
  - ii. Decreased interest or pleasure in most or all activities.
  - iii. Significant weight loss or weight gain (a change of  $\pm 5\%$  over the period of a month). In children this may present itself as a failure to gain weight, rather than a change in mass.
  - iv. Change in sleep patterns, either insomnia or hypersomnia.
  - v. Psychomotor agitation or retardation, observable by others.
  - vi. Fatigue or loss of energy.
  - vii. Feelings of worthlessness or excessive or inappropriate grief, which may be delusional.
  - viii. Diminished ability to think or concentrate, and/or more indecisiveness.
  - ix. Recurrent thoughts of death, recurrent suicidal thoughts, suicidal ideation with or without a specific plan, or a suicide attempt.
- B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- C. These symptoms are not attributable to the physiological or psychological effects of a substance or other medical condition.
- D. These symptoms must not be better explained with a diagnosis of another disorder; particularly schizophrenic or schizophreniform disorders, delusional disorders or other psychotic disorders.
- E. There has never been a manic or hypomanic episode that is not attributable to substance use.

## INTERNATIONAL CLASSIFICATION OF DISEASES

The International Classification of Diseases (ICD) is a manual developed by the World Health Organisation (WHO) used by clinicians and researchers alike, to 'define diseases and study disease patterns, as well as manage healthcare and monitor outcomes' (WHO, 2016). It is used as a diagnostic manual for mental health conditions across the world, and has been translated into 42 languages. Now in its tenth edition, its diagnostic criteria for the diagnosis of Major Depressive Disorder (MDD) is used widely by psychologists, particularly those operating across Europe.

The ICD diagnostic criteria for Major Depressive Disorder are similar in many ways to the criteria outlined in the DSM-V. There are a few variations, however:

- The ICD, unlike the DSM, details further what constitutes MDD interrupting or changing a patient's sleeping pattern. They are listed under 'somatic' symptoms, also known as 'melancholic' or 'endogenomorphic' symptoms. In addition to the symptoms listed in the DSM-V, the ICD states that symptoms of sleep change may also include waking in the morning 2 hours or more before the usual time.
- On a similar note, the ICD also states that depression may be worse in the morning.
- The 'somatic' symptoms a patient may experience also include a notable decrease in libido.

## **SUBTYPES OF MDD**

Both the DSM and the ICD include further specifications for the subtypes or additional symptoms a patient may experience or exhibit. In the DSM, a practitioner may specify MDD existing alongside:

- With anxious distress
- With mixed features- a patient may be experiencing both depressive and manic symptoms, but these may not be significant enough to warrant a diagnosis of Bipolar Disorder.
- With melancholic features- a patient is in the depths of a depressive episode; it is almost impossible for them to experience feelings of pleasure.
- With atypical features- when some patient experiences symptoms that are not typical for depressed patients; their mood may brighten when they witness a happy moment on television, for example, or during a happy song.
- With mood-congruent psychotic features- mood-congruent refers to behaviours that are congruent (i.e. appropriate) to the emotions that a patient is experiencing. Examples of mood-congruent behaviours may include crying at a funeral. Mood-congruent psychosis in depression is a psychosis that has depressive tones, e.g. an aural hallucination such as a voice telling a patient they are worthless.
- With mood-incongruent psychotic features- a patient experiences a psychosis that is incongruent with the mood a patient reports, for example a patient hears a voice telling them that they are special, and have therefore been chosen for an important task of some description.
- With catatonia- catatonia can often appear to be the most difficult and disturbing exhibitions of mental illness. It comes in two forms; one of excited delirium, such as excessive motor activity with no purpose, and the other one of stuporous and unresponsive behaviour, such as mutism or posturing.
- With peripartum onset- depression that occurs in the last few months of a pregnancy, or soon after delivery.
- With seasonal pattern (recurrent episode only)- this replaces the previous diagnosis of Seasonal Affective Disorder (SAD); the seasons directly affecting a person's mood and mental stability.

The diagnostic criteria of MDD in the ICD-10 include the above subtypes, but also include the following subtypes (MDD with):

- Recurrent depressive reactions- A depressive reaction is a reaction to a stressful life situation, and may last from two weeks to six months.
- Endogenous depression- depression that does not arise from an external stressor; it is hypothesised that this type of depression has biological causes instead.

- Reactive depression- this subtype is similar to 'recurrent depressive reactions', but are not recurrent in nature. Instead, this type of depression is continual.
- Vital depression- vital depression is diagnosed in response to a perceived need, by a practitioner, for a particular type of anti-depressants.

## **MAJOR DEPRESSIVE DISORDER: IN SOCIETY**

Major Depressive Disorder, once diagnosed, leaves the sufferer open to vast and crippling social stigma. Stigma is one of the many barriers that sufferers must overcome when pursuing treatment, and is one of the primary reasons that treatment is not sought out (Corrigan, 2004). If treatment is begun, the impact of social stigma can result in a discontinuation in treatment that is of extreme importance, given the effect that depression can exert on a patient's life (Sirey et al., 2001).

However, recent research has begun to show a shift in the societal perception of depression. Blumner and Marcus (2009), in a 10 year follow to a study completed in 1996, found that there was a shift in the beliefs about what caused depression, with 88% of participants surveyed believing that clinical depression (also known as Major Depressive Disorder) was caused by a biological imbalance, and 60% of participants prioritising a biological focus for treatments, such as medication. This change in attitudes surrounding depression, that it is not the sufferers fault but rather an imbalance that they have no control over, may result in the direct stigma towards sufferers, and indirect stigma relating to treatments and support options, being significantly reduced, and with a greater focus on educating the general public about causes and treatments of mental illness, the stigma that sufferers are faced with may completely disappear, removing this potent and influential barrier to treatment.

The move to educating the public has already begun in some nations. George W. Bush, a president of the United States of America, instigated an educational outreach and screening programme for depression in the 1990's, known as National Depression Screening Day, that is held annually every October across the USA, in institutions such as colleges and military bases.

Outreach programmes such as these are important in identifying those at risk for developing the disorder, and ensures that as few people as possible slip through the cracks, and are missed when identifying the disorder.

## **RISK FACTORS**

There is still significant debate surrounding the causes of Major Depressive Disorder. However, certain aspects of a person's life or genetic makeup have been identified as key predictors for the development of depression.

### **STRESS**

The effects of significant stress on a person's life are manifold, with studies finding that stress can be detrimental to both physical and mental health. Andrews and Wilding (2004) in a study of British university students found that the impact of significant financial and other stressors led to 9% of a previously symptom free sample developing depressive symptoms at a clinically significant level. These results are concurrent with Wong, Cheung, Chan, Ma and Tang (2009) who found that in a sample of over 7000 students attending a Hong Kong university, 21% were found to exhibit depressive symptoms of above moderate severity, and 27% reported significant levels of stress, and

after investigation, it was found that there were high levels of psychological co-morbidity for these two conditions.

Lee and Kim (2006) studied over 400 nurses, and found that perceived stress was a predictor of depressive symptoms, with perceived stress and depression having a positive correlation. It was concluded that nurses who have high levels of perceived stress are more likely to experience depression than their cohorts. Ayerst (1999) found too that stress and depression have a positive correlation. In a sample of runaway and homeless children, the extreme stress of their situation meant that they were considerably more likely to experience depression or depressive symptoms than their peers who lived at home or under the care of a primary caregiver. Runaways and homeless children were also more likely to turn to coping strategies that were deemed 'unsuitable', such as drug use and self-harm.

The positive correlation between stress and depression is not limited to the impact of current life stressors, however. In a comparative study of mothers who had been diagnosed as suffering from depression and those who had not, Webster-Stratton and Hammond (1988) found that depressed mothers were significantly more likely to have suffered a significant stressor prior to birth, such as childhood or spousal abuse, than mothers who were not depressed. Research such as this shows the impact that prior stressors can have on the future mental health of a patient, and this, combined with the previously detailed research shows how stress of any kind, whether it be extreme stressors such as homelessness or abuse, or life stressors that many people may experience, such as financial or work-related stress, can have a vast impact on a patient's likelihood of developing depression.

## **BIRTH**

Peri-partum depression is one of the most difficult mood disorders to predict, and later treat, due to how covertly a sufferer experiences this disorder. It can affect both sexes, and is defined as a depression that occurs during the last few weeks of pregnancy, or directly after birth. Though birth is not a 'cause' of depression, it can occur in women who have no previous experience of mental health difficulties, due to hormone changes or exhaustion. Post-partum mental health issues are an incredibly important area of depressive illnesses, and the prevalence of this disorder worldwide means that it is important to understand birth and pregnancy as a risk factor themselves. Gulseren et al. (2006) found that in a sample of 125 pregnant Turkish women, the prevalence of depression was highest during the 36<sup>th</sup> and 38<sup>th</sup> week of pregnancy, with 21.6% of women reporting depressive symptoms. This level fell to 9.6% at 20-26 weeks postpartum. A history of mental illness, having a first degree relative with a history of mental illness, and experiencing adverse life situations such as a low income or a negative relationship with their partners were all considered to be risk factors in the development of depression. Dubey, Gupta, Bhasin, Muthal and Arora (2011) found a similar prevalence rate, of 6%, for women in India. Cooper et al. (1999) found that the rates for this disorder were far higher in developing countries, with a study in rural South Africa finding a prevalence rate of 34.7%.

A meta-analysis of studies detailing the prevalence of women affected by peri-partum depression estimated that worldwide approximately 13% of women will experience this disorder (O'hara and Swain, 1996). Though birth is, in itself, not a direct cause of the development of depression, a rate as high as this highlights the importance of informing parents to be about peri-partum depression, and such a high prevalence also validates its inclusion as a risk factor for the development of continual clinical depression.

## **PRE-EXISTING PHYSICAL ILLNESS**

Patients with a pre-existing medical illness are considerably more vulnerable to the development of depression and other mental health conditions than those who are physically healthy. MDD accounts for approximately 50% of the psychopathology of medically ill patients (Creed and Dickens, 2006), making physical illness, particularly those that are debilitating or terminal, a significant risk factor for the development of MDD.

Diabetes is a disorder that is particularly associated with the development of MDD. Diabetes is, when managed properly and identified early, not terminal, and often patients can continue through life relatively normally post diagnosis, with most of their day to day activities remaining unchanged. Depression is associated with hyperglycaemia and leaves the patient at an increased risk for diabetic complications. A meta-analysis searching for prevalence rates of diabetes and MDD found that diabetics were twice as likely to develop depression than their non-diabetic control groups, and that diabetic women were more likely to develop depression than diabetic men, with prevalence rates of 28% and 18% respectively (Anderson, Freedland, Clouse and Lustman, 2001). These results are concurrent with those found by Ali, Stone, Peters, Davies and Khunti (2006), where prevalence rates of comorbid depression were found to affect an average of 17.6% of patients diagnosed with diabetes, higher than participants without, and females were more likely to suffer from depression than males (23.8% vs. 12.8% respectively), in a meta-analysis that encompassed over 51,000 participants. The relationship between diabetes and depression is a reciprocal one, as not only have patients suffering from diabetes been found to be more likely to develop depression than participants who do not, but patients suffering from depression early in life are also more likely to be diagnosed with diabetes later on (Lloyd et al., 2011).

Heart disease is another illness that has a high rate of co-morbidity with MDD. Much more likely to cause serious complications and reduce a patient's quality of life, heart disease remains one of the most common causes of death in the Western World. A patient having heart disease with co-morbid depression makes it less likely that they will engage in treatments, both in hospital but later in rehabilitation, and therefore, alarmingly, increases the morbidity rates for those patients who are unfortunate enough to suffer from both conditions (Shapiro, Lidagoster and Glassman, 1997; Roose and Spatz, 1998; Nemeroff, Musselman and Evans, 1998; Jiang, Krishnan and O'Connor, 2002).

Depression has been found to be co-morbid with other serious disorders, such as cancer and stroke patients (Kang et al., 2015), and has been shown to increase functional impairments, lower quality of life, and increase likelihood of mortality for these patients. It is clear from the many studies documenting the co-morbidity of depression and physical illness that the development of a physical illness, particularly one that causes impairments or severely impacts on a patient's quality of life, that physical illness must be considered a serious risk for the development of MDD, and that patients who are diagnosed with such conditions must be monitored closely to ensure that the development of MDD is, at best, prevented, and at least caught early to ensure the most efficacious course for treatment.

## **GENETICS**

Having a familial relative with MDD has been identified as presenting a significant risk in the possible development of MDD. Levinson (2006) identified that cases of patients with an early onset of

depressive symptoms, and those who have a high rate of reoccurrence, or 'relapse' in their symptoms, present the highest risk to their future offspring. The influence of inherited genetic morphisms and genetic irregularities have been believed to play a role in the development of depression in later life. Feder, Nestler and Charney (2009) found that genetic mechanisms can play a role in the way a person responds to stress, and the resilience of their physical and mental health in response to external stressors. Stress, as identified earlier, is a significant risk factor for the development of MDD. It can be hypothesised from research such as this, therefore, that if a patient has a genetic predisposition to increased resilience to stress, they may be less likely to develop MDD. Figueiredo et al. (2015) also found a genetic link to the development of MDD in pregnant women. It was found, in a systematic review of women experiencing depressive symptoms post-partum, that genetic influences left women more open to the development of MDD, and that these genetic differences also had a role in the time period in which MDD developed; the late stages of pregnancy and the early months' post-partum were identified as the most vulnerable period for genetically vulnerable women.

Lerman et al. (1998) found that a genetic difference in the dopamine receptors in depressed patients brains also made them more likely to self-medicate with smoking than depressed patients who did not have this genetic difference. This suggests, therefore, that there may be a genetic difference not only in the development of MDD, but also the patient's response to the disorder, and the likelihood that they will self-medicate with substances.

Kato (2007) in a meta-analysis of all molecular genetic papers published on MDD found that the results published regarding the genetic influence in a patient's response to stress was unsubstantiated for some genetic codes that had previously been found to be influential. It was, however, found that a patient's genetic makeup could alter how they responded to medication, and therefore, though genetics may not play as much of a role as previously thought in the development of MDD as a response to stress, they may be important in determining how successful treatment for MDD is with a particular patient.

McGuffin and Katz (1989) found, that the genetic risk is solely a risk for the development of endogenous depression, and that other forms of depression are much more heavily influenced by the familial environment.

## **GENDER**

Gender plays a significant role in the development of many mental and physical health conditions, and MDD is no different. There is little to no gender difference in the development of MDD in pre-adolescent children, but after the age of 15, pubescent girls and women become twice as likely to develop MDD than boys and men (Nolen-Hoeksema and Girgus, 1994). These results are concurrent with Ustün (2000), who found that depression is 1.5 to 3 times more likely to be diagnosed in women than men. Nolen-Hoeksema (2001) investigated this gender difference, and found that it was caused by the gender differences in response to stress and stressful events. The above stated study, Nolen-Hoeksema and Girgus (1994) found similar results, reporting that girl's development of depression was not specifically linked to their gender, but rather the experiences they had due to their gender. Girls, it was found, carried more risk factors for the development of depression, such as hormonal changes, but it was only the increased prevalence of challenges faced by girls in early adolescence that caused the development of MDD, such as peer-pressure and sexualisation at an early age.

These results were concurrent with those found by Hankin et al (1998), who in a 10-year longitudinal study on gender differences in the development of MDD, found that there was a 'critical period' for the development of MDD, during which time the gender differences became apparent. There were small gender differences identified between 13 and 15 years of age, but this sensitive time period was identified as the years between 15 and 18 years of age, when a significant gender difference in the development of MDD became most apparent.

Although there are many socio-cultural affects that must be considered when reporting on the rates and risk factors associated with a gender-based predisposition to the development of MDD, a psychologist must consider the research that is currently available, and therefore gender is considered a risk factor in the development of MDD.

## **CO-MORBIDITY**

Depression is one of the most common co-morbid disorders in patients with a pre-existing mental health condition.

### **ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)**

In a study of over 3,000 participants, Kessler et al. (2006) found that, of those diagnosed with ADHD, over 18% of participants had also been diagnosed with co-morbid MDD, a rate similar to that found by August, Realmuto, MacDonald III, Nugent and Crosby (1996). In adults diagnosed with ADHD, Sobanski (2006) found that between 65% and 89% of all patients suffer from a second, co-morbid disorder, the most prevalent of these being mood disorders such as MDD.

### **GENERALISED ANXIETY DISORDER (GAD)**

Up to 90% of patients diagnosed with an anxiety disorder will also experience co-morbid depressive symptoms (Gorman, 1996). Kessler, DuPont, Berglund and Wittchen (1999) found, in two separate sample groups of patients diagnosed with Generalised Anxiety Disorder, 58.1% and 69.7% also met the criteria for co-morbid MDD at diagnosis.

### **OBSESSIVE COMPULSIVE DISORDER (OCD)**

Due to the distress that patients suffering with OCD experience, this particular anxiety disorder is frequently found to be co-morbid with depressive symptoms. Overbeek, Schruers, Vermetten and Griez (2002) found that, when surveyed, over a third of 120 patients suffered from both OCD and co-morbid depression. Ruscio, Stein, Chiu and Kessler (2010) found that in a sample of 2073 participants, depression was the most commonly experienced co-morbid disorder, and Torres et al. (2006) found that 37% of 140 patients diagnosed with OCD had co-occurring depressive symptoms.

### **POST TRAUMATIC STRESS DISORDER (PTSD)**

Roley et al. (2015) found that around 20% of patients with a diagnosis of PTSD also had a co-morbid diagnosis of MDD, significant levels that are concurrent with those found by Stein and Kennedy (2001) who, found in a sample of 44 women who had experienced intimate partner violence, and had therefore developed PTSD, 42.9% also had a diagnosis of MDD.

Other disorders that can present as having MDD as a co-morbid disorder include Schizophrenia and Schizoaffective disorder, eating disorders such as Anorexia Nervosa and Bulimia, personality



disorders such as Borderline Personality Disorder, and Dissociative Disorders such as Dissociative Identity Disorder.

## **TREATMENT**

### **PSYCHOPHARMACOLOGICAL TREATMENTS**

Medication is frequently the treatment of choice for professionals assisting in the recovery of individuals diagnosed with MDD, whether alone or with concurrent therapeutic techniques. This treatment comes in many forms, the most popular modern option being Selective Serotonin Reuptake Inhibitors (SSRIs). There are many other forms which will be further discussed here, including Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs), Tetracyclic antidepressants and Tricyclic antidepressants.

#### **SSRIs**

SSRIs are the most widely recommended and prescribed antidepressants in much of the Western World. Wagner et al. (2003) found that usage of the SSRI Sertraline with children and adolescents diagnosed with MDD led them to experience a significant improvement in all depressive symptoms associated with MDD, and this improvement was statistically greater than a control group taking placebo drugs. Whittington et al. (2004) found that SSRIs were significantly beneficial for young people and adolescents with a diagnosis of MDD. However, this study also found that there is some evidence in unpublished data that SSRIs may incur hazards when used with children and adolescents, and therefore recommends caution when approaching the subject of medicating this subgroup.

Gorman, Korotzer and Su (2002) found that the SSRIs Citalopram and Escitalopram were both more effective than placebo drugs in the reduction of the symptoms patients diagnosed with MDD experienced. Escitalopram was found to be quicker acting, and was concluded to be a superior choice for the treatment of MDD, results that were concurrent with the Burke, Gergel and Bose (2002) study on the same two SSRIs, with Escitalopram being both quicker acting and, importantly, requiring a quarter of the dosage of Citalopram and having the same effects.

Keller et al. (2001) found in a comparative study of placebos, tricyclic antidepressants and the SSRI Paroxetine, that Paroxetine demonstrated significantly greater improvement in symptoms when used with a sample of adolescents diagnosed with MDD. As can be seen above, the consistent and popular usage of SSRIs in the treatment of MDD and other depressive disorder is well-founded, as they have been shown in many studies to be an incredibly efficacious treatment option for those patients diagnosed with these disorders.

#### **SNRIs**

SNRIs are frequently recommended as an alternative treatment for MDD. Entsuah, Huang and Thase (2001) contrasted the first and most commonly used, Venlafaxine, with SSRIs and placebo drugs in the treatment of MDD. It was found that though the reviewed subpopulations have a similar and comparable reaction to SSRIs and SNRIs, Venlafaxine caused a more rapid relief from the symptoms of MDD, and a greater likelihood of remission post-treatment. Thase et al. (2007) found concurrent results, with a comparison study of two types of SSRI, one SNRI and one placebo showing that though in patients with mild depressive symptoms both active treatments were equally effective,

SNRI was far superior in the treatment of moderate- to severe-MDD, and resulted in higher rates of remission.

Nemeroff et al. (2002) found that the SNRI Duloxetine was significantly superior in clinical trials than a placebo in the reduction of both the depressive symptoms of MDD, and the physical symptoms that often plague sufferers of MDD. Levomilnacipran, another SNRI was also found to cause a significant improvement in patients' MDD symptoms post-treatment in a study of over 700 participants (Asnis, Bose, Gommoll, Chen and Greenberg, 2013).

Another benefit of the usage of SNRIs to treat MDD is their cost-effectiveness. Doyle et al. (2001) found that SNRIs were more cost effective in almost every country surveyed than SSRIs or tricyclic antidepressants, within both inpatient and outpatient settings. Given the efficacy of SNRIs displayed in the studies above, it can be seen that SNRIs are an equally effective treatment for the symptoms of MDD. However, SNRIs are a newer form of antidepressant than SSRIs, and therefore there are comparably significantly less options for both patient and practitioner within this group. It is suggested, therefore, that given the efficacy they have already shown, with further investment and development from pharmaceutical companies and medical specialists alike, they may be considered as a front-runner for usage in the treatment of MDD.

#### **TETRA- AND TRICYCLIC ANTIDEPRESSANTS**

Tetra- and tricyclic antidepressants are similar in nature, though chemically have a slightly different structure. They act to relieve the symptoms of MDD by inhibiting the reuptake of serotonin and norepinephrine, and are among the older class of antidepressants, having been discovered in the 1970's and 1950's respectively.

They have demonstrable efficacy in the treatment of MDD, with Anderson (1998) finding in a comparative meta-analysis of studies of tricyclic antidepressants and SSRIs that tricyclic antidepressants were significantly more effective than SSRIs in the reduction of the symptoms of MDD. However, MacGillivray (2003) in a meta-analysis of studies comparing the same two drug groups did not replicate these results, finding no significant difference in the efficacy of SSRIs and tricyclic antidepressants. Studies with contrasting results such as these do not suggest that one treatment is therefore not effective, as demonstrated by Anderson and Tomenson (1994) and Arroll et al. (2005) who found equal efficacy in treatment for SSRIs and tricyclic antidepressants.

The question may be asked, therefore; why is it that SSRIs are considerably more popular in the treatment of MDD? The answer lies not in the efficacy of the treatments, but rather in the side effects these treatments have.

SSRIs, like all antidepressant medications have a long list of side effects, but unlike tetra- and tricyclic antidepressants, none of these side effects have been demonstrated to have possible long-lasting and life altering after effects.

In a study of 186 participants, Jabbari, Bryan, Marsh and Gunderson (1985) found that 15.6% of patients receiving treatment with tetracyclic antidepressants developed seizures after treatment, indicating that the risk of developing seizures after a course of tetracyclic antidepressants is relatively high.

Furthermore, Burckhardt et al. (1978) and Glassman and Bigger Jr. (1981) both found that in high doses tricyclic and tetracyclic antidepressants can have extremely detrimental cardiovascular side effects, including a marked increase in heart rate after only three weeks of drug therapy. Side effects such as these have meant that tetra- and tricyclic antidepressants have been relegated to the side-

lines of drug therapy, and are now only used in younger patients or patients who do not present a significant risk of cardiovascular issues.

## **NOVEL TREATMENTS**

In more recent years, new and innovative treatments are becoming available for the treatment of MDD.

In 2010, the European Union approved the use of the antidepressant Agomelatine in the treatment of MDD. Hale et al. (2010) found that, when compared with the more traditional treatment Fluoxetine, Agomelatine was significantly more effective in the treatment of MDD in assessments both during and post-treatment. This efficacy is concurrent with that described by Lemoine, Guilleminault and Alvarez (2007), who found that not only was Agomelatine effective in the treatment of the symptoms of MDD, but also assisted in the reduction of sleep difficulties experienced by sufferers of MDD and other depressive disorders that current medications often fail to alter.

Newer still is the research surrounding the Gamma-Aminobutyric Acid (GABA) receptors in the brain and their role in depression and the efficacy of anti-depressant treatments. Ghose, Winter, McCarson, Tamminga and Enna (2011) found after dissection of the brains of laboratory rats that the GABA system played a key part in the mediation of symptoms of MDD and the way that a brain may react to antidepressant therapy. Researchers at Penn State University in a report published in 2016, have detailed how this information has been used to create the effect of anti-depressants in the brains of laboratory mice. The researchers increased GABA signalling by disabling a GABA receptor in a specific set of neurons that are suspected to be involved in major depressive disorder. Under normal circumstances, this set of neurons known produce GABA, which reduces the activity of other neurons around them. The researchers disabled the GABA receptor, and the cells around them therefore no longer received the chemical message to 'slow down'. GABA was released excessively, which further slowed the neuronal activity of cells around them. The mice given this treatment then performed a number of behavioural tests, and were found to be acting in a similar way to mice who had been given antidepressant drugs.

Biochemical changes in brain tissue were also found, and these changes mimicked those found in the brains of mice who had been given antidepressants in separate clinical trials. Treatments such as these show obvious promise in the field of antidepressant therapies, but more trials are needed to confirm their efficacy. Trials with human subjects are also necessary.

## **THERAPUTIC TREATMENTS**

Due to the vast number of side-effects that every antidepressant has, psychopharmacological treatments are not always recommended for certain subgroups of the population. Patients diagnosed with mild to moderate MDD, and children and young people are among the groups who may be considered to be unsuitable for medication based treatments.

Casacalenda, Perry and Loper (2002) in a comparative meta-analysis of psychotherapy and pharmacological treatments for MDD, found that both approaches are equally effective in the treatment of mild to moderate MDD. Thase et al. (1997) concur, with their results showing that though it is necessary in the treatment of severe to combine a course of psychotherapeutic

treatments with medication, for mild to moderate MDD there are no statistical benefits for combined medication and psychotherapy over psychotherapy alone.

## **CONCLUSION**

As can be seen from all research above, Major Depressive Disorder is an incredibly difficult and debilitating condition to live with, and can affect all areas of a patient's life. It is also an incredible drain on the medical facilities of all countries, with extended and occasionally life-long treatments necessary to manage the symptoms that a patient may be experiencing. Currently, SSRIs for severe MDD, and a treatment using psychotherapy for mild to moderate MDD appear to be the most efficacious, but, given the new and innovative treatments constantly being developed to help tackle this devastating disorder, research must continue in the areas of SNRIs and GABA receptor medications.