USE OF KETAMINE AS A FAST ACTING ANTIDEPRESSANT FOR TERMINAL CANCER PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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ACKNOWLEDGEMENTS

After one year of new experiences and a complete change in my lifestyle, I can look back and see how much I have learned. Obviously, the certainty that there is much more knowledge ahead is a factor that keeps me motivated, but without the support from my loved friends and family I would have never achieved one more goal. Thank you all!

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My very special thanks goes to the patient who made all of this possible. You are a unique person, and your patience with the constant assessments was very kind of you. Thank you so much!
ABSTRACT

The objective of this thesis was to investigate the safety and efficacy of single and repeated administration of ketamine as a fast acting antidepressant in patients with terminal cancer. Associated with this objective was a comprehensive review of the pathophysiology of major depressive disorder, existing treatments for major depressive disorder, and a review and meta-analysis of treatments for depression in patients with cancer. The use of ketamine in treatment-resistant depression was also reviewed, along with a meta-analysis of mood responses in placebo-controlled studies, and data from case reports and case series.

The review and meta-analysis of antidepressant treatments for depression in cancer patients yielded only two small placebo-controlled randomized trials, both for mianserin. No psychotherapy trials were found that met inclusion criteria for this analysis. The two mianserin trials showed a benefit in improving mood ratings compared with placebo. The very limited amount of data on treatment of depression in this population is surprising, and further research is needed to improve knowledge in this area.

The review and meta-analysis of mood responses to ketamine in three placebo-controlled randomized crossover studies demonstrated a robust improvement in mood ratings by four hours, that was sustained up to 72 hours. Uncontrolled data from case series and case reports showed similar profile to data reported from the placebo-controlled studies.

The study investigates the effect of ketamine on mood ratings in depressed patients with cancer had three stages; (1) to assess whether a single 1 mg/kg IM dose improved mood; (2) to assess the effect of repeated 1 mg/kg IM dosing on mood; and (3) to assess the mood responses to IM doses of 0.1, 0.5 or 1.0 mg/kg IM. This thesis reports the case of a single patient who participated in Stages 1 and 2. The results in the case presented in this thesis were positive, with remission of symptoms with single dose and repeated treatment, and maintenance of remission with weekly injections of ketamine 1 mg/kg.

This thesis supports the possible use of ketamine as a fast acting antidepressant in terminal cancer patients with Major Depressive Disorder. In a population with short life expectancy, the existence of a treatment for depressive episodes with rapid onset of action would be essential, and ketamine might be the option of choice.
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LIST OF ABBREVIATIONS

ACTH  Adrenocorticotropic hormone
ACTRN  Australian New Zealand Clinical Trials Registry
AD  Alzheimer’s disease
AMPA  Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AMPARs  AMPA receptors
BD  Bipolar disorder
BDI  Beck Depression Inventory
BDNF  Brain-derived neurotrophic factor
CMI  Cell-mediated immune
COPD  Chronic obstructive pulmonary disease
CRF  Corticotropin-releasing factor
CRH  Corticotropin-releasing hormone
CVD  Cardiovascular disorder
DBS  Deep brain stimulation
DPP IV  Dipeptidyl peptidase IV
DS  Demoralization scale
DSM  Diagnostic and Statistical Manual of Mental Disorders
EAAT  Excitatory amino-acid transporter
EC  Endocannabinoid
ECOG  Eastern Cooperative Oncology Group
ECT  Electroconvulsive therapy
GABA  Gamma-aminobutyric acid
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<th>Description</th>
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<td>Gln</td>
<td>Glutamine</td>
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<tr>
<td>Glu</td>
<td>Glutamate</td>
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<tr>
<td>GluTs</td>
<td>Vesicular glutamate transporters</td>
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<tr>
<td>HADS</td>
<td>Hospital Anxiety and Depression Scale</td>
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<td>HAMMD</td>
<td>Hamilton Rating Scale for Depression</td>
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<tr>
<td>HD</td>
<td>Huntington disease</td>
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<td>HIV</td>
<td>Human immunodeficiency virus</td>
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<tr>
<td>HPA</td>
<td>Hypothalamo-Pituitary-Adrenal</td>
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<tr>
<td>5-HT</td>
<td>5-hydroxytryptamine (serotonin)</td>
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<tr>
<td>HVA</td>
<td>Homovanilic acid</td>
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<tr>
<td>IBD</td>
<td>Inflammatory bowel disease</td>
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<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
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<td>IDO</td>
<td>Indoleamine-2,3-dioxygenase</td>
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<tr>
<td>IFN</td>
<td>Interferon</td>
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<tr>
<td>IL</td>
<td>Interleukin</td>
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<tr>
<td>IM</td>
<td>Intramuscular</td>
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<tr>
<td>IV</td>
<td>Intravenous</td>
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<tr>
<td>LC</td>
<td>Locus coeruleus</td>
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<tr>
<td>MADRS</td>
<td>Montgomery-Asberg Depression Rating Scale</td>
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<tr>
<td>MAOI</td>
<td>Monoamine oxidase inhibitor</td>
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<tr>
<td>MDD</td>
<td>Major Depressive Disorder</td>
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<td>MDE</td>
<td>Major depressive episode</td>
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<tr>
<td>mGlu</td>
<td>Metabotropic glutamate</td>
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<td>mGluR</td>
<td>Metabotropic glutamate receptor</td>
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<td>Abbreviation</td>
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<tr>
<td>MRS</td>
<td>Magnetic Resonance Spectroscopy</td>
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<td>MS</td>
<td>Multiple sclerosis</td>
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<tr>
<td>mTOR</td>
<td>Mammalian target of paramycin</td>
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<td>NA</td>
<td>Nucleus accumbens</td>
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<td>NMDA</td>
<td>N-methyl-D-aspartate</td>
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<td>NMDARs</td>
<td>NMDA receptors</td>
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<td>PD</td>
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<td>PEP</td>
<td>Prolyl endopeptidase</td>
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<td>PFC</td>
<td>Prefrontal cortex</td>
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<td>SD</td>
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<td>SERT</td>
<td>5-HT transporter</td>
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<td>SLE</td>
<td>Systemic lupus erythematosus</td>
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<td>SNARE</td>
<td>Soluble N-ethylmaleimide sensitive factor attachment protein receptor</td>
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<td>SNRI</td>
<td>Serotonin-norepinephrine reuptake inhibitors</td>
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<td>SSRI</td>
<td>Selective serotonin reuptake inhibitors</td>
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<tr>
<td>TMS</td>
<td>Transcranial magnetic stimulation</td>
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<tr>
<td>TNF</td>
<td>Tumor necrosis factor</td>
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<td>TRYCATs</td>
<td>Tryptophan catabolites</td>
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<td>VNS</td>
<td>Vagus nerve stimulation</td>
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<tr>
<td>VTA</td>
<td>Ventral tegmental area</td>
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<td>WHO</td>
<td>World health Organization</td>
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CHAPTER 1

Introduction
1.1 Introduction

Major Depressive Disorder (MDD) is the most common psychiatric illness, and it affects more than 120 million people worldwide (more than 27 times the population of New Zealand). It is characterized by depressed mood and loss of interest and pleasure, but other signs and symptoms are commonly present, such as: weight loss or gain; sleep disturbance with insomnia or hypersomnia; fatigue; lack of concentration; feelings of guilt; suicidal ideation; and psychomotor agitation or retardation (Skolnick et al., 2009; Statistics New Zealand, Jan 2012; DSM IV). These symptoms must persist for at least 2 weeks, and must be accompanied by significant distress or impairment. Also, in addition to its high prevalence, depression presents the greatest proportion of burden due to nonfatal health outcomes (World Health Organization - World Health Statistics, 2007).

In patients with cancer, the prevalence of depressive episodes is higher than in general population (Mitchel et al., 2011). Although it may seem unsurprising, special attention must be given to this group, as there is a higher risk for depressed patients not to accept proper cancer treatment (Colleoni et al., 2000). Thus, any depressive symptom should be recorded and questioned in every follow-up appointment, and adequate treatment should be provided as fast as possible, in the presence of a depressive episode. Available treatments for depression will be described further in this chapter.

Ketamine is an anaesthetic agent that has demonstrated antidepressant properties (Diazgranados et al., 2010; Berman et al., 2000; Sofia and Harakal, 1975). Its unique quality is the very fast response relative to dosing, occurring within few hours (Zarate et al., 2006; Machado-Vieira et al., 2009). Also, the duration of ketamine’s antidepressant effects is of 3 days or more (Zarate et al., 2006; Berman et al., 2000), even though its half-life is of about 2.5 hours (Ketalar® - Medsafe). The reasons for these effects will be partially explained in this thesis, as the action of ketamine in the brain is not fully understood. Also, the possibility of using this medication for depressed individuals with short life expectancy, such as terminal cancer patients, will be discussed.

In summary, this thesis will cover several topics:

- **Chapter 1**: introduction and epidemiology of depression;
- **Chapter 2**: pathophysiology and treatment of MDD;
- **Chapter 3**: literature review and meta-analyses of effectiveness of antidepressant treatments in patients with cancer;
Chapter 4: ketamine overview;
Chapter 5: literature review and meta-analysis of effectiveness of ketamine in MDD and depressive episode of bipolar disorder, both case series and randomized clinical trials;
Chapter 6: description of a protocol for treating MDD in cancer patients;
Chapter 7: description of single and repeat dosing for a patient with MDD and terminal cancer;
Chapter 8: conclusions about the possible use for ketamine as a fast acting antidepressant for depressive episodes in terminal cancer patients.

1.2 History of depression
Depressive symptoms have been described since ancient history, and writings regarding them were even found in Ancient Egyptian papyri. Also, the Bible presented King Saul with symptoms of depression (Davison, 2009; Huisman, 2007). In ancient Greece, supernatural explanations were provided for these symptoms, such as evil spirits and punishment from gods, but during the 6th century BC, these explanations started losing their impact in Greek culture.

The first statement that melancholia (which in ancient times was described by depressive symptoms, among others) was caused by a dysfunction of the brain was made by Hippocrates (460- 377 BC). He believed that the excess of “black bile” in individual’s brains was responsible for melancholic symptoms, giving rise to the humoral theory (first postulated by Empedocles) for melancholia (Davison, 2009; Bos, 2009). However, centuries latter, the Christian Church stated again that melancholia was a disease of the soul. This idea brought back supernatural experiences as a possible cause for depressive symptoms, and many women were then at risk of being considered witches and condemned to be burnt at the stake (Daly, 2007).

In the 20th century, more plausible explanations for the symptoms of psychiatric illnesses were raised. Emil Kraepelin adopted a somatic approach, while Sigmund Freud emphasized psychological factors, although biological factors were also considered in his hypotheses. In 1930’s, the initiation of treatments, such as electroconvulsive therapy and psychosurgery, raised the need for clinical categories for treatment decisions (Davison, 2009).
1.3 Epidemiology of depression in Major Depressive Disorder and Bipolar Disorder

Patients with Major Depression and Bipolar Depression have depressive symptoms (such as depressed mood, diminished interest in activities, diminished ability to concentrate, alteration in appetite, fatigue, feelings of guilt, suicidal thoughts) alternately with euthymia (normal mood). In patients with BD, episodes of hypomania/mania (usually with grandiosity, reduced need to sleep, running thoughts, pressure to keep talking, excessive involvement in pleasurable activities that may be harmful, distractibility and psychomotor agitation) are also present, at some time in their lives (DSM IV).

The yearly prevalence of MDD in general population in the United States is around 6.7%. In New Zealand, according to The New Zealand Mental Health Survey 2003/4, almost the same prevalence is found, with major depressive episodes (MDE) affecting 6.6% of general population (Kessler et al., 2005; Scott et al., 2010). In the New Zealand survey, these episodes were more commonly found in females (8.1% versus 4.9% in males). Fewer than 10% of MDE episodes were considered mild, with over half being severe or very severe. Also, just one-third of patients with severe impairment received treatment from mental health services. This information may help doctors with the awareness of considerably high prevalence of depression among patients in general population and its severity.

Besides differences between MDD and BD, in BD depression is the most experienced mood (Mitchell and Malhi, 2004). In both cases, there is a correlation with cardiovascular disease, obesity, metabolic syndrome, dementia, low income, marital status, and others (Weiner et al., 2011; Ko et al., 2010; Keddie, 2011; Fiedorowicz et al., 2008; Byers and Yaffe, 2011; Kessing and Andersen, 2004; Schofield et al., 2011; Schoeyen et al., 2011; Yan et al., 2011). Some associations seem to be explainable, such as lack of exercise and eating habits associated with metabolic syndrome. However, it is hard to analyse these correlations as cause of depression, its consequence, or as part of a broader syndrome (Kahl et al., 2011). Also, these individuals have a higher risk of suicide, and there are more deaths from unnatural causes in the unipolar depression group, when compared to bipolar depression (Osby et al., 2001; Black et al., 1987). The costs of depression are high, for example, the economic burden in USA was of almost $44 billions in 1990 (Greenberg et al., 1993). General medical care costs are much higher than those with general population, even for depressed subjects that are on treatment (Bosmans et al., 2010). Although this population maintains an intense use of professional care, they have higher chances of not meeting their needs, and of having a
chronic illness, that may be due to inadequate treatment (Bijil et al., 2000; Pincus and Pettit, 2001). Not only mental health professionals should be aware of these facts, but also general practitioners, as according to Bijil et al., 2000 and Lepine et al., 1997, the majority of individuals with depression look for treatment in primary care. Thus the treatment for depressive symptoms is of great importance in both mood disorders.

For the estimation of the global burden in patients with MDD (World Health Organization – WHO), symptoms severity were split in disability weights: 0.14, 0.35, and 0.76 for mild, moderate and severe, respectively (Ustün et al., 2004). Actually, many individuals suffer from chronic or recurrent depression, with some of these patients achieving recovery only 6 months after initial treatment (50% of recovery, according to Pincus and Pettit, 2001). In Major Depression, there is less chance of recovery over time with symptomatology, and with each subsequent episode (Lavori et al., 1994; Keller et al., 1992), leading to a high prevalence of chronically affected patients, who make up 26.8% of patients with MDD (Satyanarayana et al., 2009). Moreover, according to the WHO, there is an estimative that, in 2030, unipolar depression will be the second leading cause of disability adjusted for life years. This is similar to a previous projection made for 2020 sixteen years ago (Mathers and Loncar, 2005; Murray and Lopez, 1996). The World Health Organization also states that MDD already comprises 10.7% of total global years lived with disability, and BD accounts for other 2.5% (Ustun et al., 2004; Ayuso-Mateos, 2006).

Antidepressant treatment for MDD is known to be effective, even though remission rates are considered not optimal (Khawam et al., 2006; Trivedi et al., 2006). However, its use for depressive episodes in patients with BD is not clearly beneficial, with some authors reporting response to antidepressants in this group (Pacchiarotti et al., 2011; Ghaemi et al., 2008) and a recent review (Sidor and Macqueen, 2011) suggesting that antidepressants are of little help for acute treatment of depressive episode in BD. Also, Sidor and Macqueen, 2011 state that the risk of mania switch depends on the criteria used to evaluate it. This risk has been continuously investigated, and includes cycle acceleration, mania, hypomania and mixed switch (Amsterdam and Shults, 2010; Pacchiarotti et al., 2009; Ghaemi et al., 2008; Goodnick, 2007). Considering the low response in depressive episodes achieved with antidepressant medications available, treatment alternatives are desirable.
1.4 Epidemiology of Major Depressive Disorder in cancer patients

Depression rates in individuals with advanced cancer are very high, affecting approximately 15% of patients (Mitchell et al., 2011), and when considering subsyndromal depression (the presence of depressive symptoms that do not meet criteria for MDD) the numbers are even higher (Boyes et al., 2011). Although diagnoses of adjustment disorder and of minor depression are quite common in cancer patients (Mitchell et al., 2011), initial support and follow up of depressive symptoms is very important to ensure appropriate treatment. Psychological support must be considered for cancer patients during their treatment. For better results, it should start from the time of cancer diagnosis and, in addition, support for relatives and caregivers should also be provided (McLean et al., 2011; Kang et al., 2012).

It is important to be aware that recent data demonstrates even higher rates of depression in patients prior to commencing chemotherapy, with prevalence as high as 25% (Breen et al., 2009). Furthermore, suicidal ideation has been found in 10% of cancer patients, who were more frequently females, with worse interpersonal relationships, significant pain, MDD, dysthymia and panic disorder (Madeira et al., 2011). Therefore, a complete assessment of previous and actual history of psychiatric illness, together with detailed interpersonal relationships, is vital to achieving appropriate treatment (Boyes et al., 2011). Very little information about treatment of depression was found concerning cancer patients, which will be discussed in detail further, in Chapter 3. This fact raised concerns about the lack of information concerning the possibility of different responses to treatment of MDD in this specific population.

Depressive episodes may initially start with symptoms that meet criteria for adjustment disorder (a maladaptive reaction to a stressful life event) and early intervention is essential for a better prognosis (Akechi et al., 2004). This situation is complicated, because many symptoms due to cancer or its treatment are also part of MDD criteria (for example, weight loss, fatigue, psychomotor retardation and diminished ability to concentrate). Trying to solve this problem, many researchers have assessed mood symptoms with the Hospital Anxiety and Depression Scale (HADS), which is extensively used in palliative care, due to its absence of physical symptoms on its assessment. HADS is a validated and reliable tool for medically ill patients’ assessments for anxiety and depression (Guidi et al., 2011; Castelli et al., 2011). Also, The Demoralization Scale may be a useful instrument, offering an evaluation of non-specific dysphoria, social disconnectedness, hopelessness, helplessness and suicidal ideation (Kissane et al., 2004).
The impact that MDD has on these patients may result in choices that might be different if they were not affected by the disorder. For example, a study with cancer patients showed that acceptance of adjuvant chemotherapy in patients with breast cancer and depression was 51.3%, but among patients without MDD, 92.2% accepted the abovementioned treatment (Colleoni et al., 2000). With this knowledge, there are more chances of considering a possible diagnosis of depression in this population. This awareness could also lead patients to MDD treatment, and probably to acceptance of cancer treatments, increasing their chances of survival or recovery.

Considering the high prevalence of depression in this population, studies evaluating antidepressant treatments are of great importance for the clinical practice. Unfortunately there are only two randomized clinical trials on this topic (Costa et al., 1985; van Heeringen and Zivkov, 1996). A number of other studies have been published, however these have combined patients with subsyndromal depression and MDD, usually neglecting illness severity. For patients with terminal cancer, there is an even greater lack of studies, directing attention to the fact that more could be done for this particular group. There are many studies considering subjects support via telephone and via internet (White et al., 2011; Klemm and Hardie, 2002), but usually these trials are for cancer survivors and no similar study was found for advanced cancer patients.
CHAPTER 2

Pathophysiology and treatment of Major Depressive Disorder
2.1 Pathophysiology of Major Depressive Disorder

Depression has been recognized since ancient times but is still considered a complex disease with unknown etiology (Dagyté et al., 2010). For many years the monoaminergic system was the focus for depression treatment. However, with available antidepressants (which target monoamines), patients’ response is very limited. This fact led researchers to consider the possibility that other alterations in depressed subjects’ brains might be involved in the pathophysiology of MDD. In the last decades, hippocampal neurogenesis started to be investigated in depression’s pathophysiology (Dagyté et al., 2011), and many hypotheses have been studied as an attempt to better understand it.

The hypotheses described below are interconnected, indicating that depression is a highly complex illness. For example, the locus coeruleus, which is considered a part of the central stress system, has noradrenergic innervation, and is usually overexcited and may be defective in patients with MDD. (Itoi and Sugimito, 2010; Harro and Oreland, 2001). When the locus coeruleus is activated, it fires the prefrontal cortex (PFC), and triggers the ventral tegmental area (VTA), releasing dopamine in the nucleus accumbens (NA). The PFC relays to the VTA, releasing glutamate in the last, leading to increased excitability and more dopamine release in the NA (Sara, 2009). This illustrates the interaction between different systems. Further, cytokines (through influences on synaptic plasticity, and on neuroendocrine and monoamine systems) can influence corticotropin-releasing hormone (CRH), brain-derived neurotrophic factor (BDNF), serotonin, norepinephrine, and dopamine (Miller and Raison, 2008). Figure 2.1 illustrates these interactions. The following sections will discuss some of the hypotheses that try to explain the neurobiology of depression.
**Figure 2.1:** Anatomical connections and interactions between neuroendocrine system, BDNF, monoamines, and cytokines in the brain.

Figure modified from: www.antisocial-disorder.com/page/9
2.1.1 Serotonergic system

The monoamine hypothesis of depression, which proposed that decreased levels of serotonin, noradrenaline and/or dopamine would induce depressive symptoms (Middlemiss et al., 2002), was previously converged to the serotonergic system as a possible main alteration in the brain, leading to depression (Coppen, 1967). Also, serotonin’s precursor tryptophan, proved to be decreased in subjects with MDD (Anderson et al., 1990). Treatment with tryptophan had a positive effect on mood when administered to depressed patients (Young et al., 1985; Shopsin, 1978), suggesting a role for serotonin in depressive symptoms. Also, an immune-response with consequent depletion of tryptophan has been associated with depression in cancer patients (Kurz et al., 2011). Another fact that contributes to the association between the serotonergic system and depression is the fact that many patients with MDD present chronic pain symptoms. Regarding this fact, as the serotonergic 5-HT1A receptor seems to play a role in Major Depression and in pain regulation (Ohayon, 2009), serotonin could provide a link between these symptoms, and explain their frequent coexistence.

2.1.2 Noradrenergic system

This system is considered to be related to several areas that are altered in subjects with MDD, such as attention, memory, learning, sleep, emotion and response to stress (Sara, 2009; Berridge and Waterhouse, 2003). It is also implicated in synaptic plasticity in the hippocampus (Sara, 2009), possibly playing a role in MDD. Its dysfunction has constantly been pointed as a possible mechanism in depressive symptoms (Goekoop et al., 2011; Itoi and Sugimoto, 2010). Some antidepressants with action in the noradrenergic system have been cited as possibly more effective treatments when compared to selective serotonin-reuptake inhibitors (SSRIs) however, this is still controversial. Besides these medications also act in the dopaminergic system, some authors correlate their noradrenergic action to a possible pathway to the treatment of Major Depression (Montgomery and Briley, 2011; Nutt et al., 2007).

The noradrenergic system is linked to the activation of the hypothalamic-pituitary-adrenal (HPA) axis, and vasopressin release, which are also implicated in the pathophysiology of depression (Keller et al., 2006; Goekoop et al., 2011).
2.1.3 Dopaminergic system

The role of dopamine in Major Depression seems to be highly linked to attention, psychomotor activity, and anhedonia (which is the inability of experiencing pleasure in activities that before were enjoyable). Because many antidepressants do not directly act in the dopaminergic system, this might contribute to the residual symptoms that many patients experience during their treatment. Residual symptoms frequently consist of impaired concentration, motivation and pleasure (Dunlop and Nemeroff, 2007; Nutt, 2006). In the cerebrospinal fluid of depressed subjects, homovanillic acid (HVA) seems to be decreased. Some antidepressants are likely to act in the dopaminergic system, such as sertraline, bupropion and the monoamine oxidase inhibitors (MAOIs), but the magnitude of this action still requires further studies (Boadie et al., 2007).

2.1.4 HPA axis

The hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis is the main stress system in the human body, and is responsible for stress response adaptation. It is related not only to hormones and peptides, but also to neurotransmitters, such as noradrenaline, dopamine and serotonin (Joëls and Baram, 2009). The hyperactivity of the HPA axis, which is illustrated in figure 2.2, induces an exacerbated release of corticotropin-releasing factor (CRF), thus secreting more ACTH and leading to hypercortisolemia (Keller et al., 2006). Also, HPA axis’ activation is considered to be involved in stress-induced neuronal atrophy. Two types of neuronal plasticity are impacted by chronic stress, with atrophy of dentrites in the CA3 region and repressed neurogenesis of granule cells in the dentate gyrus, in which not only glucocorticoids but also NMDA receptors play a role (McEwen, 1999). Thus, chronic psychosocial stress may lead to inhibition of neurogenesis and even neuronal loss (McEwen and Mangarinos, 2001), which may contribute to cognitive impairment in MDD.
**Figure 2.2:** HPA axis dysfunction in MDD.

Hypotheses for HPA axis dysregulation:

(a): Glucocorticoid receptor (GR) hypothesis: when patients with MDD have to deal with stressful events in their lives, the GR resistance and the reduced negative feedback in depression are the predominant causes of the elevation of corticotropin-releasing factor (CRF), adrenocorticotropine (ACTH) and cortisol.

(b): CRF hyperdrive hypothesis (consists on multiple feedback loops):

- loop 1: the excess of cortisol leads to a downregulation of GR, which fails to contain the hyperactivity of the HPA axis.
- loop 2: CRF may able to enhance its own biosynthesis in the paraventricular nucleus (PVN) of the hypothalamus.
- loop 3: continuous activation of the HPA axis up-regulates the amygdaloid CRF system, stimulating the HPA axis in turn.

Figure copied from: van Den Eede and Claes, 2004.
2.1.5 Gabaergic system

Gamma-Aminobutyric acid (GABA) is the most common inhibitory neurotransmitter in the human brain, and glutamate is involved in GABA’s synthesis. This system is involved in mood disorders, and increased GABAergic tone may lead to antidepressant effects (Brambilla et al., 2003). In the cerebrospinal fluid, and in the plasma, depressed patients have lower levels of GABA (Petty et al., 1992; Berrettini et al., 1983). However, some studies found that, even after antidepressant treatment, plasma levels of GABA remain low. Another finding was that level alterations were not associated with depression severity (Petty et al., 1992, 1993).

Different studies suggest that lower GABAergic functioning may be involved in the pathophysiology of depression (Holland et al., 2010; Zink et al., 2009). With all positive evidence, the focus on GABAergic system has also contributed to research for new antidepressant treatments (Mohler, 2012).

2.1.6 Glutamatergic system

Glutamate is the most abundant excitatory neurotransmitter found in the brain, acting in the “tripartite glutamatergic synapse” (Figure 2.3), involving different glutamate receptors and other targets with therapeutic potentials (Popoli et al., 2011; Zarate et al. 2010). A number of studies have used Magnetic Resonance Spectroscopy (MRS) as an attempt to assess activity of the glutamatergic system in specific regions in the brain (Sanacora et al., 2004; Hasler et al., 2007; Zarate et al., 2010). These studies have reported that these measures vary considerably by brain region, type of mood disorder, course, progression and phase of illness (Sanacora et al., 2012). Glutamate receptors are classified as metabotropic and ionotropic, the last one includes N-methyl-D-aspartate (NMDA), which is the receptor linked to ketamine action as a fast acting antidepressant (Paul and Skolnick, 2003).
Neuronal glutamate (Glu) is synthesized from glucose and glutamine (Gln), which is provided by glial cells. Then, vesicular glutamate transporters (vGluTs) pack glutamate and SNARE complex proteins mediate the merge of vesicles in the presynaptic membrane. In the extracellular space, glutamate is tied to:

- ionotropic glutamate receptors (NMDA receptors - NMDARs)
- AMPA receptors (AMPARs)
- metabotropic glutamate receptors (mGluR1 to mGluR8)

While connected, the receptors initiate various responses, and glutamate is cleared from the synapse through excitatory amino acid transporters (EAATs) on neighbouring glial cells (EAAT1 and EAAT2) and on neurons, in lower intensity (EAAT3 and EAAT4). Within the glial cell, glutamate is converted to glutamine by glutamine synthetase, restarting the glutamate–glutamine cycle.

Figure from: Popoli et al., 2012.
2.1.7 Cytokines

Cytokines are signalling molecules produced by immune cells and are involved in regulating immune responses. Currently, these molecules have been frequently associated with depression and have been possibly linked to anorexia, found in several depressed patients (Schiepers et al., 2005; Anderson, 1996). The communication between the central nervous system and the immune system has lead to a research focus on cytokines’ relationship with MDD. Also, several illnesses that present chronic inflammatory response are frequently known to coexist with MDD. Further, it is well established that there is an association between depressive symptoms and the use of pro-inflammatory cytokines, which are frequently used for the treatment of cancer (Yirmiya at al., 1999; O’Connor et al., 2007). Several factors are related to the role of inflammation in the pathophysiology in depression (Leonard and Maes, 2012), as demonstrated in Figure 2.4.

Figure 2.4: From inflammation to depressive symptoms.

Peripheral cell-mediated immune activation leads to increased interferon (IFN), interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6) and tumor necrosis factor (TNF). With indoleamine (IDO) activation, a depletion of L-tryptophan occurs, leading to depressive symptoms. Also, the production of tryptophan catabolites (TRYCATs) induces depression. At the same time, there is the induction of upregulation of the 5-HT transporter (SERT), diminishing synaptic dopamine (5-HT), which also induces depressive symptoms.

Figure from: Leonard and Maes, 2012.
2.2 Current treatments for depressive episodes

This topic briefly covers the main available treatments for MDD, including some options for treatment resistant depression.

2.2.1 Psychotherapy

It is widely accepted that psychotherapy is a very important tool in the treatment of several psychiatric disorders. The most studied are interpersonal, psychodynamic, cognitive and behavior therapy (Markowitz and Weissman, 2012; Feng et al., 2012; Abbass and Driessen, 2010). Differences found in responses to psychotherapeutic treatments are minor, and overall these approaches appear to be as effective as antidepressant medications for mild and moderate depressive episodes (Cuijpers et al., 2011; Härter et al., 2010).

Psychotherapy should be recommended for acute treatment of depression, together with antidepressant pharmacotherapy, as it may lead to improvement in patients’ quality of life. In treatment resistant depression results are more varied, nevertheless psychotherapy (cognitive, interpersonal and behavioral) should be indicated for these individuals (Ishak et al., 2011; Jakobsen, 2011; Trivedi et al., 2011).

This treatment together with pharmacotherapy usually takes a few weeks to result in significant response (van Calker et al., 2009). Although psychotherapy is very important for patients with cancer (Savard et al., 2006), individuals with end-stage cancer may not fully benefit from this treatment, as their life expectancy is very short.

2.2.2 Pharmacotherapy

Antidepressants are the main treatment for moderate and severe MDD. The selective serotonin reuptake inhibitors (SSRIs), due to their favorable safety and efficacy profiles, are usually the first line antidepressants to be indicated for depressive episodes. Also, although there are several SSRIs, minimal differences can be found amongst them (Souery et al., 2011; Boulenger et al., 2010). According to some authors, serotonin-norepinephrine reuptake inhibitors (SNRIs) are broadly similar to SSRIs in terms of efficacy and safety. Their rates of response and remission are similar, (Weilburg, 2004; Kornstein et al., 2009). Older agents, such as tricyclic antidepressants and monoamine oxidase inhibitors, despite being effective, present more side effects. Even, monoamine oxidase inhibitors (MAOIs) present high
toxicity, and these agents, together with tricyclic antidepressants, have higher incidence of withdrawal when compared to SSRI (Chouinard et al., 1994; Amsterdam and Shults, 2005).

**Table 2.1: Main mechanisms of action of antidepressants.**

<table>
<thead>
<tr>
<th>MONOAMINE REUPTAKE INHIBITORS</th>
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<tbody>
<tr>
<td>Serotonin selective</td>
</tr>
<tr>
<td>Norepinephrine selective</td>
</tr>
<tr>
<td>Dopamine selective</td>
</tr>
<tr>
<td>Mixed reuptake inhibitors</td>
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</tbody>
</table>

<table>
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<tr>
<th>RECEPTOR ANTAGONISTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mianserin, Mirtazapine (5HT2A, 5HT2C, alpha-2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ENZYME INHIBITORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irreversible MAOIs</td>
</tr>
<tr>
<td>Reversible MAOIs</td>
</tr>
</tbody>
</table>

2.2.3 *Electroconvulsive therapy (ECT)*

ECT is a validated treatment for several psychiatric disorders, and consists of neurostimulation by the induction of a grand mal seizure. ECT’s effects seem to rely in changes in the monoaminergic system and in the stress response system. It was first described in 1930’s and over time its efficacy and safety have been extensively studied. ECT’s efficacy is equally consistent for unipolar and for bipolar depressive episodes. (Trevino et al., 2010; Nikisch and Mathé, 2008; Coentre et al., 2009; Bailine et al., 2010). It is usually administered from 1 to 3 times a week, and a meta-analysis with 73 randomized clinical trials showed that there is no difference in efficacy between these time-points (UK ECT Review group, 2003). Although cognitive impairment is more significant for bilateral and high dose ECT, when compared to unilaterial and brief pulse, it is also more effective than lower dose treatment. Also, for continuation electroconvulsive therapy, time between session is increased, which reduces the chances of cognitive side effects (Lisanby et al., 2000; UK ECT Review group, 2003; Trevino et al, 2010).
2.2.4 Repetitive transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) was first described in 1985, and consists in an intense and brief electromagnetic field. It is a noninvasive procedure that is easily tolerated. (Dell'osso et al., 2011; Gershon et al., 2003).

Repetitive TMS is the most used modality of TMS in psychiatry, providing more prolonged results than the single-pulse modality. Also, as ECT, it acts on neuroendocrine and neurotransmitters systems (Baeken and De Raedt, 2011). Treatments are made in a daily basis for 5 days/week, usually for about 2 to 9 weeks. (Dell'osso et al., 2011; Fitzgerald and Daskalakis, 2011). Side effects are less significant than those found in ECT, such as memory impairment, which is usually not present in subjects who received repetitive TMS, except for those who presented a seizure during treatment, which is not a common side effect (Wassermann, 2000; Loo et al., 2008).

Comparatively, although repetitive TMS has fewer side effects than ECT, the latter has higher rates of remission. This fact emphasizes the utility of ECT for treatment resistant patients (Minichino et al., 2012).

2.2.5 Vagus nerve stimulation (VNS)

VNS was originally developed as a treatment for patients with epilepsy that did not respond to pharmacological treatment. Recent data has implicated it as a possible treatment for individuals with depression, although these studies are not controlled. Also, there is the possibility that it plays a role in serotonergic and noradrenergic systems as a mechanism for antidepressant response (Martin and Martín-Sánchez, 2011; Dorr and Debonnel, 2006). A recent meta-analysis showed that, although several studies demonstrate that VNS may be used as a possible treatment for depression, its efficacy is still questionable and it may actually represent a placebo effect (Martin and Martín-Sánchez, 2011). However, a positive aspect of VNS is the lack of cognitive side effects, specially when compared to ECT. As positive mood effects were related to subjects who did not have a high degree of resistance to previous treatments, the use of VNS requires careful consideration (Sackelm et al., 2001).
2.2.6 Deep brain stimulation (DBS)

DBS is an invasive procedure, which involves the insertion of stimulating electrodes in the brain. Its use is still experimental for depression, although its use for Parkinson’s disease and refractory obsessive compulsive disorder is approved by the FDA. It consists of a 2 phase procedure, with the first one performed under local anesthesia and with the patient awake, as the effects of stimulation must be evaluated. In the second phase, the insertion of a pulse generator in the subcutaneous fat, under the patient’s subclavian region, is made under general anesthesia. Then it is connected to cables under the skin, that are connected to the electrodes in the brain (Bell et al., 2009; Malone, 2010; Blomstedt et al., 2010). Studies show positive outcomes for patients with treatment resistant depression, however its action in the brain is not completely clear (Hamani and Nobrega, 2010). In 2005, Mayberg et al. used DBS for patients with treatment-resistant depression, achieving a sudden and sustained improvement in mood, in 66% of these patients. The change in mood seems to be related to a fast deactivation of Broadmann area 25, which is hyperactive in MDD (Mayberg et al., 2005; 1999). However, there are various risks involving this procedure, such as stroke, infection, paresthesia, and anxiety (Holtzheimer and Mayberg, 2010; Malone, 2010; Blomstedt et al., 2010). Thus, severity of refractory depression should be carefully evaluated before considering this treatment.
CHAPTER 3

Review and meta-analysis of available treatments for depression in cancer patients
3.1 Introduction
As stated in chapter one of this thesis, Major Depressive Disorder (MDD) has a high 12-month prevalence in general population, and higher rates are seen in patients with advanced cancer (Scott et al., 2010; Kessler et al., 2005). In addition, depression is the main mental health complication of cancer (Mitchell et al., 2011).

In patients with cancer, those with past history of Major Depression have a higher probability of developing depressive episodes after a diagnosis of cancer. As this finding implicates the possibility of early diagnosis and intervention, depression should be considered a special topic in psycho-oncology and not be misdiagnosed (Mitchell 2011; Mitchell et al., 2011). Moreover, this specific population appears to have a lower level of acceptance of adjuvant chemotherapy (Colleoni et al., 2000), and in those who will commence chemotherapy, prevalence rates of MDD may be as high as 25% (Breen et al., 2009). For patients with cancer, depression can be not only a burden, but also a risk, when considering their psychological symptoms may affect decisions for accepting treatment options.

Proper attention and treatment should be given to these individuals, as antidepressant drugs are effective in palliative care settings. However, these medications seem to be underprescribed for older patients and for those with physical illnesses, despite having MDD (Rayner et al., 2011). The objective of this chapter is to investigate the safety and effectiveness of currently available antidepressant treatments in cancer patients.

3.2 Methods
3.2.1 Search strategy
Electronic databases used were: ClinicalTrials.gov, PsychInfo and Pubmed. In all three databases, search was made with the keywords “treatment” [AND] “depression” [AND] “cancer”. In Pubmed, the limit “Randomized Controlled Trial” was applied. Articles from 1971 until January 2012 and in English, Portuguese, Spanish and Italian were reviewed. Also, citations from screened articles were verified.

3.2.2 Selection criteria
For inclusion in the review, studies had to meet the following criteria:

- double-blind Randomized Controlled Trial (RCT),
• placebo controlled,
• presence of at least 20 subjects in each arm,
• patients fulfilling DSM (Diagnostic and Statistical Manual of Mental Disorders) or ICD (International Classification of Disease) criteria for depressive episode,
• patients with cancer,
• absence of initial antidepressant treatment (or change in current antidepressant treatment) at the same time of intervention,
• psychopharmacologic or psychotherapeutic treatment for depression.

Any type of psychotherapy was considered in this search.

**Figure 3.1:** Selection of trials for meta-analysis.
3.2.3 Analysis

The selected trials for meta-analysis were analyzed with RevMan 5.1 (Cochrane Collaboration, 2008). Data for the outcomes for treatment versus placebo were statistically examined as continuous data, with random effects model, and standardized mean difference for effect measure. The $I^2$ statistic was used to assess heterogeneity of studies.

3.3 Results

After a systematic search 20 articles were selected for review, of which only 2 met criteria for meta-analysis (Costa et al., 1985; van Heeringen and Zivkov, 1996). Both trials investigated the use of pharmacotherapy for depression in cancer patients, and no psychotherapy trial met criteria for meta-analysis. Among the screened studies, several did not meet criteria for MDD, although these quoted “depression”, instead of “depressive symptoms” or “adjustment disorder” in some cases (Bruera et al., 1986; Holland et al., 1998; Roscoe et al., 2005; Savard et al., 2006; Bar-Sela et al., 2007). In other trials, patients were offered individualized treatments, thus not appropriate for comparison with other therapies (Ell et al., 2011; Ell et al., 2008; Strong et al., 2008; Dwight-Johnson et al., 2005). One study compared fluoxetine and amitriptyline for cancer patients, although it met criteria for MDD according to ICD-10 it was not included in meta-analysis because of its lack of placebo group (Pezzella et al., 2001). A psychotherapy trial was excluded because it was not clear if patients could use antidepressant medications or not (Evans and Connis, 1995).

3.3.1 Meta-analysis

Both of the selected articles compared mianserin (a tetracyclic antidepressant) to placebo, both evaluated its response in female patients (van Heeringen and Zivkov, 1996; Costa et al., 1985). Costa et al., 1985 included subjects with general gynecological cancer, and the second study assessed patients with breast cancer. Another difference between studied populations was the cancer’s severity, with Costa et al., 1985 including more severely ill patients (several of them with terminal cancer).

While Costa et al., 1985 showed positive results within 7 days after the initiation of the use of mianserin, van Heeringen and Zivkov, 1996 reported positive outcome starting on day 14 post-treatment. In the first week patients received 30 mg/day of mianserin, in the following weeks the dose was increased to 60 mg/day. Mianserin was given to patients three times a day.
in the trial from Costa et al., 1985 and once a day in van Heeringen and Zivkov, 1996. In these trials, there were no significant differences in side effects when comparing intervention and control group. Also, higher rates of premature terminations were observed in controls, and these were linked to lack of efficacy. Mianserin 60 mg/day was safe when used together with chemotherapy and with radiotherapy in both trials. The low I² value (0%) suggests lack of heterogeneity in these two sets of clinical trial data. The forest plot of these two studies is shown in figure 3.2, and indicates a moderate statistically significant effect size (SMD= -0.68), p= 0.0002.

**Figure 3.2:** Meta-analysis of antidepressant trials in patients with MDD and cancer (HAMD).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mianserin Mean</th>
<th>Mianserin SD</th>
<th>Placebo Mean</th>
<th>Placebo SD</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costa 1985</td>
<td>8.19</td>
<td>6.38</td>
<td>13.2</td>
<td>9.79</td>
<td>-0.60 [-1.07, -0.13]</td>
</tr>
<tr>
<td>van Heeringen 1996</td>
<td>-13.0</td>
<td>7.67</td>
<td>28</td>
<td>11.17</td>
<td>0.78 [-1.33, -0.23]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>64</td>
<td>100.0%</td>
<td>-0.68 [-1.03, -0.32]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 1 (P = 0.61); I² = 0%
Test for overall effect: Z = 3.71 (P = 0.0002)

3.4 Discussion
Although there are many studies considering depressive symptoms and their treatment in cancer patients, most of these did not include patients with Major Depression. These studies frequently included patients with mild symptomatology and/or adjustment disorder (Bruera et al., 1986; Holland et al., 1998; Roscoe et al., 2005; Savard et al., 2006; Bar-Sela et al., 2007), making it impossible to analyse treatment response for MDD in this population. After applying selection criteria, only two studies were suitable for analysis (van Heeringen and Zivkov, 1996; Costa et al., 1985). This shows a deficit of appropriate research in this area, which was an unexpected result. Other reviews that presented similar objectives to this chapter were then assessed, and the included trials in these studies did not meet criteria for Major Depression (Akechi et al., 2008; Williams and Dale, 2006). All the studies that were excluded because of individualized treatment addressed patients with MDD, usually with mild depression. In these trials, treatments included psycho-education, psychotherapy, and the use of antidepressants (Ell et al., 2011; Ell et al., 2008; Strong et al., 2008; Dwight-Johnson et al., 2005). Also, the type of treatment offered to the patient varied according to symptomatology, patient’s choice and level of social support. As provided treatments were different for each
individual, it was not possible to make an analysis comparing the results from these studies with the data available from other research.

The time of onset of MDD plays an important role in the treatment of depression, and chronic illness and lack of response to previous treatments may occur, resulting in individuals with more severe symptomatology and lower response to treatment (Rush et al., 2006). In the selected studies for meta-analysis, Costa et al. analysed subjects with Major Depression succeeding or paralleling cancer diagnosis, while van Heeringen and Zivkov, 1996 did not consider the time of onset of depression. Thus, the second trial may have included patients with chronic or potentially treatment resistant depression as exclusion criteria were not described. Nevertheless, the statistical analysis shows no heterogeneity in the outcomes of the compared studies. Both used Hamilton Depression Rating Scale (HAMD), but the numbers of items used was different in each trial, with 17 items in Costa et al., 1985, and 21 in van Heeringen and Zivkov, 1996. To manage this, standardized mean differences were used as the effect measure.

Mianserin was significantly more effective than placebo in both studies, and adverse events were similar to control group, despite use of cytotoxic drugs. These findings support the use of mianserin in depressed patients with cancer, even for those who are receiving aggressive treatment for malignant neoplastic disease. The fact that Costa et al., 1985 prescribed the medication 3 times a day may reduce patient’s adherence when they are outpatients (Santiago-Rodriguez et al., 2002). Thus, van Heeringen and Zivkov, 1996 presented a better plan of administration, with once-a-day dosing, as mianserin’s half-life is 21 to 61 hours and justifies this posology (Tolvon®-Medsafe). Besides the fact that Costa et al., 1985 reported statistically significant improvement in the intervention group after 7 days, when evaluating response of treatment as a reduction in 50% from baseline scores, both trials present response to mianserin in day 14 after treatment initiation. Neither of the studies presented remission (HAMD 21 and 17 ≤ 7) of symptoms during treatment (Rudolph and Feiger, 2000; Zimmerman et al., 2004).

3.5 Conclusions

Depression is a disorder that is common amongst patients with terminal cancer, however there are only two treatment trials in this population. Mianserin seems to be a safe option for this
group, however its efficacy for remission of depressive symptoms is still not clear. Considerable additional research in this population is required.
CHAPTER 4

Ketamine overview
4.1 Ketamine
Ketamine is an NMDA antagonist with a range of medical and non-medical uses. These will be reviewed in the following section. These different use patterns are associated with different doses (see Figure 4.1).

**Figure 4.1:** Relation between ketamine and its indications.

![Diagram of ketamine indications](image)

Figure from: Glue et al., 2011.

4.2 Ketamine as an anesthetic
Ketamine is a general anesthetic that produces dissociative anaesthesia and is generally used in children, with doses that vary from 9-13 mg/kg when given via intramuscular injection (Ketalar® - Medsafe). It has been used since 1970, most extensively during wars, as it does not require mechanical ventilation when few resources are available (Bonanno, 2002).

4.3 Ketamine as a drug of abuse
Due to its dissociative effects, some people consume it as a drug of abuse, known as “K”, “Special K” and “Cat Valium”, but it has not been associated with dependence syndrome (Britt and McCance-Katz, 2005). There are two extremes related to experiences reported by subjects with a history of ketamine abuse: when the substance is used in lower doses, there is the "K Land", a feeling of extreme relaxation; while at high doses they may experience the "K-hole", which is like a near-death experience, and the feeling of being at high speed in a tunnel, usually described as not a pleasurable experience (Britt and McCance-Katz, 2005; Dillon et al., 2003). In addition, ketamine abusers frequently report: lack of coordination, blurred vision, confusion, visual hallucinations, and dizziness.
Some studies were conducted to assess the effects of this medication when used repeatedly as a “club drug” on a long-term basis. However, as concomitant use of other drugs and alcohol is very common, the results of possible cognition impairment may be due to other substances (Dillon et al., 2003). A finding that is consistent with prolonged ketamine use, is severe lower urinary tract symptoms, with inflammation and hematuria, many times leading to a diagnosis of ulcerative cystitis at biopsy, which shows slow response to treatment. Although it is not a common complication (Mason et al., 2010; Mak et al., 2011), the use of pentosane polysulfate (Shahani et al., 2007), seems to be the best option as a treatment for ulcerative cystitis, together with ketamine cessation. Also, ketamine is often prescribed as an analgesic, and has been studied as a fast acting antidepressant.

4.4 Ketamine as an analgesic

Low doses of ketamine are used for analgesia, commonly between 0.1 and 2 mg/kg. Its use as an analgesic has been studied in children, patients with chronic pain, patients in Emergency Departments, and in postoperative settings. (Laskowski et al., 2011; Dadu et al., 2011; Lester et al., 2010; Deng et al., 2009; Kwok et al., 2004). The duration of analgesic effects closely follows ketamine plasma concentrations. Thus, most studies have found a significant duration in early (30 minutes to 4 hours) pain scores, but some authors have also demonstrated pain relief in late (24 to 72 hours) pain scores (Noppers et al., 2011; Laskowski et al., 2011; Dadu et al., 2011; Kwok et al., 2004).

A recent meta-analysis concluded that ketamine improves the quality of pain control, and decreases opioid consumption (Laskowski et al., 2011).

4.5 Ketamine as a fast acting antidepressant

Ketamine, a noncompetitive antagonist of the glutamate receptor NMDA (N-methyl-D-aspartate), has been suggested as a possible option for treatment resistant Major Depression (Berman et al., 2000; Zarate et al., 2006; aan het Rot et al., 2010).

The mechanism of ketamine’s action on mood is not completely clear, but a signaling cascade leading to synaptogenesis has been studied (Duman et al., 2012). Phelps et al. (2009) have suggested a better response in patients with familial history of alcohol dependence, because
its pathophysiology is also linked to the glutamatergic system. The correlation between depressive symptoms and pain has not been assessed during ketamine use for depression.

In addition to the rapid onset of antidepressant action, there is a sustained response as well, for up to one week. This appears to be unrelated to presence of ketamine (half life ~ 3 hours) or its weakly active metabolite norketamine (half life ~ 2 hours). Recent research suggests this may be attributable to changes in secondary signaling, and not via receptor blockade. Therefore, the activation of a protein kinase, mammalian target of rapamycin (mTOR), may exert the sustained antidepressant effect by the formation of new synapses – synaptogenesis. Also, mGlu2/3 receptors, seem to activate mTOR signalling, but do not seem to be involved in ketamine’s acute antidepressant response (Koike et al., 2011).

The response to ketamine occurs within hours or days, usually with maintenance of response for up to seven days (Zarate et al., 2006; Liebrenz et al., 2009). The doses studied to treat Major Depressive Disorder (MDD) are low, around 0.5mg/kg, and ketamine’s administration is usually made with intravenous infusion over 40 to 60 minutes (Machado-Vieira et al., 2009). Nevertheless, dosage and administration can vary, usually from 0.2mg/kg to 1.5mg/kg, and administration can also be oral and intramuscular (Goforth and Holsinger, 2007; Irwin and Iglewicz, 2010; Paslakis et al., 2010; Messer et al., 2010; Larkin and Beautrais, 2011; Glue et al., 2011). Main side effects found with this treatment are dizziness, psychotomimetic and dissociative effects, which are transient and moderate, dissipating in 80 minutes post infusion (Zarate et al., 2006).

4.6 The possible use of ketamine as a fast acting antidepressant for terminal cancer patients

Considering terminal cancer patients are in their last days or months of life, an improvement in quality of life would mean much, not only for those who are sick, but for their families, who also suffer greatly. Even, the fact that many people with a diagnosis of cancer present pain related to their illness, ketamine may be effective for both, depressive symptoms and pain, as it is frequently used for pain relief in palliative care settings.
CHAPTER 5

Review and meta-analysis of ketamine as a fast acting antidepressant
5.1 Introduction

Major Depressive Disorder (MDD) is a common disease, with a 12-month prevalence of 6.7% and a lifetime prevalence of 16.2% (Kessler et al., 2005). A recent study showed that only around 33% of patients with severe impairment due to MDD receive treatment in mental health services, indicating that the majority of patients with MDD lack proper treatment and follow up (Scott et al., 2010). Even more, in 2004, the World Health Organization (WHO) determined Major Depressive Disorder (MDD) as the main global cause of years lost due to disability. This data shows that there are major, social and economic, impacts related to MDD worldwide.

The classical understanding of MDD neurobiology focused on the monoamines, such as serotonin, norepinephrine and dopamine, and most antidepressants are characterized by interactions with these systems in the brain. More recently, new treatments for depression that interact with non-monoamine systems have been studied (Hashimoto, 2009). The glutamatergic system has been linked to MDD’s pathophysiology in many studies (Hasler et al., 2007; Hashimoto, 2009; Zarate et al., 2010; Sanacora et al., 2012). This might explain the lack of remission of depressive symptoms, which occurs in two-third of patients, with medications that target only monoamine systems (Trivedi et al., 2006).

Ketamine, a noncompetitive antagonist of the glutamate receptor NMDA, is approved in New Zealand as a general anesthetic (Ketalar® - Medsafe). After been used in Vietnam War, its use was very extensive in the 1970’s, with the advantage of rarely causing respiratory depression (Bonanno, 2002). Its applicability is also prominent for analgesia, being widely used in clinical practice (Sih et al., 2011), however it is not approved in New Zealand for this indication.

Ketamine was first studied as a possible antidepressant medication in 1975, when it was compared to imipramine and placebo in rats, and showed positive results with doses of 40 and 80 mg/kg. In this study, ketamine was less effective than imipramine, however it was significantly more effective than placebo (Sofia and Harakal, 1975). Importantly, this research presented ketamine as possible treatment for depression. In 2000 the first clinical trial evaluating ketamine as an antidepressant agent identified a rapid and sustained response, with depression scores being reduced up to 3 days after a single IV infusion (Berman et al., 2000). Since then, several studies have addressed the same objective, usually with similar outcomes (Zarate et al., 2006; aan het Rot et al., 2010).
In this review and meta-analysis, changes in depression ratings after dosing, from case reports and randomized clinical trials, will be analyzed separately. The purpose of this analysis is to determine the effectiveness, speed of onset, and duration of response, after a single infusion of ketamine in patients with MDD.

5.2 Methods

5.2.1 Search strategy
Search was made in Pubmed, PsychInfo, Embase and ClinicalTrials.gov with the use of the keywords “Ketamine” AND “depression”, “bipolar disorder”, OR “mood disorder”. No limits were added, but only articles in English, Portuguese, Spanish and Italian were reviewed. The search was made from any 1957 until present (November 2011). Also, citations in screened articles were checked.

5.2.2 Selection criteria
Studies were required to meet the following criteria:

- patients with a diagnosis of MDD or bipolar disorder (BD) in a depressive episode according to DSM criteria (DSM III, III-R, or IV, American Psychiatric Association, 1980, 1987, 2000),
- presenting moderate or severe depressive symptoms,
- use of ketamine with IV infusion over 40 to 60 minutes,
- dosage of 0.5mg/kg for racemic ketamine, or 0.25 mg/kg for S-ketamine.

Antidepressant response had to be assessed with reliable validated scales, such as Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Rating Scale for Depression (HAMD), Beck Depression Inventory (BDI), Hospital Anxiety and Depression Scale (HADS) and/or The Quick Inventory of Depressive Symptomatology (QIDS-SR16).

Studies were analyzed to reach a consensus on what variables could be accepted within the studies. Thus, patients with no history of ketamine treatment, and patients who had prior ketamine use (for any treatment) could be included in review and meta-analysis. Current medication could be suspended or maintained. Four studies used ketamine as an induction agent for patients with MDD who were treated with electroconvulsive therapy (ECT). These were not included in the review, as the use of ECT was a complicating factor.
Data were included from case series and placebo-controlled randomized clinical trials (RCTs).

**Figure 5.1**: Selection of studies for review and meta-analysis for ketamine as a fast acting antidepressant.
5.2.3 Analyses

RCTs were analyzed using RevMan 5.1 (Cochrane Collaboration, 2008). Placebo versus treatment were compared as an intervention review, with continuous data, random effects as the analysis model and mean difference as effect measure along with 95% confidence intervals.

Case reports and case series were compared with results from one of the RCTs. The choice of using Diazgranados et al. data for this comparison was due to this study reporting changes in three different depression scales. In total, 12 case reports/series results were compared to the abovementioned RCT. Most of them (7) utilized MADRS for depressive symptoms assessment, with a minority using HAMD and BDI.

5.3 Results

Fifteen studies were selected for comparison and review. All were published, with the first one published in 2000 (Berman et al., 2000). There were 3 RCTs that analyzed the outcome for ketamine as a fast-acting antidepressant.

5.3.1 Randomized clinical trials

Zarate et al. presented a crossover study design with 18 patients, and Diazgranados et al. used a very similar study design 4 years latter. The primary diagnosis was the main difference between these studies, as the first included only patients with MDD and the second, patients with bipolar depression (BD).

Demographic and clinical characteristics of RCTs are presented on Table 5.1, where time to response and time to relapse are clearly different when comparing the two most recent trials, although the percentage of response and remission are very similar, 71% and 30%, respectively. Unfortunately, the Berman et al., 2000 did not provide enough data for this comparison. A substantial difference while comparing Berman et al., 2000 with the abovementioned studies is that one of the inclusion criteria was depressive episode, with no distinction between a diagnosis of MDD or BD, which may lead to different outcomes for these patients’ subgroups.
MADRS and HAMD were used as standard scales for depressive symptoms, which led the possibility of a comparison of these trials using HAMD. There is a clear significant response to ketamine when compared to placebo, and its best response occurs within 1 to 3 days in most patients. As Berman et al., 2000 did not report depressive symptoms scores after 3 days, subsequent results from other studies are not presented in figure 5.2, but will be discussed.

All RCTs reported ketamine side effects, with special attention to dissociative and euphoric symptoms, which disappeared within 110 minutes after infusion and were not correlated to change in depressive symptoms. Also, changes in vital signs were not clinically significant and did not require any intervention. Most prevalent reactions were: dissociation, dizziness, and changes in blood pressure and pulse.

Rates of response and side effects after infusion were very similar in all three studies, and the fastest mood improvement could be observed within 40 minutes after infusion (Diazgranados et al., 2010). Significant response (reduction of 50% or more in depression scales) within 24 hours was met in all RCTs (Berman et al., 2000; Zarate et al., 2006; Diazgranados et al., 2010) and it lasted from 3 up to 7 days in most patients, with some of these subjects (11.7% in Zarate et al., 2006) maintaining response for at least 2 weeks. In general, ketamine was effective for 50% of patients in Berman et al., 2000 and for 71% in the other two RCTs.

**Table 5.1:** Demographic and clinical data for RCTs.

<table>
<thead>
<tr>
<th>Study</th>
<th>Berman et al., 2000 (n=9)</th>
<th>Zarate et al., 2006 (n=18)</th>
<th>Diazgranados et al., 2010 (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression scales used</td>
<td>HDRS; BDI</td>
<td>HDRS21; BDI</td>
<td>HDRS17; BDI; MADRS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>37 (± 10)</td>
<td>46.7 (± 11.2)</td>
<td>47.9 (± 13.1)</td>
</tr>
<tr>
<td>Gender</td>
<td>55.5% female</td>
<td>66% female</td>
<td>67% female</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>88.9% recurrent MDD *</td>
<td>Recurrent MDD</td>
<td>BD - depressive episode</td>
</tr>
<tr>
<td>Medication wash-out</td>
<td>yes</td>
<td>yes</td>
<td>yes **</td>
</tr>
<tr>
<td>Treatment resistant</td>
<td>data not available</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Length of illness (years)</td>
<td>data not available</td>
<td>23.7 (± 12.5)</td>
<td>27.6 (± 11.2)</td>
</tr>
<tr>
<td>Length of current episode (months)</td>
<td>data not available</td>
<td>33.6 (± 37.4)</td>
<td>15.1 (± 13.3)</td>
</tr>
<tr>
<td>Time to significant improvement</td>
<td>240 minutes***</td>
<td>110 minutes</td>
<td>40 minutes</td>
</tr>
<tr>
<td>Time to relapse (days)</td>
<td>7 to 14</td>
<td>7 days</td>
<td>3 days</td>
</tr>
<tr>
<td>Response during treatment (%)</td>
<td>50</td>
<td>71</td>
<td>71</td>
</tr>
<tr>
<td>Remission during treatment (%)</td>
<td>26</td>
<td>29</td>
<td>31</td>
</tr>
</tbody>
</table>

* 8 patients with recurrent MDD and 1 patient with BD – depressive episode.
** Patients were allowed to use lithium and/or valproate.
*** First assessment after baseline.
Figure 5.2: HAMD mean values for Diazgranados et al., 2010, Zarate et al., 2006, and Berman et al., 2000.
5.3.2 Case reports and case series

All patients had a diagnosis of Major Depressive Disorder, and most of them presented a treatment resistant depressive episode, even though this information was not provided in one study (Valentine et al., 2011) and was not applicable to one patient (Stefanczyk-Sapieha et al., 2008).

In all cases, as in the RCTs, patients who responded to ketamine infusion did so within the first 24 hours. In most of them, improvement in depressive symptoms could be noted in the first 4 hours (Stefanczyk-Sapieha et al., 2008; Liebrenz et al., 2009; Machado-Vieira et al., 2009; Phelps et al., 2009; Denk et al., 2011; Ibrahim et al., 2011; Salvadore et al., 2011; Valentine et al., 2011). Time to relapse was not clear in some cases (Machado-Vieira et al., 2009; Phelps et al., 2009; Denk et al., 2011; Ibrahim et al., 2011; Salvadore et al., 2011), but when available they varied from 3 to 22 days, as summarized in Table 5.2.

Results from most cases corroborate to findings in RCTs. Figure 5.3 illustrates the analysis between results from case reports/series and outcomes from Diazgranados et al., 2010 using HAMD scale. In the first 168 hours, studies from Paul et al., 2009 and Liebrenz et al., 2009 more clearly illustrate the similar outcomes when compared to the RCT. This is due to the timing of post-infusion assessments, which made the comparisons of ratings possible. Antidepressant response to ketamine is also illustrated in Figure 5.4, with MADRS for depressive ratings, and in Figure 5.5, with BDI as depression scale for assessments.
<table>
<thead>
<tr>
<th>Study</th>
<th>Caric et al., 2007 (n=1)</th>
<th>Stefanczyk-Sapieha et al., 2008 (n=1)</th>
<th>Liebrenz et al., 2009 (n=1)</th>
<th>Denk et al., 2011 (n=1)</th>
<th>Paul et al., 2009 (n=2)</th>
<th>Valentine et al., 2011 (n=10)</th>
<th>Salvadore et al., 2011 (n=14)</th>
<th>Machado-Vieira et al., 2009 (n=23)</th>
<th>Phelps et al., 2009 (n=26)</th>
<th>Mathew et al., 2010 (n=26)</th>
<th>Ibrahim et al., 2011 (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression scales used</td>
<td>BDI</td>
<td>HDRS21; BDI</td>
<td>BDI; HDRS21</td>
<td>BDI; HDRS21</td>
<td>HDRS25</td>
<td>MADRS</td>
<td>MADRS</td>
<td>MADRS</td>
<td>MADRS; HDRS17; BDI</td>
<td>MADRS; QIDS-SR16</td>
<td>MADRS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>32</td>
<td>50</td>
<td>55</td>
<td>56</td>
<td>54.5</td>
<td>41.7 (± 12)</td>
<td>50.1 (± 10.4)</td>
<td>43.9 (± 13.9)</td>
<td>43.5 (± 14.1)</td>
<td>48.2 (± 11.8)</td>
<td>46.5</td>
</tr>
<tr>
<td>Gender</td>
<td>male</td>
<td>male</td>
<td>male</td>
<td>female</td>
<td>60% female</td>
<td>50% female</td>
<td>35.8% female</td>
<td>39% female</td>
<td>39% female</td>
<td>39% female</td>
<td>40% female</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>MDD</td>
<td>MDD</td>
<td>MDD</td>
<td>MDD; recurrent MDD</td>
<td>MDD</td>
<td>MDD</td>
<td>MDD</td>
<td>MDD</td>
<td>MDD</td>
<td>MDD</td>
<td>MDD</td>
</tr>
<tr>
<td>Medication wash-out</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>NA</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Treatment resistant</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>NA</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Length of illness (years)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>7.5</td>
<td>21.2 (± 17.4)</td>
<td>28.9 (± 14.2)</td>
<td>24.8 (± 12.4)</td>
<td>23.7 (± 12.5)</td>
<td>29.7</td>
<td>25.3</td>
</tr>
<tr>
<td>Length of current episode</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>3.3 years (± 4.3)</td>
<td>13.2 years (± 15)</td>
<td>1.7 years (± 2.26)</td>
<td>6.8 years (± 8.6)</td>
<td>24.3 years (± 16.3)</td>
<td>8.3 years</td>
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<tr>
<td>Time to significant improvement</td>
<td>24 hours</td>
<td>2 hours</td>
<td>24 hours</td>
<td>NA</td>
<td>24 hours</td>
<td>1 hour</td>
<td>4 hours</td>
<td>3.83 hours</td>
<td>3.83 hours</td>
<td>2 hours</td>
<td>3.83 hours</td>
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<tr>
<td>Time to relapse (days)</td>
<td>10</td>
<td>3</td>
<td>7</td>
<td>NA</td>
<td>6</td>
<td>7</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>22</td>
<td>NA</td>
</tr>
<tr>
<td>Response during treatment</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>% NA</td>
<td>50%</td>
<td>yes</td>
<td>% NA</td>
<td>47.8%</td>
<td>43%</td>
<td>73%</td>
</tr>
<tr>
<td>Remission during treatment</td>
<td>yes</td>
<td>no</td>
<td>not clear</td>
<td>yes</td>
<td>no</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>26%</td>
<td>50%</td>
<td>NA</td>
</tr>
</tbody>
</table>
Figure 5.3: Cases outcomes and Diazgranados et al., 2010 (HAMD).

A) Mean of each selected study for HAMD comparison (0- 168 h)

B) Mean of each selected study for HAMD comparison (0- 24 h)

C) Mean of each selected study for HAMD comparison (0- 6 h)

Ketamine effect on depression in case reports and case series over time according to changes in HAMD ratings. Graphs (B) and (C) show changes over shorter time intervals.
Figure 5.4: Cases outcomes and Diazgranados et al., 2010 (MADRS).

A) Mean of each selected study for MADRS comparison (0-24 h)

B) Mean of each selected study for MADRS comparison (0-4 h)

Ketamine effect on depression in case reports and case series over time according to changes in MADRS ratings. Graph (B) shows changes over a shorter time interval.
Figure 5.5: Case outcome and Diazgranados et al., 2010 (BDI).
5.3.3 Meta-analysis

In all selected RCTs, a significant antidepressant response was found within 230-240 minutes post-infusion. Also, this response was sustained for at least 3 days. HAMD ratings were relatively stable after 230-240 minutes post-infusion in the outcomes from Berman et al., 2000 and Diazgranados et al., 2010. However, Zarate et al., 2006 had a continuous decrease in depression ratings until day 3 post-infusion (Figure 5.2).

Although Diazgranados et al., 2010 presents a significant treatment effect at 40 minutes after ketamine infusion, the two other RCTs do not have a significant response within this time. Thus, the test for overall effect in the meta-analysis results was not statistically significant (Figure 5.6 A). Diazgranados et al., 2010 presented a faster response than other RCTs and a shorter duration of ketamine’s antidepressant effects. The possible reasons for this difference only in Diazgranados et al., 2010 will be discussed further.

At 230–240 minutes post-infusion, the three studies are homogeneous and the change in HAMD scores compared with placebo are substantial and highly statistically significant (5.6 B). At days 1, 2, and 3 post-infusion there are also substantial reductions in HAMD scores (Figures 5.6 C, D, E). Heterogeneity was evident at days 1, 2, and 3 (highest I² scores), which was due to data from Diazgranados et al., 2010.
Figure 5.6: Meta-analysis results based on change in HAMD scores.

A) Antidepressant response 40 minutes post-infusion.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>ketamine Mean</th>
<th>SD</th>
<th>Total</th>
<th>placebo Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berman, 2000</td>
<td>-8.4</td>
<td>8</td>
<td>8</td>
<td>-1.8</td>
<td>1.3</td>
<td>8</td>
<td>-1.6</td>
<td>-5.21, 2.0</td>
<td>2000</td>
</tr>
<tr>
<td>Diazgranados, 2010</td>
<td>-8.33</td>
<td>3.96</td>
<td>16</td>
<td>-3.24</td>
<td>3.96</td>
<td>16</td>
<td>-2.54</td>
<td>-5.59, -0.23</td>
<td>2010</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>42</td>
<td></td>
<td>42</td>
<td>100.0%</td>
<td></td>
<td>42</td>
<td>-2.17</td>
<td>-4.60, 0.27</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau^2 = 1.29; Chi^2 = 2.73, df = 2 (P = 0.25); I^2 = 27%
Test for overall effect: Z = 1.75 (P = 0.08)

B) Antidepressant response 230 – 240 minutes post-infusion.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>ketamine Mean</th>
<th>SD</th>
<th>Total</th>
<th>placebo Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berman, 2000</td>
<td>-4.08</td>
<td>8</td>
<td>8</td>
<td>-0.8</td>
<td>7.9</td>
<td>8</td>
<td>-1.11</td>
<td>-7.90, 5.73</td>
<td>2000</td>
</tr>
<tr>
<td>Zarate, 2006</td>
<td>-12.05</td>
<td>5</td>
<td>17</td>
<td>-2.5</td>
<td>6.25</td>
<td>17</td>
<td>-3.76</td>
<td>-10.20, -0.76</td>
<td>2006</td>
</tr>
<tr>
<td>Diazgranados, 2010</td>
<td>-8.59</td>
<td>3.96</td>
<td>16</td>
<td>-2.06</td>
<td>4.08</td>
<td>16</td>
<td>-2.54</td>
<td>-5.53, -0.51</td>
<td>2010</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>42</td>
<td></td>
<td>42</td>
<td>100.0%</td>
<td></td>
<td>42</td>
<td>-8.22</td>
<td>-10.96, -5.49</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau^2 = 15.67; Chi^2 = 9.57, df = 2 (P = 0.008); I^2 = 79%
Test for overall effect: Z = 3.44 (P = 0.0006)

C) Antidepressant response 1 day post-infusion.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>ketamine Mean</th>
<th>SD</th>
<th>Total</th>
<th>placebo Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berman, 2000</td>
<td>-5.1</td>
<td>8</td>
<td>8</td>
<td>-0.5</td>
<td>3.3</td>
<td>8</td>
<td>-4.1</td>
<td>-6.94, 2.74</td>
<td>2000</td>
</tr>
<tr>
<td>Zarate, 2006</td>
<td>-13.72</td>
<td>5</td>
<td>17</td>
<td>-2.68</td>
<td>6.25</td>
<td>17</td>
<td>-7.36</td>
<td>-13.00, -1.73</td>
<td>2006</td>
</tr>
<tr>
<td>Diazgranados, 2010</td>
<td>-7.36</td>
<td>3.9</td>
<td>17</td>
<td>-2.54</td>
<td>3.96</td>
<td>16</td>
<td>-4.82</td>
<td>-9.48, -0.26</td>
<td>2010</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>42</td>
<td></td>
<td>42</td>
<td>100.0%</td>
<td></td>
<td>42</td>
<td>-9.61</td>
<td>-14.14, -5.05</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau^2 = 15.67; Chi^2 = 9.57, df = 2 (P = 0.008); I^2 = 79%
Test for overall effect: Z = 3.44 (P = 0.0006)

D) Antidepressant response 2 days post-infusion.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>ketamine Mean</th>
<th>SD</th>
<th>Total</th>
<th>placebo Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berman, 2000</td>
<td>-12.8</td>
<td>8</td>
<td>8</td>
<td>-0.8</td>
<td>7.9</td>
<td>8</td>
<td>-1.6</td>
<td>-5.21, 2.0</td>
<td>2000</td>
</tr>
<tr>
<td>Zarate, 2006</td>
<td>-12.05</td>
<td>5</td>
<td>17</td>
<td>-2.5</td>
<td>6.25</td>
<td>17</td>
<td>-3.76</td>
<td>-6.47, -0.23</td>
<td>2006</td>
</tr>
<tr>
<td>Diazgranados, 2010</td>
<td>-8.59</td>
<td>3.96</td>
<td>16</td>
<td>-2.06</td>
<td>4.08</td>
<td>16</td>
<td>-2.54</td>
<td>-5.53, -0.51</td>
<td>2010</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>42</td>
<td></td>
<td>42</td>
<td>100.0%</td>
<td></td>
<td>42</td>
<td>-8.22</td>
<td>-10.96, -5.49</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau^2 = 1.17; Chi^2 = 2.76, df = 2 (P = 0.25); I^2 = 28%
Test for overall effect: Z = 5.90 (P < 0.00001)

E) Antidepressant response 2 days post-infusion.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>ketamine Mean</th>
<th>SD</th>
<th>Total</th>
<th>placebo Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berman, 2000</td>
<td>-13.2</td>
<td>8</td>
<td>8</td>
<td>-0.2</td>
<td>7.9</td>
<td>8</td>
<td>-1.6</td>
<td>-5.21, 2.0</td>
<td>2000</td>
</tr>
<tr>
<td>Zarate, 2006</td>
<td>-11.22</td>
<td>5.125</td>
<td>17</td>
<td>-2.5</td>
<td>6.25</td>
<td>17</td>
<td>-6.94</td>
<td>-8.72, -5.21</td>
<td>2006</td>
</tr>
<tr>
<td>Diazgranados, 2010</td>
<td>-6.94</td>
<td>4.08</td>
<td>16</td>
<td>-2.06</td>
<td>4.08</td>
<td>16</td>
<td>-2.54</td>
<td>-4.88, -0.68</td>
<td>2010</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>42</td>
<td></td>
<td>42</td>
<td>100.0%</td>
<td></td>
<td>42</td>
<td>-7.79</td>
<td>-11.81, -3.76</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau^2 = 7.46; Chi^2 = 5.21, df = 2 (P = 0.07); I^2 = 62%
Test for overall effect: Z = 3.79 (P = 0.0001)
5.4 Discussion

Several RCTs and multiple case reports/series have consistently showed ketamine to be a rapidly acting antidepressant. Researches with ketamine as a fast acting antidepressant have not been limited to intravenous administration; some authors have explored alternative routes, such oral (Irwin and Iglewicz., 2010; Paslaskis et al., 2010) and intramuscular routes (Glue et al., 2011). The optimal dose and whether it can be used repeatedly, is also not clear. For example, 0.2mg/kg of ketamine in bolus has demonstrated to be effective for suicidal ideation (Larkin and Beautrais, 2011). Even more, another study has contributed to these findings, with promising results for suicidal ideation in treatment resistant MDD, with 0.5mg/kg of ketamine administered over 40 minutes intravenously (Price et al., 2009). To evaluate dose response, Glue et al., 2011 compared results for the same patients (n=2) when receiving 0.5, 0.7, and 1mg/kg of intramuscular ketamine. A better outcome was found with the dosage of 1mg/kg, leading us to the question: Would patients, who did not respond to ketamine in other studies, have a significant response with higher doses? Further investigation is required to establish how this possible treatment could get to its best results.

In this review, S (+)-ketamine 0.25mg/kg was considered for comparison with racemic ketamine 0.5mg/kg, as the first is considered to be twice as potent as the racemic mixture (Hering et al., 1994). According to some studies, S(+) and racemic ketamine do not differ significantly on hemodynamic changes (White et al., 1985; Ihmsen et al., 2001), being as safe as racemic ketamine.

The studies analyzed included treatment resistant patients, and their positive outcomes may indicate an option for this population. Although there were differences in patients’ response when analyzing MDD and depressive episode in BD (possibly due to the different diagnoses, use of lithium and valproate in patients with BD, and/or severity of illness) both groups had generally similar mood responses (Zarate et al., 2006; Diazgranados et al., 2010). Group with BD may possibly have had faster responses but shorter durations of positive effects (Diazgranados et al., 2010). This requires future study A similar methodology with a complete medication washout could exclude the medication factor for analyses. In all studies, difficulty in maintaining blinding of groups and researchers was clear, as ketamine side effects (such as euphoria and depersonalization) were easily recognizable. Also, in all RCTs, depersonalization was not correlated to change in depressive symptoms, indicating that psychomimetic effects are not required to a positive result.
Continuous infusions (with the same methodology used for the first infusion) were present in 3 of the reviewed cases. Stefanczyk-Sapieha et al., 2011 presented a patient who had a shorter response (24 hours) to ketamine after a second infusion, while the first infusion provided depression response for up to 3 days. By the other hand, Paul et al., 2009 and Liebrenz et al., 2009 presented outcomes in a second infusion that were similar to the first ketamine administration.

Types of rating scales, and timing of ratings, varied across reports. The MADRS and HAMD were the most commonly used depression scales. Ideally, time points from baseline to 40 minutes, 120 minutes, 240 minutes, 1 day, 3 days, 7 days and more days if response is maintained may provide important observations for future reviews, as this information was not reported in many studies. Results were consistent between 4 hours and 3 days post-infusion, and may be of important consideration for future studies.

5.5 Conclusions
Ketamine has been extensively studied as an antidepressant in the last decade. There are promising data in terms of rapidity of mood improvement in RCTs involving patients with refractory unipolar and bipolar depression. Data from case reports and case series are generally similar to those reported in the RCTs. Significant areas that require clarification include what the optimal dose and route of administration are, and whether ketamine can be used in patients with less refractory mood disorders. Although mood responses in unipolar and bipolar depression appear to be similar, it may be prudent to only include one or other patient group in future RCTs, and not to combine them. Methodologically, it would be important for investigators to use similar rating scales and time-points, to maximize comparisons between studies.
CHAPTER 6

Protocol for testing ketamine in Major Depressive Disorder in terminal cancer patients
6.1 Introduction

This protocol was based on studies that present positive results of ketamine as a fast acting antidepressant (Diazgranados et al., 2010; Zarate et al., 2006; Berman et al., 2000). Considering that patients with terminal cancer have a short life expectancy and high rates of depression, ketamine may be a possible treatment for this population. This trial has been approved by the Lower South Regional Ethics Committee and is a registered trial -ACTRN 1261000101107. It is one of the first trials of ketamine for depression in patients with cancer. In particular, this group of patients may benefit from the analgesic effects of ketamine, as pain rates are also high in this population. Its design addresses a number of key clinical questions in a scientifically rigorous manner, including:

1- Confirmation that low dose ketamine is an effective antidepressant in a palliative care cancer population;
2- Demonstration that repeated doses are safe and effective;
3- Characterization of dose-response profile, particularly as this patient group may be physically debilitated.

The trial consists of 3 stages, each one concerning to the abovementioned objectives, and all stages take place in a hospital room, with emergency support if needed.

6.2 Stages

6.2.1 Stage 1

Open label characterization of safety and efficacy of 1 mg/kg single dose IM ketamine in 10 depressed patients with cancer. If an antidepressant response can be demonstrated in 5/10 patients, with tolerable side effects, subjects are eligible to proceed to stages 2 and 3. A 50% improvement in depressive symptoms in MADRS is considered response to treatment (Zimmerman et al., 2004; Zarate et al., 2006).

6.2.2 Stage 2

Open label characterization of safety and efficacy of 1mg/kg repeat dose IM ketamine in 10 depressed patients with cancer. Subjects that present a sustained response, with tolerable side effects, are eligible to keep receiving treatment if symptoms recurred. Patients had the option to drop out of the trial at any time.
6.2.3 Stage 3

Double blind, randomized, dose-response assessment of single dose IM ketamine in 30 depressed patients with cancer. Injection dose might be 0.1mg/kg, 0.5mg/kg or 1mg/kg. Subjects can decide not to participate on Stage 3 at any time.

6.3 Inclusion and exclusion criteria

6.3.1 Inclusion criteria:

- ECOG performance status ≤ 3 (Table 6.1),
- MADRS >20 (Figure 6.1),
- Comparative Pain Scale ratings ≤ 5 (Table 6.2),
- presence of terminal (incurable) cancer,
- life expectancy of at least 3 months,
- aged 20 to 65 years-old,
- adequate hematological, renal and hepatic function,
- signed informed consent.

MADRS scores >20 are standard for entry into antidepressant clinical trials (Machado-Vieira et al., 2009; Diazgranados et al., 2010). Patients with mild to moderate levels of pain were eligible, but patients with severe pain were excluded, as there might be a bias in patients’ outcomes (as a response in depressive symptoms might be due to pain relief). Subjects could be confined to bed or chair more than 50% of waking hours and with limited self-care, but not totally confined to bed or chair or completely disabled, as this would limit data collection. Further, considering the risk of arrhythmias, slow urinary excretion, and slow hepatic metabolism, cardiac, renal and hepatic function had to be adequate. Also, patients had to provide written informed consent.

6.3.2 Exclusion criteria:

- presence of psychosis or delirium,
- presence of cerebral metastasis,
- current use of ketamine,
- current use of another experimental medication,
- any antidepressant treatment started within the last 4 weeks.
Considering psychosis and delirium, as there is a lack of reasoning and judgment, patients would not be able to give informed consent, and the use of ketamine in these population, might cause a worsening in their symptoms (Ketalar- Medsafe). The presence of cerebral metastasis may cause neurologic and psychiatric symptoms and change the permeability of the blood-brain barrier (Chakrabarti et al., 2011; Lee 2010; Abbott et al., 2006). The last might lead to a different dosage of the medication acting in the brain. Current use of ketamine was not allowed because it might be already impacting patient’s mood, and experimental medication because of possible unknown influence in depressive symptoms. Subjects could not be receiving any new treatment for depression in the last 4 weeks (including psychotherapy), to avoid positive results that might not be linked to ketamine administration. Entry criteria assessment sheets can be found in attachments.

**Table 6.1:** ECOG performance status.

<table>
<thead>
<tr>
<th>Grade</th>
<th>ECOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>

Table from: Oken et al., 1982.
Figure 6.1: MADRS.

Montgomery-Asberg Depression Scale (MADRS)

Instructions: The ratings should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5). It is important to remember that it is only rare occasions that a depressed patient is encountered who cannot be rated on the items in the scale. If definite answers cannot be elicited from the patients, all relevant clues as well as information from other sources should be used as a basis for the rating in line with customary clinical practice. This scale may be used for any time interval between ratings, be it weekly or otherwise, but this must be recorded.

1. Apparent Sadness
   Representing dejection, gloom and despair, (more than just ordinary transient low spirits) reflected in speech, facial expression, and posture.
   Rate on depth and inability to brighten up.
   0  No sadness
   1  Looks dispirited but does brighten up without difficulty.
   2  Appears sad and unhappy most of the time.
   3  Looks miserable all the time. Extremely despondent.

2. Reported Sadness
   Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, dejection, or feeling of being beyond help without hope. Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.
   0  Occasional sadness in keeping with the circumstances.
   1  Sad or low but brightens up without difficulty.
   2  Pervasive feelings of sadness or gloominess.
   3  Mood is still influenced by external circumstances.
   4  Continuous or unvarying sadness, misery or despondency.

3. Inner Tension
   Representing feelings of ill-defined discomfort, edginess, inner turmoil mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.
   0  Placid. Only reflecting inner tension.
   1  Occasional feelings of edginess and ill-defined discomfort.
   2  Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
   3  Unrelenting dread or anguish. Overwhelming panic.

4. Reduced Sleep
   Representing the experience of reduced duration or depth of sleep compared to the subject’s own normal pattern when well.
   0  Sleeps as usual.
   1  Slight difficulty getting off or sleep slightly reduced light or fitful sleep.
   2  Sleep reduced or broken by at least two hours.
   3  Less than two or three hours slept.

5. Reduced Appetite
   Representing the feeling of loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.
   0  Normal or increased appetite.
   1  Slightly reduced appetite.
   2  No appetite. Food is tasteless.
   3  Needs persuasion to eat.

6. Concentration Difficulties
   Representing difficulties in collecting one’s thoughts mounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.
   0  No difficulties in concentrating.
   1  Occasional difficulties in collecting one’s thoughts.
   2  Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
   3  Unable to read or converse without great effort.

7. Inability to Feed
   Representing a difficulty getting started or slowness initiating and performing everyday activities.
   0  Hardly any difficulty in getting started. No sluggishness.
   1  Difficulties in starting activities.
   2  Difficulties in starting simple routine activities which are carried out with effort.
   3  Complete inactivity. Unable to do anything without help.

8. Pessimistic Thoughts
   Representing thoughts of guilt. Inferiority, self-reproach, sinfulness, remorse and guilt.
   0  No pessimistic thoughts.
   1  Fluctuating ideas of failure, self-reproach or self-deprecation.
   2  Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.
   3  Delusions of rain, remorse or unremendable sin. Self-accusations which are absurd and unshakable.

9. Suicidal Thoughts
   Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and the preparations for suicide. Suicidal attempts should not in themselves influence the rating.
   0  Enjoying life or takes it as it comes.
   1  Wary of life. Only fleeting suicidal thoughts.
   2  Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
   3  Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

Total Score: __________________________
Table 6.2: The Comparative Pain Scale.

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No pain. Feeling perfectly normal.</td>
</tr>
<tr>
<td>1 Very Mild</td>
<td>Very light barely noticeable pain, like a mosquito bite or a poison ivy itch. Most of the time you never think about the pain.</td>
</tr>
<tr>
<td>2 Discomforting</td>
<td>Minor pain, like lightly pinching the fold of skin between the thumb and first finger with the other hand, using the fingernails. Note that people react differently to this self-test.</td>
</tr>
<tr>
<td>3 Tolerable</td>
<td>Very noticeable pain, like an accidental cut, a blow to the nose causing a bloody nose, or a doctor giving you an injection. The pain is not so strong that you cannot get used to it. Eventually, most of the time you don't notice the pain. You have adapted to it.</td>
</tr>
<tr>
<td>4 Distressing</td>
<td>Strong, deep pain, like an average toothache, the initial pain from a bee sting, or minor trauma to part of the body, such as stubbing your toe real hard. So strong you notice the pain all the time and cannot completely adapt. This pain level can be simulated by pinching the fold of skin between the thumb and first finger with the other hand, using the fingernails, and squeezing real hard. Note how the simulated pain is initially piercing but becomes dull after that.</td>
</tr>
<tr>
<td>5 Very Distressing</td>
<td>Strong, deep, piercing pain, such as a sprained ankle when you stand on it wrong, or mild back pain. Not only do you notice the pain all the time, you are now so preoccupied with managing it that your normal lifestyle is curtailed. Temporary personality disorders are frequent.</td>
</tr>
<tr>
<td>6 Intense</td>
<td>Strong, deep, piercing pain so strong it seems to partially dominate your senses, causing you to think somewhat unclearly. At this point you begin to have trouble holding a job or maintaining normal social relationships. Comparable to a bad non-migraine headache combined with several bee stings, or a bad back pain.</td>
</tr>
<tr>
<td>7 Very Intense</td>
<td>Same as 6 except the pain completely dominates your senses, causing you to think unclearly about half the time. At this point you are effectively disabled and frequently cannot live alone. Comparable to an average migraine headache.</td>
</tr>
<tr>
<td>8 Utterly Horrible</td>
<td>Pain so intense you can no longer think clearly at all, and have often undergone severe personality change if the pain has been present for a long time. Suicide is frequently contemplated and sometimes tried. Comparable to childbirth or a real bad migraine headache.</td>
</tr>
<tr>
<td>9 Excruciating Unbearable</td>
<td>Pain so intense you cannot tolerate it and demand pain killers or surgery, no matter what the side effects or risk. If this doesn't work, suicide is frequent since there is no more joy in life whatsoever. Comparable to throat cancer.</td>
</tr>
<tr>
<td>10 Unimaginable Unspeakable</td>
<td>Pain so intense you will go unconscious shortly. Most people have never experienced this level of pain. Those who have suffered a severe accident, such as a crushed hand, and lost consciousness as a result of the pain and not blood loss, have experienced level 10.</td>
</tr>
</tbody>
</table>
6.4 Informed consent

For each subject, a consent form, which was written in lay terms, was given and thoroughly explained. After having complete understanding of the trial, patients had up to 2 days to think, talk to friends, family, other doctors, etc. Further, individuals were reassured that they could withdraw their consent at anytime, without needing to explain or giving a reason for it. It was also emphasized that withdrawing would not affect their health treatment in any way. A copy of the informed consent is attached to this thesis (Appendix I).

6.5 Assessments

In all three stages, two main scales were used to access depression ratings (MADRS; Figure 6.1) and pain (The Comparative Pain Scale; Table 6.2). These were performed at screening (20 minutes before injection) and 1, 2, 4, 24, 48, 72, and 120 hours post-injection. Other scales used in the study were: Hospital Anxiety and Depression Scale (HADS; Figure 6.2) and Demoralization Scale (Figure 6.3), which were performed at baseline and 24 hours post-injection.

MADRS is a well known and validated scale to access depression (Phelps et al., 2009; Diazgranados et al., 2010). Also, it includes all DSM-IV criteria for MDD (Montgomery and Asberg, 1979). Its main difference when compared to HADS is that the last one does not include physical symptoms in its rating. Therefore, HADS is often used in patients with cancer and other somatic diseases (Zigmond and Snaith, 1983; Bjelland et al., 2002). Demoralization Scale consists of 24 questions with a total score ranging from 0 to 96, and a score > 30 is considered high. This suggests the presence of adjustment disorder or even a depressive episode (Kissane et al., 2004). Considering the fact that cancer patients usually experience pain, Comparative Pain Scale was used to assess its intensity. This scale consists of scores that range from 0 to 10, considering 0 as “no pain” and 10 as “unspeakable pain”. Also, it is going to be useful to check correlation between pain and depression, as many studies report their high correlation, even though its neural basis is not yet elucidated (Bair et al., 2003; Strigo et al., 2008).

Vital signs were assessed on baseline, 1, 2, 3, and 4 hours post-injection on stage 1 and 3. At stage 2, if patients maintain a stable and normal blood pressure, after 3 repeat dosing, assessments are made on baseline, 1, and 2 hours post-injection. Vital signs assessments are repeated at any time if patients present distressing side effects or report possible cardiac
symptoms, such as tachycardia, palpitation, tachypnoea or bradypnea, feeling of syncope, etc. Side effects are monitored all the time, for up to 2 or 4 hours, depending on the stage in which patients are.

Figure 6.2: HADS.
**Figure 6.3:** The Demoralization Scale.

For each statement below, you are asked to indicate how strongly the statement has applied to you over the last two weeks by circling the corresponding number. Over the past two weeks how often have you felt...

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Seldom</th>
<th>Sometimes</th>
<th>Often</th>
<th>All the Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. There is a lot of value in what I can offer others.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. My life seems to be pointless.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. There is no purpose to the activities in my life.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. My role in life has been lost.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. I no longer feel emotionally in control.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. I am in good spirits.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. No one can help me.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. I feel that I cannot help myself.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9. I feel hopeless.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10. I feel guilty.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11. I feel irritable.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>12. I cope fairly well with life.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>13. I have a lot of regret about my life.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>14. Life is no longer worth living.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>15. I tend to feel hurt easily.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>16. I am angry about a lot of things.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>17. I am proud of my accomplishments.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>18. I feel distressed about what is happening to me.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>19. I am a worthwhile person.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>20. I would rather not be alive.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>21. I feel sad and miserable.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>22. I feel discouraged about life.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>23. I feel quite isolated or alone.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>24. I feel trapped by what is happening to me.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

**Thank You!**

Note when scoring: items 1, 6, 12, 17 and 19 are reverse scored.
6.6  Statistical Analysis

All data were listed, and summary statistic (mean, SD) calculated. Change scoring in MADRS and pain ratings were calculated by subtracting scores post-dosing from baseline values. Correlation of change in pain and depression scores was made using Pearson’s method.

6.7  Conclusions

This protocol presents similarities with previous studies, however it adds pain scores. Ketamine has analgesic properties, thus correlation between pain and depression responses can be assessed. Results found with this methodology may shed light to the relationship between pain and depression as they are frequently coexistent and some authors claim their interdependence (Mongini et al., 2007; Waters et al., 2004). Also, another aspect of this protocol is the possibility of repeated ketamine injections for Major Depression.
CHAPTER 7

Acute and maintenance IM ketamine for a depressed patient with terminal cancer
7.1 Introduction

This chapter describes a patient enrolled in a clinical trial to assess the effects of Ketamine in MDD in patients with terminal cancer. The trial was approved by the Lower South Regional Ethics Committee, Southern Health District Board and Dunedin School of Medicine, University of Otago, New Zealand (ACTRN 12610001011077). The patient participated in Stages 1 and 2 of this trial.

7.2 Case Report

A. is a 37-year-old patient with metastatic ovarian carcinoma. She has a diagnosis of Major Depressive Disorder (MDD) and Dysthymic Disorder since she was 18 years old. Although she has used various antidepressants, A. reports her mood was never fully improved. For the past 10 years she presented a worsening of her depressive symptoms, which persisted at the time of her entrance in the study, including: irritability, low mood, lack of energy, easy crying, sleep disturbance, poor concentration, intense and excessive feelings of guilt and suicidal ideation. Her domestic circumstances were very stressful, due to concern about the future of her 11-year-old daughter and the lack of support from her friends and family.

The most distressing symptoms of her metastatic ovarian carcinoma, was visceral pain in the right iliac fossa, which started 4 months after her diagnosis of cancer. Her diagnosis was made in January of 2010, and her pain was in the same location as a metastatic tumor, which was about 7cm in diameter on palpation in November of 2011. For pain intensity assessment, The Comparative Pain Scale, with a range from 0 to 10 was used (Harich- online resource). She also has a previous history of drug abuse, which started when she was 17 years old, with the use of cannabis. At 21 years old, she used cocaine, heroin and methamphetamine. With time, her drug of choice was methamphetamine. In 2004 she was able to quit the use of drugs after starting methadone for opioid substitution therapy. A. has been abstinent since then. There is also a family history of alcoholism (both grandfathers and one uncle).

When first assessed for this ketamine trial, A. was taking venlafaxine 150 mg/day, quetiapine 50 mg/day, and methadone 95 mg/day. All her medications were continued during her ketamine treatment with doses unchanged. She was also receiving chemotherapy once a week (a combination of carboplatin and gemcitabine). After informed consent was given, she received ketamine 1 mg/kg IM open-label, and her dosing was performed on an outpatient basis in a hospital clinic.
The Montgomery-Asberg Scale (MADRS) was used as the main scale to assess her depression severity. This scale consists of 10 items, each one scored from 0 to 6 (total range from 0 to 60). Scores > 20 are standard for entry into antidepressant clinical trials (Diazgranados et al., 2010; Machado-Vieira et al., 2009). Mood and pain assessments were obtained at baseline (20 minutes before injection), 1, 2, 4, 24, 48, 72 and 168 hours post-injection. The Hospital Anxiety and Depression Scale (HADS) is often used in patients with cancer or other somatic diseases, and its optimal cut off scores are > 7 on both HADS-A and HADS-D for anxiety and depression respectively (Zigmond and Snaith, 1983; Bjelland et al., 2002). No physical symptoms are included in this scale, permitting a focus on affective and behavioral symptoms (Zigmond and Snaith, 1983). The Demoralization Scale (DS) consists of 24 questions (with a total score range from 0 to 96), and a score > 30 is considered high (Kissane et al., 2004). HADS and DS were assessed at baseline and 24 hours.

The patient’s initial MADRS score was 24, dropping to 7 one hour after the first dose of ketamine (Figure 7.1 A). For the next 2 days her MADRS remained low (lowest score was 5 points), with improvement in all MADRS items. Depressive symptoms returned after 6 - 7 days post-injection. Also, her pain score was reduced within 15 to 20 minutes after the first ketamine dose, however her scores for pain returned to baseline within 24 hours (Figure 7.1 A). A. reported moderate but tolerable dissociative side effects, such as depersonalization and immobility, starting 5 minutes post-injection and resolving within 45 to 60 minutes. Vital signs were unchanged.

The patient subsequently received repeat ketamine doses at intervals of 8 to 10 days, based on return of her depressive symptoms, initially receiving treatment when her depressive scores were higher than 20. Her mood response to repeat injections has been identical each time, in terms of speed, magnitude of response and duration (Figure 7.1 B). Onset of pain relief continued to be fast, nevertheless the durability of analgesic response was much more variable (Figure 7.1 C). Reported side effects were similar in timing of onset and intensity to those noted after the first dose of ketamine. Scores on HADS and DS demonstrated consistent improvement in her mood symptoms (Figure 7.2). Correlation between changes in depression and pain scores over time were initially robust, but decreased over the next 168 hours (Figure 7.3).
Figure 7.1: Antidepressant and analgesic response to IM ketamine 1mg/kg.

A) Antidepressant and analgesic effects after first IM injection of ketamine 1 mg/kg – Stage 1.

B) Consistency of antidepressant response after 6 injections.

C) Inconsistency in pain response after 24 hours after 6 injections.
Figure 7.2: Changes in HADS and Demoralization scales with IM ketamine 1 mg/kg.
**Figure 7.3:** Pearson’s correlation between change in depression and pain scores.

Correlation was based on the first 6 injections, which were not administered in a weekly basis, but according to recurrence of depressive symptoms.
The improvement in the patient’s mood was noticed by her family, even on the phone when talking to her sister. Also, her daughter noted she was calmer and more patient. In visits to A.’s house to collect mood assessments these reported comments were verified.

After a total of 7 injections, A. asked for dosing before recurrence of her depressive symptoms. As her depression was in remission for 7 days, with MADRS starting to increase 8 to 10 days post-injection, the patient started to receive ketamine on a weekly basis. With the treatment at every 7 days, following the same protocol for the previous injections, she obtained remission of MDD. There were two occasions, when her MADRS scores increased to > 10, when she was unable to attend the clinic appointments, with delays between dosings of 8 and 9 days respectively. Using this method of administration, her depression has continued to respond to weekly ketamine dosing over 8 months (Figure 7.4). During this time, the patient had changes in her cancer treatment, without demonstrating changes in her response to ketamine injections for her depression. Except for the two time-points abovementioned, the patient has maintained remission, with no complaints of cognitive impairment. Also, side effects (such as depersonalization, inability to move, and dizziness) were less notable with this dosage regimen.
Figure 7.4: Antidepressant response to repeated dosing, at intervals of 7 days and > 7 days.
7.3 Discussion

This is the second case report with ketamine being used as a fast acting antidepressant in patients with a diagnosis of cancer (Stefanczyk-Sapieha et al., 2008). The present report extends information on ketamine use by assessing simultaneous effects on mood and pain ratings, and by demonstrating the reproducibility of the antidepressant response with multiple repeated doses.

The patient had remission (MADRS < 10; Hawley et al., 2002) of her depressive symptoms within one hour after receiving the first injection of IM ketamine at a dose of 1mg/kg. This finding is consistent with previous research, which noted a rapid mood response for more than 70% of patients within 24 hours (aan het Rot et al., 2010; Zarate et al., 2006). A.’s improvement was sustained for 6 to 7 days, with depression scores gradually returning to baseline, which was also consistent with recent studies (aan het Rot et al., 2010; Berman et al., 2000). Some authors have reported the fact that some patients present a sustained mood response for even longer periods of time (aan het Rot et al., 2010; Messer and Haller, 2010).

Most previous researchers used ketamine intravenously (usually over 40 minutes) rather than IM injections, as used in this case. In a recent study, pharmacokinetic simulations suggested comparable exposures after IV infusion and IM injection (Glue et al., 2011). In the present case, the dose used (1mg/kg) was higher than those administered in most published cases, which used 0.5mg/kg of Ketamine (aan het Rot et al., 2010; Zarate et al., 2006; Berman et al., 2000), and the optimal dose for MDD treatment is still unclear. Changes in the Demoralization Scale and HADS ratings were consistent with the MADRS data.

The analgesic effects of ketamine were also fast in onset, however its durability was variable after 24 hours post-injection. Changes in pain scores and depression ratings were most closely correlated 1 hour post-dosing (Pearson’s $r = 0.61$) with progressively weaker correlations over the next 168 hours. This finding suggests that the sustained antidepressant effects of ketamine are mediated differently from the mechanisms associated with immediate changes in pain and mood. One possible mechanism may be via stimulation of mTOR signaling and via synaptic protein synthesis (Duman et al., 2012).

A. did not experience tachyphylaxis to repeated ketamine injections, as demonstrated by the consistent improvement in her mood scores at every injection and by her sustained remission with weekly dosages. Messer et al., 2010 reported similar findings, with maintenance of remission in one patient for more than 15 months, with ketamine infusions given every 3 weeks. In contrast, it should be noted that Liebrenz et al., 2009 reported a different response
to a second ketamine infusion, with the same route of administration and dose for both, in one patient. The subject in their study had worsening of depressive symptoms 2 days after the second infusion, while after the first dosage the patient had presented a response sustained for 7 days. This data suggests that individual differences may influence mood responses to repeated doses of ketamine.

According to Phelps et al., 2009 the patient’s positive mood response to ketamine might be related to her family history of alcoholism, affecting 2 of her second-degree relatives. In the abovementioned study, ketamine response was compared between 2 groups of depressed subjects, one with family histories of alcoholism and the second without. Their results suggest that a family history of alcohol dependence may be a marker for mood response to an NMDA antagonist but, as this was the first study analyzing family history of alcohol dependence in patients with MDD, it requires confirmation.

Administration by IM injection may have benefits when compared to IV infusion, such as:

- faster administration,
- less discomfort to patients,
- reduced costs, without the need of a pump for the infusion.

These aspects, together with her positive outcome, support the use of IM injections in future research.

7.4 Conclusions

The use of a 1 mg/kg IM dose was well tolerated and achieved remission of depressive symptoms. The optimal dose for the treatment of MDD has not yet been established (Glue et al., 2011), and further data are required to define this. Considering that standard oral antidepressants have a delay in their response of usually 4 to 6 weeks, these findings may justify the use of IM ketamine as an antidepressant agent for a population with a short life expectancy, as described in this case report. Also, this case illustrates the potential for repeated use of ketamine, with maintenance of response and no complications during the treatment. Future research is also needed to clarify the role of ketamine as a long-term treatment option.
CHAPTER 8

Conclusions
8.1 Conclusions

Ketamine, administered intramuscularly in a dose of 1mg/kg was effective as an antidepressant agent. In the patient presented in this thesis, there was an improvement in mood within 1 hour post-injection, which was maintained for up to one week, consistent with results from published data from RCTs and case reports/ case series (Chapter 5).

Although most studies used intravenous administration of ketamine, intramuscular injections have also been used successfully. This route of administration was chosen due to its simpler and more convenient administration, with no need of an infusion pump. This choice made its administration easy and well accepted by the patient. Side effects, such as depersonalization, dizziness, and elevation in blood pressure, were reported, but none of them required treatment in the previous studies reviewed in this thesis, nor in the case report presented here. Also, side effects disappeared within two hours post-administration. This indicates that ketamine administration should be done in a hospital, but patients might be safely discharged after side effects are gone and vital signs are stable. The patient’s antidepressant response was consistent after repeated injections, with no evidence of tolerance. Although this may be an inconvenient treatment method for long term use, the observation that tolerance was not developed means that long-term use can be considered if no other treatments are effective or tolerated. The positive outcome with injections on a weekly basis, with maintenance of remission of symptoms (which means the patient did not meet criteria for MDD with continuous injections) is very promising.

Although other studies must be done in this population, the promising results for ketamine has indicate that it can be a useful medication for terminal cancer patients with depression. One unexpected finding from this thesis was the very limited number of high quality treatment trials from depression in cancer patients (Chapter 3). Potentially, the availability of a new drug treatment may stimulate research in this area. For patients with terminal cancer, time is probably the most pressing factor when they have depressive episodes, as current antidepressant treatments take a relatively long time for therapeutic effect to occur. Then, a fast acting antidepressant would be important to improve quality of life in terminal cancer individuals with depression, and provide their family more positive memories after their loved ones are gone.
CHAPTER 9

References
9.1 References


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Appendix I

Informed consent
RAPID DEPRESSION TREATMENT IN PATIENTS WITH CANCER – INFORMATION SHEET FOR INTERESTED INDIVIDUALS

Thank you for showing an interest in this project. Please read this information sheet carefully before deciding whether or not it is appropriate for you to take part. Your participation is entirely voluntary. If you decide not to take part, it will not affect any future care or treatment. If you do agree to take part in the study, you are free to withdraw at any time without having to give a reason and this will in no way affect any future health care. The following sheet explains what the study will involve.

Please read the information in the rest of this information sheet carefully.

What is the Aim of the Project?

Rates of depression in patients with terminal cancer are high - up to 70% have clinically significant symptoms of depression, and up to 25% may meet criteria for major depression. Although antidepressant drugs can be effective in patients with terminal cancer, they are slow to work (there can be a delay of up to 6-8 weeks between starting dosing and mood improvement), and are therefore not that helpful to patients needing rapid relief. Having an antidepressant that lifts mood fast might be very helpful, especially to improve quality of life for patients with cancer and their families.

Low doses of ketamine, a drug that blocks the brain chemical glutamate, can improve symptoms of depression rapidly (within 2 hours), for up to 7 days (see Figure). This effect can be sustained by use of repeated doses. Ketamine is commonly used to treat pain. The doses we plan to use in this study are similar to doses used for treating pain, and are safe and well tolerated. Ketamine has been used extensively in man for over 40 years.

Ketamine was originally developed as an anaesthetic drug, and is also commonly used to treat pain. The doses used for anaesthesia are about 10 times greater than the doses used for treating pain. The doses we plan to use in this study are similar to those used to treat pain.

We have local experience with ketamine in major depression and can report similar positive outcomes to those described above.

We plan to test the antidepressant effects of ketamine in 3 stages:

Stage 1: Participants will receive a single intramuscular injection of ketamine (1mg/kg). We will assess changes in your mood over the next 7 days.
Stage 2: Participants who have shown improvement in their depression can receive further intramuscular injections of ketamine. We anticipate this will be once weekly (based on how long the effects of ketamine last).

Stage 3: Participants will receive one of three dose levels of ketamine (0.1, 0.5 or 1.0mg/kg). We will assess changes in your mood over the next 7 days.

We will advise you what stage we are inviting you to participate in.

What Type of Participants are we looking for?

- Men and women, aged between 20-65 years;
- You can have any type of cancer, and a life expectancy at least 3 months;
- You must be medically stable;
- You must have significant symptoms of depression (we will measure this using a rating scale).

You can discuss your suitability to participate in more detail with your doctor/oncologist.

What will Participants be Asked to Do?

Day 1: At the first visit, we will collect details about you and your cancer. We will rate your mood. Ketamine will be given as an injection into your buttock. After the ketamine injection we will rate your mood several times out to 4 hours, and record any side effects you might experience. This part of the study will take about 4 ½ hours, and will occur in an outpatient clinic in the oncology department.

Day 2, 3, 4, 8: We will again rate your mood and record any side effects. Each of these visits will last no more that 15-20 minutes, and could take place at the hospital or at your house (whatever is most convenient for you). There may be fewer scheduled visits for patients enrolled in Stage 2, where repeated ketamine doses are used.

What Are The Side-Effects And Risks?

The most common side effects of ketamine include feeling woozy in the head, drowsy, and dizzy; numbness in the face and tongue; having your arms and legs feeling heavy or not connected to you; feeling unsteady on your feet. These side effects are most noticeable around 10-20 minutes after injection, and are gone after 40-60 minutes.

Risks include: discomfort from an intramuscular injection; the side effects from the ketamine injection (as described above). The ketamine injection does not improve mood in some patients: if this occurs, your doctor can discuss alternative treatments for your depression with you. Even in those patients where the ketamine helps lift your depression, further injection(s) may be needed, and/or other antidepressant treatments.
Will I be paid for my participation on this project?
No. The benefits will come from the treatment provided by the medicine used in the study.

Will it be any costs for my participation on this project?
No. It will be no costs for yourself or family regarding this project.

Can Participants Change their Mind and Withdraw from the Project?
You may withdraw from this project at any time and without any disadvantage of any kind.

What Data or Information will be Collected and What Use will be Made of it?
We are collecting information about changes in your mood after ketamine, including how quickly this occurs, and how long it lasts for. We will record any side effects you report, and other safety measures (blood pressure, etc). We will analyse this information statistically to determine the following:

- how effective ketamine is as an antidepressant,
- how fast it works,
- how long the effects last for, and
- what is the best dose to use.

The results will be published in an international scientific journal. The data included in this publication will in no way be linked to any specific participant and your identity will not be recorded with the data. If you want access to your personal data later you will need to record the identification number used for your particular tests. You are most welcome to request a copy of the results of the project should you wish.

The data collected will be securely stored in such a way that only those involved in the research program will be able to gain access to it. At the end of the project any personal information will be destroyed immediately except that, as required by the University’s research policy, any raw data on which the results of the project depend will be retained in secure storage for ten years, after which it will be destroyed.

What if you have any Questions?
If you have any questions about our project, either now or in the future, please feel free to contact us via the details given below.
Contact Details:

Professor Paul Glue, Dept of Psychological Medicine; tel 03 470 3867; email: paul.glue@otago.ac.nz

Associate Professor David Perez, Dunedin Public Hospital; tel 03474 0999; email: david.perez@southernhbr.govt.nz

Dr Claudia Zanicotti, Dept of Psychological Medicine; tel 03 470 9451; email: claudiagrrott@hotmail.com

ACC statement:

In the unlikely event of a physical injury as a result of your participation in this study, you will be covered by the accident compensation legislation with its limitations. If you have any questions about ACC please feel free to ask the researcher for more information before you agree to take part in this trial.

Health and disability statement:

If you have any queries or concerns about your rights as a participant in this study you may wish to contact a Health and Disability Services Consumer Advocate, telephone: (03) 479 0265 or freephone 0800 37 77 66 or freefax 0800 2787 7678 (0800 2 SUPPORT) or email advocacy@hdc.org.nz If there is a specific Maori issue/concern please contact Linda Grennell at 0800 377 766.

This project has been reviewed and approved by the Lower South Regional Ethics Committee (LRS/10/11/050).
RAPID DEPRESSION TREATMENT IN PATIENTS WITH CANCER–

CONSENT FORM FOR PARTICIPANTS

I have read the “RAPID DEPRESSION TREATMENT IN PATIENTS WITH CANCER” Information Sheet concerning this project. All my questions have been answered to my satisfaction. I understand that I am free to request further information at any stage.

I know that:

1. I am free to withdraw from testing at any time without any disadvantage;
2. I understand the data will be destroyed at the conclusion of the project but any raw data on which the results of the project depend will be retained in secure storage for ten years, after which it will be destroyed;
3. I understand the results of the project may be published but my anonymity will be preserved.

I agree to take part in this project.

.............................................................................
(Full name)

.............................................................................
(Signature) ..................................................
(Date)

.............................................................................
(Full name)

.............................................................................
(Doctor’s / Researcher Signature)  (Date)

This project has been reviewed and approved by the Lower South Regional Ethics Committee
(LRS/10/11/050)

Rapid depression treatment in cancer patients/Information Sheet, Consent Form  Ver 20/12/10
Appendix II

Case report – in press (page proofs)
Mood and Pain Responses to Repeat Dose Intramuscular Ketamine in a Depressed Patient with Advanced Cancer

Claudia G. Zanicotti, M.D.,1 David Perez, M.D., FRACP,2 and Paul Glue, M.D., FRCPsych1

Abstract
Depression is highly prevalent in patients with advanced cancer, commonly affecting quality of life. Considering the response delay with conventional antidepressants and the short life expectancy for these patients, treatments for Major Depressive Disorder (MDD) with faster onset of action are desirable. In this case report, a female patient with metastatic ovarian cancer reported rapid and sustained response to intramuscular (IM) injections of ketamine (1mg/kg). Over a course of six treatments, her mood response was identical on each occasion and provided remission of her depressive symptoms. Pain was also improved, although for a shorter duration. These findings support the use of IM ketamine as a possible antidepressant option for this population.

Introduction
The prevalence of Major Depressive Disorder (MDD) in adult patients with cancer is high. In those receiving palliative care the rate is considered approximately 15%,1,2 and the rate of severe depression in advanced cancer patients is around 11%.3 Current antidepressants target the monoaminergic system and typically have a slow onset of action. More recently, there has been an awareness of the role of the glutamatergic system in the pathophysiology of mood disorders.4 Ketamine – a noncompetitive NMDA (N-Methyl-D-Aspartate) antagonist – has recently been identified as a possible fast-acting treatment for MDD.5,6 Moreover, the use of ketamine for pain in advanced cancer patients might also pose an extra benefit as an adjuvant therapy.7

The following case report describes a patient enrolled in an ongoing clinical trial, which was approved by the Lower South Regional Ethics Committee, Southern Health District Board and Dunedin School of Medicine, University of Otago, New Zealand. This trial is registered (ACTRN 12610001011077).

Inclusion criteria are diagnosis of MDD (DSM IV-TR);9 MADRS > 20; presence of incurable cancer; written informed consent; life expectancy > 3 months; age between 20 and 65 years old; ECOG status < 4; and adequate hepatic, renal, and hematological function. Exclusion criteria are current use of ketamine; presence of psychosis or delirium; presence of cerebral metastases; Comparative Pain Scale10 score of > 5; and any antidepressant treatment started within the previous 4 weeks.

Case Report
A. is a 36-year-old female patient with metastatic ovarian carcinoma. She has had MDD and Dysthymic Disorder diagnosed since she was 18 years old. Even though she has tried various antidepressants, the patient reports that her mood was never completely improved. For the past 10 years she had a worsening of her depressive symptoms, which persisted at the time of her first assessment, and included low mood, lack of energy, irritability, easy crying, sleep disturbance, lack of concentration, excessive feelings of guilt, and passive death wish. Her domestic circumstances were stressful, due to concern about the future of her 11-year-old daughter and the lack of support from her ex-boyfriend (the child’s father) and her family.

Along with depression, A. has had visceral pain for ~8 months in the right iliac fossa, in the same location as a metastatic tumor, which is about 7cm in diameter on palpation. For pain intensity assessment, The Comparative Pain Scale,10 with a range from 0 (no pain) to 10 (short unconsciousness),

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was used. She also has a previous history of drug abuse (methamphetamine), being abstinent for more than six years, and a family history of alcoholism (both grandfathers and one uncle).

When first assessed for ketamine treatment, A. was taking venlafaxine 150 mg/day, quetiapine 50 mg/day, and methadone 95 mg/day. All her medications were continued during the ketamine treatment with doses unchanged. She was also receiving weekly chemotherapy (combination of carboplatin and gemcitabine). After informed consent was given, she received ketamine 1 mg/kg IM open-label. Dosing was performed on an outpatient basis in a hospital clinic.

MADRS was used as the main scale to assess her depression scores. This is a validated scale that includes most DSM-IV criteria for MDD.6 It consists of 10 items, each one scored from 0 to 6 (total range from 0 to 60). Scores >20 are standard for entry into antidepressant clinical trials.6,11 Mood and pain assessments were obtained at baseline (20 minutes before injection), 1, 2, 4, 24, 48, 72, and 168 hours post-injection. The Hospital Anxiety and Depression Scale (HADS)12,13 is often used in patients with cancer or other somatic diseases, and its optimal cut-off scores are >7 on both HADS-A and HADS-D for anxiety and depression respectively. There are no physical symptoms in its assessment, lessening the effects of physical illness over depression and anxiety symptoms.13 The Demoralization Scale (DS)14 consists of 24 questions (total score range = 0 to 96), and a score >30 is considered high. HADS and DS were assessed at baseline and 24 hours.

The patient’s initial MADRS score was 24, which dropped to 7 one hour after the first dose of ketamine. For the next two days her MADRS remained low (5 points), with improvement in all MADRS scale items. Her depressive symptoms returned within 6 to 7 days post-injection. Also, her pain score was reduced within a few minutes after the first ketamine dose, however returned to baseline within 24 hours (Figure 1A). She reported moderate but tolerable dissociative side effects, such as depersonalization and immobility, that started 5 minutes post-injection and which resolved within 45 to 60 minutes. Vital signs were unchanged.

The patient has subsequently received repeat ketamine doses at intervals of 7 to 8 days, based on return of her depressive symptoms. Her mood response to repeat injections has been identical each time, in terms of speed and magnitude of response (Figure 1B). Onset of pain relief continued to be rapid, however the durability of analgesic response has been much more variable (Figure 1C). Reported side effects were similar in timing of onset and intensity to those noted after the first dose. Scores on HADS and DS showed consistent improvement in her mood symptoms (Table 1).

The improvement in the patient’s mood was noticed by her family, even on the phone while talking to her sister. Also, her daughter said she was calmer and more patient. In visits to A.’s house to collect mood assessments these reported findings were verified.

Discussion

This is the second case report of ketamine being used as a fast acting antidepressant in patients with cancer.15 The present report extends information on ketamine use by assessing simultaneous effects on mood and pain ratings, and by demonstrating the reproducibility of the antidepressant response with repeated dosing.

The patient had remission of her depressive symptoms within one hour after receiving the first injection of IM ketamine (MADRS <10).15 This is consistent with previous research that noted a rapid mood response for more than 70% of patients within 24 hours.17,18 The patient’s improvement was sustained for 6 to 7 days, with a gradual return to baseline in her depression scores, which is also consistent with the literature.19 Some authors have noticed that there are patients with a mood response sustained for even longer periods of time.19,20 Most previous studies have used an IV infusion over 40 minutes rather than IM injections, as used in this case. Pharmacokinetic simulations suggest comparable exposures after IM injection and IV infusion.21 The dose used in this case (1 mg/kg) is higher than the dose used in most published cases (0.5 mg/kg)17,18,19 and the optimal dose for treating
differences in mood responses to repeated doses of ketamine. A second injection. This suggests that there may be individual patient, with worsening of depressive symptoms two days after not yet been established.

Achieved remission of MDD. However, the optimal dose has nature research.

Need of a pump for the infusion. These aspects, together with costs, without the need of a pump for the infusion. These aspects, together with immediate changes in pain and mood. One possible mechanism may be via stimulation of mTOR signaling and via synaptic protein synthesis.

Our patient had no tachypnoea, as demonstrated by the consistent improvement in her mood scores at every injection. Messer and colleagues reported similar findings, with maintenance of remission in one patient for more than 15 months, with ketamine infusions given every three weeks. It should be noted that Liebrenz and colleagues reported similar findings, with consistent improvement in her mood scores at every injection.

According to Phelps and colleagues, the patient’s positive mood response might be related to her family history of alcoholism, affecting two of her second-degree relatives. In the above mentioned study the authors compared ketamine response in two groups of depressed patients, one with family histories of alcoholism and the second without. Their results suggest that a family history of alcohol dependence may be a marker for mood response to an NMDA antagonist but, as this was the first study with depressed patients, it requires further studies for confirmation.

Administration by IM injection may have benefits when compared to IV infusion, such as faster administration, with less discomfort to the patient; and reduced costs, without the need of a pump for the infusion. These aspects, together with her positive outcome, support the use of IM injections in future research.

The use of a 1 mg/kg IM dose was well tolerated and achieved remission of MDD. However, the optimal dose has not yet been established. Further data are required to determine optimal use of ketamine as a fast-acting antidepressant. Considering that antidepressants available today have a delay in their response of usually 4 to 6 weeks, these findings may justify the use of IM ketamine as an antidepressant agent for a population with a short life expectancy, as described in this case report.

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Authors Disclosure Statement

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