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"TREATMENT-RESISTANT DEPRESSION" AND USE OF INTRAVENOUS KETAMINE AND INTRANASAL ES-KETAMINE

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ABSTRACT

Treatment-Resistant Depression (TRD) is defined as a major depression that does not respond to two or more antidepressant therapies (adequate for dosage and duration). TRD is associated with a high incidence of comorbidities, more marked impairment of socio-occupational activities, and greater risks of relapse, recurrence and suicidality.

The high incidence of TRD has addressed scientific research to identify new molecules that have an antidepressant action and use different mechanisms of action than those used by molecules based on the monoaminergic theory. Ketamine is one of these molecules. Ketamine is a non-competitive antagonist of the glutamate N-methyl-D-aspartate (NMDA) receptor, mainly used in clinical practice as an anaesthetic and analgesic agent. It has recently been shown that ketamine exerts an antidepressant activity with few and transient side effects at sub-aesthetic doses.

Esketamine is the S-enantiomer of ketamine. In the USA, ketamine has been recently approved by the Food and Drug Administration for treating depression failed to respond to two or more antidepressant therapies.

Although the complete molecular mechanism of ketamine is complex and partly unknown, some studies hypothesized that NMDA blockade induces a modulation of several synaptogenic signalling pathways, such as brain-derived neurotrophic factor (BDNF), thus improving synaptic plasticity of the prefrontal cortex and hippocampus.

This observational and retrospective study evaluated the clinical response to repeated administrations of intravenous ketamine (*off-label* use) or intranasal esketamine in a sample of 16 patients affected by TRD and treated at the Psychiatric Clinic of the Siena University Hospital. The efficacy was assessed using the Montgomery-Asberg Depression Rating Scale (MADRS). An experienced clinician administered MADRS before and during each treatment cycle of ketamine or esketamine.

From our findings, both intravenous ketamine or intranasal S-ketamine therapies improve TRD symptoms, especially on the core symptoms of depression, such as sadness, apathy, inability to concentrate and fatigue, as demonstrated by the reduction of 27% in the total MADRS score. The most significant effects were achieved in the first four weeks of administration. The main limitation of the study is due to the small sample size.

To date, ketamine and S-ketamine are among the few, innovative, efficacious, and safe drug therapies for the treatment of TRD.

Introduction

The term depression derives from the Latin *de-premo*, which means to lower or bring to a lower level. Commonly, the term depression has a broader semantic meaning as it includes multiple aspects of everyday life. Geographically, the term depression defines a formation lower than sea level or surrounding areas. In other fields, depression is used to indicate a negative relative pressure, an extratropical cyclone, or a crisis period in the economy.

The medical meaning of the term depression, derived from the more technical "Major Depression," has forcefully entered daily life after the awareness campaigns promoted on this subject by the World Health Organization (WHO). Since 2012, the WHO has launched a series of initiatives to increase knowledge about major depression, thus breaking down its stigma. The World Mental Health Day was established in 2012. Since 2017, the "*Depression: let's talk*" campaign has been introduced.

In everyday language, the term depression is overused because it has become synonymous with a sense of laziness, listlessness, boredom, sadness, and distrust. These events represent the expected emotional response of an individual to unpleasant circumstances or daily repetitiveness. Therefore, the term depression is used to report symptoms far from underlying symptomatology or a properly depressive experience (Rossi Monti, 2002).

To date, major depression is considered one of the most common diseases worldwide, as it affects more than 300 million people of all ages and represents a significant cause of disability. It is estimated that this pathology will be more frequent, reaching the sad record of the most widespread disease in the world in 2030 (WHO, 2017).

The overall well-being of an individual is determined by several factors, among which Mental Health plays a crucial role. A recent New Zealand proposal would overcome the use of the gross domestic product (GDP per capita) as a measure of the nation's wellbeing moving to the wellbeing budget (literally "welfare budget"). The first action to reach this goal is to improve the well-being of the population through the strengthening of the Mental Health (Government of New Zealand, 2019).

Given the similar incidence of mental disorders in New Zealand and European populations, New Zealand can be considered a valuable and important model for a better and more effective management of people's mental health.

The first references to depressive pathology date back to the ancient Egyptians, in 2600 BC. Some authors described a sort of living pain that led to suicide in the Nile (Infrasca, 2007). In 400 BC, Hippocrates coined the term melancholia defining this state as a condition linked to temperament, not a disease. He correlated it to an imbalance of black bile, one of the four humors of the human organism, localizable in the spleen, and treatable assuming mandrake and hellebore. Galen, another pillar of Hellenic medicine, in the second century AD, slightly modified this theory. He linked neuro-pathologies to a hypochondriac state due to the secretion, by the liver, stomach, or intestine, of black humor that causes the formation of a dark vapor that rises to the brain and envelops it as in a fog (Minois, 2005). Since ancient times, therefore, the brain has been considered the organ biochemically connected with psychic alterations.

Before discovering the organic brain alterations or lesions responsible for mental disorders, Hippocrates and Galen's conceptions remained substantially unchanged. Psychiatry concentrated its efforts on the meticulous cataloging of patients' abnormal behaviors and experiences. In the eighteenth century, Pinel and his disciple Esquirol initiated the history of psychiatric nosology and nosography and lay the foundations for current classifications. Esquirol (1772-1840) recognized simple melancholy as a nosological entity, characterized by the prevalence of sad and depressing ideas, and defined it as lipemania.

Subsequently, in 1879 Bini proposed a phenomenological classification of mental illness. He included melancholy in "simple madness" and correlated it with the prevalence of some of its phenomena: moral melancholy with delirium, stupid or agitated. Finally, Emil Kraepelin (1856-1926) classified psychiatric pathology according to a biological model with an organicist, neuro-physiological, and anatomopathological approach. He marked a revolution that give birth to the nosology still present in contemporary psychiatry, albeit with the limits linked to reduced possibilities of the time to investigate the etiology and anatomy-pathology of the brain. Kraepelin divided the psychoses, according to the determining cause, into exogenous and endogenous; subsequent, he subdivided the endogenous ones, in turn, into two broad categories, postulating the dichotomy that is also inherited from modern psychiatry: manic-depressive psychosis and

dementia praecox. Amid the manic-depressive psychosis, he inserted the monopolar, bipolar, and mixed states forms (Salomone and Arnone, 2009). The Kraepelin model has remained practically unchanged, albeit with an evolution of the terminology used, up to the present day. In the latest edition of the DSM, mixed states have been included as particular subtypes of the monopolar or bipolar forms and no longer independent nosological entities.

Nowadays, corroborated by genetic research and the effectiveness of some drug classes, the mood spectrum concept is becoming predominant. It is theorized that there is a continuum that goes from "pure" mania to "pure" depression, in which affective disorders are included without a clear demarcation (Benvenuti, 2015). This concept starts from the evidence that there is a common substrate for all affective pathologies; therefore, an exclusively phenotypic variation of the same pathology is possible.

Over time, the approach to depression has changed: the first question is not more "what is depression?" but it is "how should depression be treated?". Galen's naturalistic therapies are maintained for a prolonged time, substantially devoid of decisive scientific discoveries in the field of psychiatry. At the beginning of the twentieth century, Freud introduced the possibility of a systematized psychotherapeutic approach. In the 1950s, coinciding with the spread of Electro Convulsive Therapy (ECT) and starting with the discovery of the euphoric effect of iproniazid (anti-tuberculosis drug) through serendipity, the first specific pharmacological molecules have been discovered, thus passing from I-MAO to tricyclic antidepressants (imipramine first). In 1987, there is the mainstream turning point: the FDA approved Prozac (Fluoxetine), a Selective Serotonin Reuptake Inhibitor, with greater tolerability than previous therapies, thus widening the number of patients who can benefit from psycho-pharmaco-therapy.

Prozac has become the example of a global social phenomenon, become part of culture and language, so much that it also appears in the Oxford English Dictionary and legitimizes the depression in the popular culture. The attention of public opinion towards Mental Health and, particularly, depression, is growing considerably, in parallel with the growth of knowledge about psychopharmacology. In the USA, we speak of the "brain decade," emphasizing mental health issues, until then little considered in Medicine. Despite this, the total number of people with depression continues to increase over the years to over 300 million affected individuals globally (WHO, 2017).

Depression is also the most common mental disorder in Italy. ISTAT estimated that those who suffered from it in 2015 (latest available data) were over 2.8 million, about 5.4% of people aged 15 and over. Furthermore, the World Health Organization has recognized depression as the leading cause of disability worldwide, with a total global estimate of over 50 million years lived with disability (Years Lived with Disability, YLD) in 2015 alone (WHO, 2017).

It is, therefore, natural to ask ourselves where we are with the treatment of this pathology and how effective are the interventions available today. The two most important clinical studies on the subject, STAR * D (Sequenced Treatment Alternative to Relieve Depression) and CO-MED (Combining Medications to Enhance Depression Outcomes), with a total sample of over 4000 patients, showed modest remission clinical rates, less than 40% (Rush et al., 2011).

Following some limitations on the possibility of recovery from some "new" antidepressants, a little-explored line of research has highlighted different therapeutic options for the treatment of the so-called Treatment-Resistant Depression (TRD), identifying molecules that go beyond the mechanisms of the monoaminergic theory and also involve other neurotransmitter systems present within the human brain (or even the whole organism). At the same time, evidence emerged on the etiopathogenesis of mental pathologies involving the glutamate and GABAergic systems (Abdallah et al., 2014), thus leading to great interest in the therapeutic possibilities of some glutamate NMDA receptor antagonists.

Ketamine appears to exert a rapid, effective, and prolonged therapeutic action, acting on the nuclear aspects of depression, including the immediate decrease of suicidal ideation (Diaz Granados et al., 2010) through mechanisms not yet fully understood but which, for sure, promote synapse plasticity (Zanos and Gould, 2018).

This thesis starts from my direct involvement, during the four years of training in this Postgraduate School, in a phase III study before marketing about the intranasal formulation of S-ketamine. In this experimental thesis, in particular, we considered the use of ketamine within the treatment of TRD by the intravenous and intranasal forms carried out in the University Psychiatric Clinic of the Siena Hospital.

The intravenous formulation was used off-label, at subanesthetic doses; the intranasal formulation was administered in its S-Ketamine form (levorotatory ketamine enantiomer) within the phase III study.

Yogi Berra argued that "in theory, there is no difference between theory and practice, but in practice there is." This thesis provided us with the opportunity to describe the clinical practice in the use of ketamine, albeit with some limitations determined by the small sample examined, and to draw some reflections from it.

CHAPTER 1 – THE MAJOR DEPRESSIVE DISORDER

1.1 Epidemiology

Major Depression is estimated to affect approximately 322 million people worldwide, making it a widespread ailment in the population. In the decade 2005-2015, the total number of people living with depression increased by almost 20%. The World Health Organization estimates that in 2020, depression will become the most widespread mental illness in the world and the second most widespread illness, after cardiovascular diseases alone, with an enormous social cost linked to its negative effects (WHO, 2017).

The prevalence of depression in the global population is 4.4%, with a double incidence in women than in men (5.1 versus 3.6%). However, prevalence varies widely between regions of the world, ranging from the lowest of the male population in the Western Pacific region (2.6%) to the highest of the female population in the African area (5.9%). Prevalence rates also vary according to the age factor, with a peak in adulthood (55-74 years old) (Vos et al., 2016, 2017; WHO, 2017). The lifetime risk of developing a depressive episode is between 10 and 15% (Briley and Lépine, 2011). The low average age at the time of diagnosis (about 27 years) (Malhi et al., 2015) combined with the high degree of disability associated with this pathology account for the high social cost of depression. WHO considers depression as the leading cause of disability in the world, estimating a total of over 50 million years lived with disability (Year Lived with Disability, YLD) in 2015 alone, representing the single most significant disability factor among non-fatal diseases (7.5% of total YLD) (Alonso et al., 2011; WHO, 2017).

Major Depression is a widespread psychiatric disorder in the Italian population and represents an important cause of temporary or permanent disability. In Italy, it affects about 2.8 million patients (5.4% of the population over 15 years old), a rate slightly lower than the European average (National Institute of Statistics, 2018). The prevalence increases with increasing age, so much that in the over-65 population, the propensity to report the disorder in 12 months doubles compared to the average. In addition to sex differences, in which

Italy is aligned with the global trend of disadvantage for women, there are also socio-economic determinants associated with depression. It occurs more frequently among inactive or unemployed people (10.8%) than to employed peers (3.5%); in the adult and elderly population with a low level of education, the prevalence approximately doubles that of peers with greater educational background (3.4% versus 7.5% for adults, 6.3% versus 16.6% for the elderly) (National Institute of Statistics, 2018).

According to WHO data, of the approximately one million suicides recorded annually globally, 60% are attributable to depressive episodes, with an increase in risk up to 20 times compared to the general population (Briley and Lépine, 2011). In Italy, the death rate from suicide is 6/100,000 residents (almost half of the European average), representing a significant cause of death in the early youth (12% of deaths in the 20-34 age group). Furthermore, the risk of suicide increases with the severity of the depressive episode in progress (Kessing, 2004).

The data of the Italian Medicines Agency provide an idea of the extent of depressive pathology in Italy. Between 2015 and 2017, the national consumption of antidepressant drugs reached an average of 40 daily doses per thousand inhabitants, and the prevalence of use has estimated that 3.6 million inhabitants received a prescription for at least one antidepressant drug in 2017 (AIFA Agenzia Italiana del Farmaco., 2018).

The social cost of depression is also high in Italy: the direct costs borne by the National Health Service are estimated at an average cost for treatment of about 5,000 euros per year per depressed patient (including hospital admissions, outpatient specialists, pharmacotherapy) to which are added the number of working hours lost for the disease, corresponding to 4 billion euros a year (National Observatory on Women's Health and Gender, 2019). Studies in economics and health use depression as a paradigm of how the timeliness of diagnosis and treatments are real investments from a clinical, social, and economic perspective.

This general framework provides a comprehensive motivation for the drive towards the search for new therapies that can reduce the impact of depression on society.

1.2 Psychopathology of depression

The history of depression begins with the history of man himself. One of the first civilizations to hand down in writing situations similar to depression as we know today was the Egyptian one. The Egyptians described some *taedium vitae* cases, a condition suitable to lead, as far back as 2600 BC, to cases of suicide in the Nile river (Infrasca, 2007). Even the Assyrians wondered where the so-called "black mood" came from, a sort of depressive state caused to man by the loss of divine protection. There are references to dark evil in Babylonian culture, described as a combination of anguish, fear, and oppression suitable for appropriating desires. Homer in Book VII of the Iliad describes Ajax's deep despair with great accuracy, which ended with his suicide. It is precisely the Greeks, since the end of the fifth century, to consider μέλας (mèlas, "black") as the mood (what today we would call endogenous substance) the cause of crazy actions and pictures of sadness, loneliness, suffering, and boredom. Until then, every disease had a magical, superstitious or religious reason.

Around 400 BC, Hippocrates formulated an all-encompassing etiological theory based on substances present in the body (four "humors": red bile, blood, yellow bile, black bile, and phlegm) whose imbalance generated all known pathologies. Melancholia (derived from μέλας "black" and χολή "bile") is defined as an imbalance of black bile (a slow and heavy fluid, cold and dry, which is the negation of life), located in the spleen, and manifests itself with "aversion to food, irritability, psychomotor agitation, drowsiness." Galen (about 129-201 AD) expanded the humoral theory and corroborated it with scientific studies. He argued that the temperament derives from the infinite combinations within the human soul of the four humors and linked neuropathologies to a hypochondriac state due to the secretion, by the liver, stomach, or bowel, of black humor that causes the formation of a dark vapor that rises to the brain and envelops it as in a clouding fog (Minois, 2005).

The theory of excess bile has dominated medical knowledge for a long time, profoundly influencing the prescribed therapy, which used diets, purgatives, and bloodletting to eliminate excess bile (Siracusano et al., 2014). However, we can note that since ancient times the brain has been considered the organ biochemically connected with psychic alterations and that the most modern monoaminergic theory has shifted the fulcrum of this biochemical alteration, involving the neurotransmitters serotonin, noradrenaline, and dopamine. Still,

substantially it has kept in its nucleus the imbalance of endogenous substances responsible for the clinical picture.

Over time, the studies have distinguished between a physical form of melancholy (which is part of the galenic humoral alteration) and a psychic form linked to temperament, spirituality, or psychological reactivity. In 1621 Robert Burton wrote The Anatomy of Melancholy. He subdivided forms of "causeless" melancholy and others related to life events (mourning, alcohol abuse, very intense emotions, autumn season); first, he bound madness, melancholy, and suicide. Esquirol (1772-1840) systematically described melancholia as an alteration of effect characterized by the prevalence of sad and depressing ideas and defined it as lipemania, also describing a delusional form ("monomania" because a single delusion dominates it). In 1879, Bini proposed a phenomenological classification of mental illness. He included melancholy in "simple madness" and defined it as a prevalence of some of its phenomena: moral melancholy, delirium, stupid or agitated.

Shortly after, Kraepelin (1856-1926) theorized a classification of psychic pathologies according to a biological model with an organicistic, neuro-physiological, and anatomopathological approach, albeit with the limits linked to the reduced possibilities of the time to investigate etiology and anatomy pathology of the brain. In this way, Kraepelin became responsible for a sort of Copernican revolution in psychiatric nosography. He divided the psychoses, according to the determining cause, into exogenous and endogenous; subsequent he subdivided the endogenous ones, in turn, into two broad categories, devising the dichotomy that has been inherited since current psychiatry: manic-depressive psychosis and praecox dementia (which with Bleuler will become schizophrenia). Amid the manic-depressive psychosis, he inserted the monopolar, bipolar, and mixed states forms (Salomone and Arnone, 2009). For Kraepelin, the core symptoms of depression are represented by lowering mood and a slowing of physical and mental processes.

However, all nineteenth-century psychiatry has continued to honor the descriptive-organicistic model. A-psychological psychiatry, considering the presence of brain organic alterations or lesions responsible for mental disorders, dedicates itself to meticulous cataloging of patients' abnormal behaviors and experiences while waiting to discover them. The idea that the patient's personal history, his world, his interiority can have a weight in the expression of the disease is ascribed to a psychopathological epiphenomenon until two

neurologists, Sigmund Freud and Karl Abraham, which successfully propose a key to the psychological-psychoanalytic reading of depression (Rossi Monti, 2002).

Psychoanalysis (and subsequently psychopathology, starting with Karl Jaspers) expresses the need to attribute meaning to the symptom and demolishes the reassuring barrier that a century of positivistic psychiatry has erected between disease and normality. Psychoanalysis identifies proximity between the normal and the pathological fields, given that the unconscious mental activity and the conflicting fixations, capable of conditioning action, unite both the normal and the pathological fields. The psychoanalytic theory on the origin of melancholic depression, expressed by Freud in Mourning and melancholy in 1915, postulates a link between the premature loss of the object of love (object not real, unlike mourning in which the loss is linked with a real object) and the anger that is introjected towards oneself for the identification put in place by the patient with the lost object. From this anger derive the self-criticism, self-disapproval, and loss of self-esteem, typical signs of depressed patients. A few years later (in the text The Ego and the Id of 1922), Freud inserted this view into the three instances' theory. He believed that depressed patients are characterized by a severe superego, linked to the guilt of having shown aggression towards loved ones. Edith Jacobson (1897 - 1982) reviewed this theory, suggesting that depressed patients can themselves be the lost object of love or the sadistic superego, concretized by hallucinatory phenomena of a disparaging nature often present into the most severe depressive symptomatology. Karl Abraham in 1924 expanded Freud's theory, linking the depression with the childhood past: according to Abraham, depressed individuals have suffered severe blows to their self-esteem as children, so that in adulthood, new losses or disappointments are capable of evoking intense feelings negative towards figures (present or past) who have hurt the patient by denying him their love, in a real or imaginary way, inducing depressive pictures. Both Freud and Abraham, in their works, always attribute to depression the presence of dissociative pain, experienced as not belonging to the patient's world, because it presents in itself not only the loss of the object but also of the subject.

Subsequently, Melanie Klein (1882 - 1960) linked depression to a failure to overcome the "depressive position," the regular phase of the child's psychic development, in relation to poor quality of the first maternal-infant relationships: the patient never overcomes the guilt of having transformed the introjected parents from good to bad, due to their destructive impulses and fantasies. Furthermore, Klein noted that a

depressive episode can follow success or promotion; in this case, she attributed the onset of depressive feelings to the anguish born from the experience of the manic defense, aimed at the desire to triumph over one's parents to reverse the child-parent relationship. In the Attachment Theory, Bowlby (1907 - 1990) inserted the possibility of developing depressive symptoms when, after an unstable or broken attachment (for example, due to the loss of a parent), an image of oneself unworthy of love is created and an image of the unreliable caregiver. Consequently, any experience of loss in adult life can reactivate the feeling of unworthiness and abandonment, generating depressive pictures.

Only Bibring (1894 - 1959) deviated from the centrality of the super-ego and aggression, linking the appearance of depressive symptoms to the distance between narcissistic aspirations and the inability to live up to these parameters. At the end of the twentieth century, Blatt summarized these different currents of thought by dividing the population of depressed patients into two macro-categories: the anaclitic type, dependent on relationships and characterized by a chronic fear of abandonment, and the introjective type, excessively perfectionist and competitive. Hence, anaclitic depression mainly manifests itself with feelings of abandonment, loss, and loneliness, while the introjective one is characterized by feelings of failure, guilt, and worthlessness.

Almost all psychoanalytic perspectives, therefore, emphasize the presence of a narcissistic vulnerability or fragile self-esteem, often also implying anger and aggression with the sense of guilt and self-denigration they induce. The perspectives find the initial point of depression in wrong object or attachment relationships that the child establishes with the parental figures, which are then recalled in adult life when, the experience of situations of loneliness, abandonment or failure (real or imaginary) evokes the appearance of depressive symptoms (Gabbard, 2015).

If psychoanalysis has researched the causes of depression, phenomenological psychopathology has focused on "understanding" what the patient expresses, the world experienced by the depressed: for phenomenology, the center of the melancholic world is essentially an inability to establish a relationship with the mood alteration, of suffering pain that the patient does not feel like his or her own. Freud and Abraham had already characterized melancholy depression as a great debasement of the feeling of self. Karl Jaspers (1883 - 1969) also described depression as a fading of the consciousness of existence, a loss of the feeling of

the Ego that can go so far as to "overcome the metaphysical limit towards the being of not being forever" (Barison, 1993), typical of Cotard syndrome. Initially, endogenicity is postulated as fundamental in the definition of depression-disease, a motivation for vital sadness, which becomes unmotivated and almost substantially incomprehensible. However, the independence of melancholy from life events is much more complex, so much so that Binswanger in Melancholia and Mania (1960) emphasized the possibility that events become meaningful experiences for that person, reflecting on the fact that everyday life events can be seen in a very different way, calling into play the history of the person, his style of relationship with the Self and with the world of others. Tellenbach (1914 - 1994) recalled the case of a mother who entered a deep melancholy state at the news of her son lost in the war and who had not improved at all at the subsequent immediate denial: a simple positive event can “cancel” a negative event. In depression-illness, the quality of the so-called vital mood changes: patient feels a loss of vital momentum, stasis in the flow of psychic life, deep pain and apparent apathetic detachment ("pseudo-apathy"), signs of a modification of lived time and of the experience of temporality which favors the past instead of the present and, above all, the future.

The analysis of the melancholic world leads to highlight three fundamental themes, which for Kurt Schneider (1887 - 1967) correspond to the primordial anxieties of every man: fear for the salvation of the soul, for physical health, and for the material subsistence of the world, which would be "revealed" in depression as themes of guilt, doom, and hypochondriac. These themes may not be pathological in themselves, but the abnormality is linked to appearing for no reason, to the abnormal structure, and to the way of living them. All these themes can, of course, lead to a picture of delirium (or, better, deliroid), which becomes a confirmation of a state of mind fixed in self-denigration, or in anger (Callieri, 2016; Callieri et al., 1965).

The theme of guilt constitutes the stamp of the melancholic world directed towards others, life, or one's body, as a fault of existing, and the active search for faults from experience as guilty itself never ends (Di Petta, 2003). The suffering that the patient experiences are defined as unworthy and captures the patient, which a metaphor by Rossi Monti may well represent: an infinite spiral motion which, by constraining the vital space, wraps itself around itself, however, accompanied by an emotional increase, until it is reduced to a single point, irremediably closed in itself, isolated, and nullified.

For Tellenbach, in the premorbid life of the melancholic future (*typus melancolicus*), the experience of guilt has a particular configuration. He underlined the real presence of a marked conscientiousness, meticulousness, and exactness, for which his conscience places continuous prohibitions, tending to avoid any guilt, always to keep his conscience meticulously immaculate since guilt constitutes too significant a burden even when the extent of fault is minimal, or the fault is an involuntary error. In the *typus melancolicus*, "the distance between being and duty becomes an abyss" and he paradoxically remains wedged between inclusion and remanence, succumbing under the weight of guilt (Tellenbach et al., 2015). Another declination of the theme of guilt is the melancholic ideation permeated by the feeling of lying or having always lied, for example, by simulating illness. According to Kraus, the inner theme of lying has a precise connection with the pre-melancholic personality type, which must be excessively adherent to external norms, up to the premorbid sensation of an ego that is neither authentic nor spontaneous (Kraus, 1994).

The second theme, ruin, concerns the total eradication of the usual world, which will never be the same again and which spares no one. In this theme, the ability to react comes into play where economic well-being occupies the individual assessment scale, contaminated by the type of culture and society in which man lives. Ruin is expressed “as an uprooting from all that is possession of goods that guarantee security” (Callieri, 2016); the focus is not on feeling responsible for the ruin but on being overwhelmed by it, without the possibility of pulling yourself out of the current situation. The patient changes his way of being. The experience of impoverishment, which represents a delusional construct derived from the falsification of reality, is confused with the reaction to impoverishment and becomes difficult to distinguish from it.

The third theme concerns the change of the patient's relationship with his own body, which becomes ruined, degraded, rotten. Minkowski described the interview with a delusional melancholic patient, convinced that all the rubbish had been put aside to be then introduced into his abdomen; the patient thus becomes the receptacle of waste discarded by humanity and repellent for every human being (Minkowski and Leoni, 1971). For the phenomenological school, if in the state of health, the experience of one's own body represents only a background to other experiences of relationship with the world; in illness, the experience of the sick body emerges and affirms itself, at the expense of every different experience. The body transforms and deforms according to the subject's attention, making the experience of bodily unity uneven. Callieri

identified four fundamental modalities of altered body experience that can be experienced by the melancholic: somatized anxiety, vital sadness, somato-psychic depersonalization, and hypochondria. Somatized anxiety expresses a body experienced with an accentuated feeling of activity, which concretizes the anxious person's existential situation and becomes a place of manifestation of being threatened. Vital sadness is experienced as a weakening of instincts, drives, and energies, up to a feeling of somatic insufficiency. In the somato-psychic depersonalization, the experience of the natural unity of one's body is lost, which becomes extraneous, no longer belonging to itself, an object among other objects, with self-analytic attention aimed at understanding the body that is more than the body that one has, typical instead of the fourth theme, hypochondria. It is precisely hypochondria that occupies a prominent place among depressive themes. It represents a way of being for the depressed person and the topic of his reflection. Through this duplicity, it can become a type of delusional experience. Hypochondriac ideas (framed from time to time as cenestopathies, psychesthesia, pain without apparent cause, somatization of anxiety) are present in all forms of depression, without necessarily becoming deliroid. Schipkowensky argued that hypochondria does not exist without hypochondriac ideas, without a system of intuitions, beliefs, and judgments rooted in a conception and experience of the sick body. Basaglia noted that hypochondria is not a real syndrome but more a "hypochondriac situation," a way of experiencing the alteration of the body in the various psychic syndromes (Basaglia, 1956). Callieri found in this definition a confirmation that the hypochondriac experiences his body only as the "body-that-I-have". Janzarik (1920 -) identified a connection between hypochondria and guilt, as a causal relationship (the disease makes one guilty), self-centered (the disease was acquired guiltily, for example by neglecting one's health or with excesses in vices) or punitive (illness is a deserved punishment for guilt).

Finally, Eugéne Minkowski gave centrality in the melancholic world to the alteration of the consciousness of time: according to this author, the time of the ego (immanent time, subjective perception, and at the same time actual duration that defines the continuous flow of our psychic life) slows down compared to that of the world (transitive time, in common with other human beings, homogeneous or measurable by the "hands of the clock") and becomes eternal, until it stops. There is then the loss of synchrony, of the orientation towards the future, the end of "normal" life (which pushes forward), the cessation of the ability to liquidate the present, which finds itself encumbering the entire psychic field (Minkowski and Leoni, 1971). The past is

immobilized in the ideas of guilt. It expands to excess, swallowing up every possibility into the present space, which is denied, in turn, under the forms of unworthiness and ruin. The future becomes a desperate horizon, barred by the expectation of an imminent punishment. Binswanger argued that when the depressed gaze turns to the future, it is only to establish that everything is already done and nothing different can be hoped. Therefore, the significance of time and temporality represents the constituent moment of the melancholic and depressive experience. Kimura Bin (1931 -) inserted vital anguish into the theme of time, which in the pre-melancholic typus is anguish for the past, such as to make the future itself only an extension of the past itself.

1.3 Neurobiological theories

Parallel to the drafting of the different classification models and the phenomenological analysis of melancholy, the progress of man's technological abilities has led, since the 1950s, to a better understanding of how the brain works and to the discovery of neurotransmitters (i.e., those chemicals that allow communication between neurons) and neurohormones.

In the early 1950s, in the National Institute of Health laboratories in Bethesda (Maryland), Bernard Brodie observed that reserpine, an antihypertensive and antipsychotic molecule capable of collaterally causing depression, produced almost total depletion of serotonin in the brain of rats. Later, Carlson demonstrated that reserpine also induces depletion of brain levels of norepinephrine and dopamine. Thus, he originated the aminergic hypothesis of the pathogenesis of depression. Subsequently, this hypothesis appeared excessively simplistic and in stark contrast to the efficacy times of antidepressant drugs that act on monoamines (Ciccocioppo et al., 2018).

Over the years, the ability to see and record brain activity live has increased, thanks to functional magnetic resonance imaging, thus highlighting which areas are activated when a specific emotion is experienced. Consequently, biological studies on depression developed. As it becomes increasingly clear that the mechanism of action of antidepressant drugs is considerably more complex than initially believed,

phenomena of up-regulation or down-regulation of the receptors that make up the synaptic structures are called into question, concluding that there is a complex neuro-receptor alteration at the basis of depressive pathogenesis.

The year 1953 represented a critical moment in the path of scientific research: Watson and Crick postulated the double-helix model of DNA and brought the invisible into the visible world, thus addressing research towards what neither the human eye nor the simple microscope can manage and see. In 1983, the invention of the Polymerase Chain Reaction allowed Mullis to win the Nobel Prize in chemistry, legitimized DNA sequencing, and gave way to large-scale genetic studies, bringing great hopes in searching for the etiology of psychiatric diseases.

Far from the initial positivism that seeks a single lesion in the brain as the *primum movens* of the depression, the studies revealed the picture of a complex disorder in which numerous genetic, environmental, immunological, and endocrine factors interact with each other.

The data obtained from the studies indicate that the genetic component is of great importance in the pathogenesis of mood disorders. Studies on twins suggest a heritability of 40-50%, and studies on households indicate a lifetime increase in the risk of developing depression twice among first-degree relatives (Lohoff, 2010). Some studies carried out on subjects of the same households, on twins, and on adopted individuals provide evidence of a substantial genetic contribution to the development of depression (Klein et al., 2004; Mondimore et al., 2006). There is also a greater extent of hereditary factors in the female population than in the male population, which would justify the higher incidence and prevalence of depressive disorders in women (Kendler et al., 2001).

Part of the responsibility in the pathogenesis of depression is also ascribed to non-genetic factors: environmental factors which, interacting with genetic factors, influence the response to stressful life events and influence, starting from them, the establishment of a pathological picture (Malhi et al., 2000).

According to recent studies, a possible link between the various pathogenetic agents involved in depression is represented by the hypothalamus-pituitary axis (Bondy, 2002; Pariante and Lightman, 2008). In this hypothesis, environmental stress activates a series of immunological responses, triggering functional and

structural changes in various brain areas. This leads to alterations in neurogenesis and neurotransmission, which, clinically, are capable of generating depressive phenotypes (Charney, 2004; Sharpley and Agnew, 2011; Sharpley and Bitsika, 2010). The result is abnormal activation of the hypothalamus-pituitary axis and, therefore, an increase in CRF secretion (Cortisol Releasing Factor) with consequent hypercortisolemia (Gillespie and Nemeroff, 2005; Merali, 2004). Hypercortisolemia can directly cause structural and functional alterations in the prefrontal cortex, hippocampus, and amygdala, which seem strongly involved in the genesis of the psychic, cognitive, physical, and emotional symptoms of depression. Thus, there is a reduction in the proliferation rate of neurons in the hippocampus inhibiting neurogenesis (Heine et al., 2004; Levin et al., 2007; MacQueen et al., 2008; van Eijndhoven et al., 2009).

It seems that inflammatory cytokines also play a role in the pathogenesis of depression: an increase in the pro-inflammatory component appears to reduce the production of serotonin, inhibit the down-regulation of CRF (with consequent hypersecretion of cortisol) and interfere with cerebral neuroplasticity and with the monoamine system (Dantzer et al., 2008; Dinan, 2009; Hayley et al., 2005).

1.3.1 The monoaminergic theory

As previously mentioned, the study of the neurobiological mechanisms underlying depression begins in the National Institute of Health laboratories in Bethesda in the mid-1950s, when Bernard Brodie, carrying out studies on Parkinson's disease, decided to study reserpine. In particular, Brodie was interested in the neurochemical mechanism by which this alkaloid, taken at appropriate doses, causes a severe depressive crisis indistinguishable from endogenous depression. He tried to understand whether reserpine can also modify the serotonin, a monoamine content in the brain of rats and discovered a few years earlier in the intestine by Espamer at the La Sapienza University of Rome. Brodie and his team found that an intraperitoneal administration of reserpine in a few hours almost totally clears the serotonin levels in the rat brain. A few months later, Brodie's student Arvid Carlsson discovered that norepinephrine and dopamine levels are almost entirely removed in mice treated with reserpine. For the first time, these monoamines

appear directly involved in controlling the affective sphere: the reduction of their brain levels is identified as the pathogenetic mechanism underlying depression, giving rise to the monoaminergic hypothesis (Biggio, 2019; Ciccocioppo et al., 2018; Hirschfeld, 2000). The discovery of the mechanism of action of iproniazid, a euphoric and psycho-stimulating agent capable of improving appetite and sleep, provides further confirmation: the action of this molecule lies in the ability to inhibit Mono-Amino-Oxidase (MAO), the main enzyme system responsible for the breakdown of catecholamines (norepinephrine, serotonin, and dopamine).

From the studies, then, it emerges that the brain has a high number of noradrenergic, serotonergic, and dopaminergic neurons. Noradrenergic neurons spread from the brainstem to almost all areas of the brain where norepinephrine (NE) modulates the function of the prefrontal cortex, processing of working memory, and regulates behavior and attention. NE also plays a role in acquiring emotionally relevant memories. Serotonin (5-hydroxytryptamine, 5HT) innervates all brain areas and is the most extensive cohesive neurotransmission system in the brain, while dopamine (DA) regulates reward and motivation functions, working memory and attention. The monoaminergic theory hypothesizes an alteration of these neurotransmitter systems underlying the core symptoms of depression, such as inflected mood, anhedonia, asthenia, and psychomotor slowing (Atzori et al., 2016; Grace, 2016; Maletic et al., 2017; Treadway, 2015). In particular, abnormal serotonin levels are linked to behavioral and somatic alterations (variations in circadian rhythms, hypno-alimentary patterns, and the response to pain) observed in depression. Post-mortem studies found a reduction in serotonin levels in the brains of depressed patients compared to healthy subjects. Likewise, dopamine abnormalities are linked to motivational, decision-making, and concentration dysfunctions and episodes of aggression. Low levels of norepinephrine also correlate with a broad spectrum of depressive symptoms, including alterations in sexuality, appetite, concentration, and interests (Landén and Thase, 2006; Salamone et al., 2016; Seo et al., 2008; Stockmeier, 2003).

Precisely based on this neurobiological principle, an intense drug development activity is initiated, which, in the early 1970s, led to the discovery of fluoxetine, the first selective serotonin reuptake inhibitor (SSRI).

Most of the fundamental brain functions depend on the neurotransmitters present in the synaptic wall. Still, they must also be linked to their presence and activity in the pre- and post-synaptic membranes of the billions

of brain neurons. According to the monoaminergic hypothesis, reduced availability of the main monoamine neurotransmitters (5HT, NE, and DA) would decrease neurotransmission and consequent impairment of the cognitive performance, which would lead to the development of the disease. The functional deficiency of monoamines observed in depression could also result from a reduction in protein transport functions and/or abnormalities of neurotransmitter receptors (Bondy, 2002).

This neurotransmitter dysfunction appears to be mediated by the degrading effects of Mono-Amino-Oxidase (MAO) in the synaptic space. This is supported by the experimental results of increased MAO enzymatic activity in depressed subjects. The constant action of these enzymatic systems would significantly reduce the availability of biogenic amines, with a consequent reduction of neurotransmission.

However, the monoaminergic hypothesis alone appears excessively simplistic and unable to explain the 4-6 week latency in the action of SSRIs and other antidepressants. It appears that the stress response mechanisms induced by depression interact with some neurotransmitters, including glutamate, NE, and histamine, contributing to the decrease in the production of the substrate serotonin (Strawbridge et al., 2017). Transporter proteins also play a crucial role in nerve communications. In the brain, these proteins facilitate the presynaptic reuptake of neurotransmitters, reducing their levels in the synaptic space and preventing their degradation by MAOs to be available for almost continuous transmission. Therefore, a reduction in the number and/or an alteration in the functionality of the transporter proteins would contribute to the decrease in the levels of monoamines.

Alterations in receptor function also appear to be involved in the genesis of depression: anomalies in the interaction between receptor and neurotransmitter (usually due to the decrease in the affinity of the receptors for neurotransmitters or to the down-regulation of receptors) and/or the transduction cascade of the signal downstream would result in ineffective or abnormal transmission (Ananth et al., 2018; Jesulola et al., 2018; Kaufman et al., 2016; Wang et al., 2016).

Positron Emission Tomography (PET) has provided further information on the neurochemical processes that occur during depression. PET is used to evaluate physiological functions *in vivo* (such as metabolism, neurotransmission, receptor occupation) without particular alterations in the subject's physiological homeostasis under examination. It has recently been used to monitor structural and functional brain changes

induced by pharmacological and non-pharmacological interventions in depressed individuals (Brendel et al., 2016; Feuerstein et al., 2016; Fu et al., 2017; Tamura et al., 2016).

Numerous PET studies have corroborated the roles of 5HT, NE, Glutamate, and DA in the pathophysiology of depression. Dysfunction of the 5-HT1A and 5HT-2A receptor binding capacity has been highlighted in depressed patients, particularly in the prefrontal cortex, anterior cingulate, and hippocampus (Iscan et al., 2017; Tiger et al., 2016). Changes in NE were found in patients with Major Depressive Disorder (Moriguchi, Yamada, et al., 2017) and after taking effective antidepressant therapy (Moriguchi, Takano, et al., 2017; Yatham et al., al., 2018).

1.3.2 Gene-environment interaction

Environmental stress influences and develops the course of depression, sharing a series of mediators and circuits with it (Gold et al., 2015; Kendler and Halberstadt, 2013). Experimental animal studies have shown that stress induces structural and functional changes in brain areas related to depression, such as the prefrontal cortex, amygdala, hippocampus, and nucleus accumbens (Dranovsky and Hen, 2006; Duncan et al., 2016). Environmental factors and stressed life events affect the possibility of developing depressive pathology, conferring greater vulnerability to the subject and can negatively affect both the possible clinical improvement and the likelihood of relapse (Jesulola et al., 2018; Kendler et al., 2005; Paykel, 2001). In particular, these factors include the death of a spouse, separation from a partner, loss of work and retirement, social isolation, child abuse or rape, trauma, and serious accidents. Numerous data derived from studies carried out on homozygous twins have showed how significant life events or negative experiences, especially if they last over time or are of a large number, influence the pathogenesis of depression. Type of stress and duration of exposure to the stressor seem to affect the phenotype of the depressive episode. (Lichtenberg and Belmaker, 2010). Conversely, positive events such as marriage, the birth of a child, work and financial successes, an optimal social network seem to improve the clinical outcome of depression, also

being able to represent protective factors for depressive pathogenesis (Keller et al., 2007; KENDLER et al., 2001; Paykel, 2001). Therefore, the existence of a diathesis-stress model has been postulated, i.e., an interaction between a predisposition already present but latent in the subject (diathesis), which is activated by exposure to perturbing environmental conditions (stress), leading to the triggering of the psychopathological process. According to this hypothesis, some levels of diathesis to the disease are present in everyone, with a different threshold above which symptoms appear, and stressful events affect precisely this activation threshold (Arnau-Soler et al., 2019). Some studies have tried to find a mathematical relationship within the GxE (gene-by-environment interaction) paradigm, finding a significantly increased risk in subjects in which the combination of a high genetic predisposition to depression and an increased number of “personal” stressful events, mainly in the female population (Arnau-Soler et al., 2019).

1.3.3 Endocrine and immunological factors

A possible link between the diathesis-stress model and the modifications of the monoamine receptor system seems to be represented by the endocrine system and the immune system. At the endocrinological level, the altered levels of growth hormone (GH), the abnormalities of the thyroid hormones, and the dysfunction of the hypothalamic-pituitary-adrenal axis seem to be related to the pathogenesis of depression (Dean and Keshavan, 2017; Segerstrom and Miller, 2004). In depressive episodes, there appears to be a defective release of GH, and the responses of the same hormone in depressed patients appear altered compared to healthy controls. In apomorphine and clonidine GH stimulation tests, patients with recurrent Major Depression showed "flat" or "blunt" responses, while this was not seen when other selective α2-adrenoceptor agents were used. These data suggest an implication of the GH system in depression (Jesulola et al., 2018).

The active forms of thyroid hormones, tri-iodothyronine (T3) and tetra-iodothyronine (T4) are physiologically responsible for the homeostasis of the body's metabolism. The thyroid gland produces these two hormones following the stimulation of the thyrotropic hormone (TSH) by the pituitary. TSH secretion is, in turn, modulated by the hypothalamic hormone TRH (Thyrotropin Releasing Hormone). Some of the depressive symptoms, such as weight loss, sleep disturbances, and psychomotor slowdown, could be attributable to abnormalities in thyroid function, which also appear to involve the serotonergic and adrenergic systems. It

has been shown that these hormones act both indirectly on the serotoninergic system, through an increase in the cortical secretion of serotonin stimulated by T3 and T4, and as co-transmitters in the adrenergic nervous system (Hage and Azar, 2012). Furthermore, it is now known that the administration of T3 represents an effective adjunct therapy in treatment-resistant depressed patients (Peng and Li, 2017).

The hypothalamic-pituitary-adrenal (HPA) axis also appears to play a significant role in the pathogenesis of depression. Specific depressive signs and symptoms such as feelings of guilt, decreased appetite, weight loss, reduced libido, altered hypnic pattern and psychomotor activity, as well as hyperreactivity to stressful stimuli, have been linked to HPA axis dysfunction (Gillespie and Nemeroff, 2005; Lopez-Duran et al., 2009). Furthermore, in depressed subjects, alterations in the production of the Corticotropin Release Factor (CRF) and Cortisol, abnormalities in the feedback mechanisms of glucocorticoids, insufficient suppression of the HPA axis in response to exogenous administration of glucocorticoids, and a dysfunction in the signaling process of corticosteroid receptors (Holsboer, 2000; Juruena, 2014; Martinac et al., 2017; Sher et al., 2013; Vreeburg et al., 2009) are observed.

The CRF is physiologically responsible for modulating the HPA axis, stimulating the production of ACTH (AdrenoCorticoTropic Hormone) in the anterior pituitary, enabling the release of cortisol from the adrenal gland but is also present in brain extra-hypothalamic regions, where it performs neurotransmitter functions of coordination of behavioral, autonomic, endocrine and immune responses (Bonfiglio et al., 2011; Smith and Vale, 2006). Many data support a central role of CRF in depressive pathogenesis: in the cerebrospinal fluid of depressed patients, a higher level of CRF than normal was found; the administration of CRF in the Central Nervous System generates, on animals, the development of depressive-like symptoms (Jesulola et al., 2018); post-mortem there is a lower density of CRF receptors in the frontal cortex and a higher concentration of cerebral CRF in depressed subjects (Austin et al., 2003; Merali, 2004); the elevated concentrations of CRF in the CSF tend to normalize after electroconvulsive therapy or with fluoxetine. Furthermore, a CRF antagonist appears to reduce depressive symptoms (Held et al., 2004; Künzel et al., 2003). The implication of HPA axis alterations in depression is further confirmed by plasma and salivary cortisol levels significantly higher in depressed subjects than in healthy controls (Chrousos and Zoumakis, 2017; Gillespie and Nemeroff, 2005; Vreeburg et al., 2009). In depressed patients, elevated cortisol levels appear to be associated with greater

intensity and severity of the disease, while their persistence increases the risk of recurrence (Chrousos and Zoumakis, 2017; Gillespie and Nemeroff, 2005; Ising et al., 2005). Finally, the experimental use of anti-glucocorticoids to inhibit cortisol synthesis appears to produce clinically relevant symptomatologic improvements (Ising et al., 2007; Surget et al., 2008).

As for the implication of immunity, the cytokine system seems to play a role in the pathogenesis of depression. Cytokines are inflammatory mediators produced by lymphoid cells (mainly white blood cells) in response to pathogenic antigens. They play the role of modulators of other immune cells involved in inflammation processes. Cytokines include Interferons (INF), Interleukins (IL), Tumor Necrosis Factor (TNF), and C-Reactive Protein (CRP) and are usually divided into pro-inflammatory (such as IL-1, IL-6, and TNF) and anti-inflammatory (e.g., IL-4, IL-8, IL-10, and IL-13) (Jesulola et al., 2018; Song et al., 2009). Although the studies are not unanimously agreed, some Interleukins, Interferon Gamma, CRP, and TNFα seem to play a relevant role in the association between chronic stress and impaired immune response, with implications for the development of depression (McEwen, 2000; Raison et al., 2006; Strawbridge et al., 2017).

According to the theory of sickness behavior, pro-inflammatory cytokines respond to an infectious agent acting on specific brain receptors to generate a series of "adaptive" responses, including hyperthermia, nausea, loss of appetite, sleep disturbances, anhedonia, and fatigue. In some animal models, this response appears to produce depressive-like symptoms. Furthermore, the administration of immunotherapeutic cytokines has symptoms similar to those typical of depression (Dantzer et al., 2008; Dinan, 2009; Hayley et al., 2005).

The link between inflammation (particularly neuroinflammation) and Major Depression is also evidenced by several clinical conditions, characterized by significant neuroinflammation (e.g., Systemic Lupus Erythematosus, traumatic brain injury, and multiple sclerosis), and associated with high prevalence rates for Major Depression. Some authors have argued that depressive symptoms can be produced by the action of peripheral inflammatory cytokines, which, by crossing the blood-brain barrier, induce neuroinflammation that contributes to behavioral responses similar to the classic signs of depression (Hosoi et al., 2002; Juengst et al. al., 2017; Maes et al., 2011; McCusker and Kelley, 2013).

To conclude, the role of neurogenesis should be mentioned: in adult individuals, this process allows the creation of neurons and new neuronal connections in some brain areas. It is assumed that a lack or reduction in neurogenerative capacity may contribute to depressive pathogenesis (Curtis et al., 2012; Gandy et al., 2017; Miller et al., 2013; Sahay and Hen, 2007). Neurogenesis appears to be essential for restoring the structure and functionality of the hippocampus, and it has been shown that various treatments with antidepressant drugs facilitate this neurogenerative process, significantly reducing the levels of ceramide, a molecule capable of blocking cell growth in the brain (Eisch and Petrik, 2012; Gulbins et al., 2015; Hanson et al., 2011; Surget et al., 2008; Vollmayr et al., 2007).

1.4 Clinical-diagnostic framework: the DSM-5

Since the 1950s, the drafting of the Diagnostic and Statistical Manual of Mental Disorders (DSM) have aimed to leave behind the Babel of languages, the contrasts between schools that starting from different etiopathogenesis assumptions, proposed different classifications of mental disorders. The declared atheoretical approach of the DSM presupposes the identification of a series of clinical conventions, leaving aside any etiological hypothesis on classified disorders to provide the world of research with a standard and universal language (Rossi Monti, 2002).

In the most recent version of the manual (5th edition), Major Depressive Disorder (MDD) is described as a mood dysfunction that affects many aspects of the individual's daily life, including the affective sphere, psychomotor reactivity, and cognitive abilities (American Psychiatric Association, 2013). It is characterized by high incidence rates throughout life, with a typical early-onset, high chronicity, and severe impairment of social and occupational functioning (Solomon et al., 2004).

MDD can be divided into "Single Episode" or "Recurrent" depending on whether the symptomatology is present in single or multiple episodes. According to the DSM-5, the symptoms necessary to make a diagnosis of Depressive Episode must last for at least two consecutive weeks and consist of two characterizing aspects (at least one of the two must be present for diagnosis):

1. Depressed mood for most of the day, almost daily for the period under observation. This aspect differs from sadness both quantitatively and qualitatively: feelings of despair, incurability, and

inconsolability emerge that are not comparable to other experiences previously lived (the comparison with mourning is only partially fitting)

2. Lack of interest or pleasure for usual activities: a state of lack of emotion is configured for previously involved well-being such as social relationships, playful activities, or work.

Associated with symptoms of thymic flexion and anhedonia are:

- Alteration of the hypno-alimentary pattern: the patient usually complains of sleep interrupted by awakenings and not restful (or sometimes hypersomnia) and decrease (but in some cases increase) in weight and appetite. Insomnia and hypersomnia, and sleep disturbances in general, are often associated with alterations in circadian, social, and biological rhythms and can be considered both a symptom and an independent risk factor for the onset of the Depressive Episode (Murphy and Peterson, 2015).
- Psychomotor slowdown or agitation: more frequently, there is an evident slowdown in facial expression and speech production and movements in general. Less frequent is the finding of a sensation of acceleration of ideas.
- Decreased energy and easy fatigue: patients report a burdensome feeling of asthenia that compromises the performance of almost all daily activities, mainly affecting the act of starting them. The presence and severity of somatic symptoms, such as easy fatigue and physical pain, appear to be associated with more significant clinical impairment (Brnabic et al., 2012; Fava et al., 2014).
- Concentration difficulties: parallel to what happens from the motor point of view, there is a slowing down of thought or constant indecision. The cognitive alterations typical of Depression include disturbances in attention, executive functioning, memory, and processing speed (Ahern and Semkovska, 2017; McIntyre et al., 2013; Papakostas, 2014; Snyder, 2013). These deficits significantly compromise the patient's daily functioning and quality of life (Evans et al., 2014; McIntyre, JZ Soczynska, et al., 2015) and can persist even when remaining symptoms have remitted (Bora et al., 2013; Rock et al., 2014).

- Feelings of guilt, inadequacy, and devaluation with thoughts of death and suicidal ideation: patients tend to feel a burden to others, feelings of guilt emerge that are not linked to a real plan, and the ability to project themselves into the future is so compromised that to self-damaging ideas and/or gestures.

To make a diagnosis according to the DSM-5 criteria, at least one characterizing symptom (depressed mood and anhedonia) must be present; besides, the symptoms must not be attributable to the effects of underlying pathologies or medical conditions or the use of drugs.

As part of MDD diagnosis, some specifiers are coded to provide more precise diagnoses within the broad spectrum of clinical presentations of depression, fundamental at the prognostic and therapeutic level. Specifiers introduced with DSM-5 include anxious symptoms, which may be present even without complete comorbidity with a diagnosis of anxiety-sphere disorder (the presence of elevated levels of anxiety during a Depressive Episode increases suicidal and chronic risk, on addition to decreasing the response to treatment) and the mixed characteristics that allow to include symptoms previously considered as manic or hypomanic in a diagnosis of unipolar depression (present in about 30% of depressed patients and associated with an increased suicidal risk) (Goldberg, 2015; McIntyre, JK Soczynska, et al., 2015; Perugi et al., 2015; Seo et al., 2011). The specifiers already present in previous editions are maintained: melancholic, atypical, psychotic, and seasonal manifestations (American Psychiatric Association, 2013).

Compared to the previous classification, Persistent Depressive Disorder is introduced, including the previous Chronic Major Depressive Disorder and Dysthymic Disorder. MDD is distinguished from Dysthymic Disorder as the latter presents symptoms similar to the first (depressed mood and loss of pleasure and interests) but of lower intensity, not classifiable as a Depressive Episode, and a long duration (two years) (American Psychiatric Association, 2013).

Similarly, the latest edition of the International Classification of Diseases (ICD-10) describes Major Depression as lowering mood, reduced energy levels, and decreased activity. There is a reduction in the ability to feel pleasure and concentrate; there is marked fatigue even after minimal efforts. Sleep is usually disturbed, and appetite decreased. Self-esteem and self-confidence are almost always reduced. The depressed mood is

accompanied by ideas of guilt and/or worthlessness and does not change in response to external events. The clinical picture is usually also characterized by somatic symptoms such as marked psychomotor retardation, agitation, decreased appetite, weight loss, and reduced libido. We distinguish the extent of the episode (mild, moderate, or severe) and possible recurrence of the same episodes (World Health Organization., 2016).

To conclude, we cannot mention the current shift in psychiatric diagnostics from the categorical to the dimensional approaches. If the existence of disorders as clearly separate and independent entities is essential for a definite classification, dimensionality is defined as "a continuous rather than discrete conception of psychopathological phenomena, which is based epistemologically on a hypothesis of continuity between psychopathology and normality" (Zennaro, 2011). Dimensional diagnostics distributes disturbances on a continuum that goes from normality, through quantitative variations, to pathology. The categories have a limited ability to faithfully describe the phenomenological and neuro-psychopathological reality concerning the excessive reduction of pathological complexity. On the other hand, the dimensions can make a fundamental contribution in this area while increasing its complexity and, consequently, the difficulty in using it in clinical practice. In this view, one or more fundamental dimensions can be identified for each disorder which, generally, are associated with a variable number of other dimensions. In depression, the central dimension is lowering mood, reducing psychomotor initiative, and impairing hedonic abilities. This can be associated in various ways with others, which express anxiety, tension, somatization, paranoia, and characterizing the clinical picture of the individual depressed patient in multiple ways (Desantis et al., 2019).

1.5 Suicidal course and risk

Major Depressive Disorder can occur at any age, although the first episode is more frequently diagnosed in puberty. The course of the disease is remarkably variable: fair percentages of patients undergo remission (complete, when there is a period of two or more months in the absence of symptoms, or partial when one or two mild depressive symptoms persist), while in other cases there is a recurrence of depressive episodes interspersed with periods of well-being in the absence of clinical symptoms. Usually, the depressive pictures

that tend to become chronic underlie concomitant aspects of pathological personality, anxiety disorders, or disorders related to the use of substances and, longitudinally, less frequently undergo a complete symptomatologic resolution (Andrade et al., 2003). In 40% of patients, clinical recovery (complete remission in the absence of symptoms for at least two months) usually begins approximately three months after clinical onset (four out of five patients recover within 12 months). Sometimes, the Depressive Episode presents a spontaneous resolution. The risk of recurrence of symptoms is inversely proportional to the duration of the remission period. It frequently occurs higher in those patients with a history of multiple relapses and only partial remission. The Depressive Episode can also be ascribed to within a Bipolar Disorder, representing the first manifestation. It can rarely evolve into a Psychotic Disorder (almost always in depressive pictures presenting severe psychotic symptoms). Notwithstanding the higher incidence of the disorder in the female population (in the general population 5.1 versus 3.6%), there does not seem to be any gender differences in phenomenological presentation, course, and response to treatment (American Psychiatric Association, 2013; Richards, 2011).

An essential variable in defining the course of depressive pathology is the comorbidity with other illnesses, psychiatric and otherwise. Major Depression is, in fact, often associated with a large number of chronic medical conditions: heart disease, diabetes, arthritis, arterial hypertension, migraine, and chronic lung disease, prevalent among the elderly (Bogner et al., 2005; Roy and Lloyd, 2012). Depression represents an independent risk factor for cardiac ischemic events and in general for cardiovascular mortality, given to be related to the frequent association with smoking, sedentary life with a greater risk for the development of obesity and metabolic syndrome (Brunet et al., 2014; Charlson et al., 2013; Hryhorczuk et al., 2013; Mansur et al., 2015; Seligman and Nemeroff, 2015). Depressive pathology is also frequently found in conjunction with neurological diseases such as vascular dementia, Alzheimer's disease, and Parkinson's disease (Bennett and Thomas, 2014; Marsh, 2013; Novais and Starkstein, 2015). According to some clinical studies, the risk associated with the presence of comorbidities does not end in the sum of the symptoms that characterize the various pathologies but being affected by depression seems to be correlated with overall lower adherence to therapies and seems to negatively interfere with access and participation in care (Beer and Skarbinski, 2014; Susin et al., 2016). Furthermore, in the presence of comorbidities, the possibility of a missed diagnosis of depressive illness is higher when other pathologies mask it: a meta-analysis on 41 scientific

studies (for a total of over 50,000 patients) highlighted a high percentage of missed diagnoses or erroneous in general practitioners' clinics (Mitchell et al., 2009). The presence of depressive symptoms and/or a diagnosis of Major Depression increases the degree of disability of individuals with chronic diseases and reduces their quality of life (Burgel et al., 2013; Deschênes et al., 2015; Faller et al., 2015; Schowalter et al., 2013).

Concerning psychiatric comorbidities, Major Depression frequently recurs together with Panic Disorder, Obsessive-Compulsive Disorder, Anorexia and Bulimia, Borderline Personality Disorder, and Substance Use Disorders (APA, 2013). In a recent clinical study, on a sample of 190 patients with Major Depression, 35% had at least one psychiatric comorbidity, and more frequently, there was a concurrent anxiety disorder (21%). The suicidal risk, found in 32% of patients, was also higher in those who presented comorbidity with an anxiety sphere disorder (Ittasakul et al., 2014).

Suicide is a global phenomenon, constituting one of the most frequent causes of death in the world. Nearly 800,000 people commit suicide every year, more than those murdered or killed in the war. This figure becomes even more critical if we consider that suicide is the second leading cause of death in the 15-29 age group. About 80% of suicides are carried out in low- and middle-income countries (it is estimated that around 10 million people in China have committed suicide attempts in their lifetime) (Cao et al., 2015; WHO, 2017). In Italy, the latest ISTAT data available (year 2015), reported 3,935 cases of suicide in 2015, with one of the lowest rates in the European context (6.5 per 100,000 inhabitants). The most involved age groups are represented by the over 45s (72%), while in the age group between 20 and 34 years, suicide accounts for 12% of annual deaths. There has been an increase in death risk from suicide in adulthood (35 - 64 years) in recent years. The phenomenon seems to affect men the most (10 per 100,000 against 3 per 100,000 in women) and subjects with a low education level. Between 2011 and 2015, about 20% of subjects who completed suicide had physical or psychiatric comorbidity (most frequently depression or anxiety) (National Institute of Statistics, 2018).

A meta-analysis on over 3000 completed suicide cases highlighted the presence of a psychiatric diagnosis, at the time of the suicide or previously, in 87% of cases. Furthermore, it is estimated that about 50% of subjects who commit an anticonservative act suffer from an affective sphere disorder (Arsenault-Lapierre et al., 2004;

Hegerl, 2016; Pompili et al., 2013). It is, therefore, evident that there is a close relationship between psychiatric pathologies (the literature tells us, in particular, Depression and Bipolar Disorder) and suicidal risk. Assuming that the risk of self-injurious severe gestures is present throughout depressive episodes (both in Unipolar Depression and in Bipolar Disorder), some authors consider these pathologies, already in themselves, risk factors for anticonservative acts (Dong et al., 2018; Turecki and Brent, 2016). Among other risk factors, the history of suicide attempts or threats appears to be the most indicative factor of high suicidal risk, although most completed suicides are not documented with previous unsuccessful attempts (American Psychiatric Association, 2013; Bostwick et al., 2016).

Additional risk factors are considered to be male sex, being single or living alone, a positive family history of psychiatric illness, comorbidity with anxiety disorders and/or alcohol and drug abuse, and the presence of profound despair (Hawton et al., 2013). In bipolar patients, decision-making processes characterized by an impulsive solid component have been linked to suicide attempts. Impulsivity has been related to suicide attempts with high lethality in patients with Borderline Personality Disorder. Even in patients with unipolar depression who show signs of impulsivity, higher rates of suicide attempt are present, regardless of the severity of the depressive symptoms (McGirr et al., 2008; Soloff et al., 2014; Wang et al., 2015).

Suicidal behavior is characterized by a complex interaction between numerous agents that contribute synergistically to the conception and fulfillment of anticonservative gestures: genetic, neurobiological, psychiatric, physical, social, economic, cultural, and moral factors are involved in addition to stressful life events. In particular, stressful life events appear to be closely linked to the pathogenesis of depression and suicidal risk (De Berardis et al., 2018; Lin et al., 2018; O'Connor and Nock, 2014; Pompili et al., 2011).

Despite this knowledge, the chances of predicting an anticonservative gesture remain limited: a meta-analysis found that 95% of patients considered to be at high suicidal risk do not commit suicide attempts, unlike 50% of low-risk patients (Large et al., 2016). Even targeted clinical interventions are not always effective in suicide prevention: 6.3% of patients with Depression and 14% of bipolar patients continue to present severe suicidal ideation even if adequately treated for months (Kasckow et al., 2016; Köhler-Forsberg et al., 2017; Zalsman et al., 2016).

In recent years, research has tried to combine discoveries in the neurobiological field (neurotransmitter alterations, dysfunctions of the hypothalamus-pituitary axis, and neuroinflammation) with psychopathological theories and the diathesis-stress model, trying to develop a model capable of understanding the actions suicidal and of identifying possible biological markers of suicide (Oquendo et al., 2014; Turecki et al., 2014). In preclinical studies, it has been seen that individuals carrying a particular genetic variant ("short" version of the allele of the promoter zone of the gene for the serotonin transporter) have more intense depressive symptoms and a greater propensity to suicidality than subjects without (Caspi, 2003; Hariri, 2002; Murphy et al., 2013).

The role of γ-aminobutyric acid (GABA) and glutamate transmission in suicidal behaviors has become the subject of intense research in recent years. It has recently been shown that genes encoding the glutamate NMDA receptor subunit (in particular the GRIN2B gene) and an enzyme that regulates the rate of polyamine synthesis (ornithine-decarboxylase, encoded by the ODC1 gene) are associated with attempts of particularly severe suicide as well as traumas (primarily physical assaults) suffered in childhood and adolescence, which in turn increase the risk of suicide attempts, within a gene-by-environment model (Sokolowski et al., 2013). In suicidal patients, a significant increase in the enzyme responsible for the synthesis of GABA starting from glutamate (GAD, Glutamic Acid Decarboxylase) has been reported at the hippocampal level (Gos et al., 2009).

The cognitive alterations affecting suicidal behaviors seem to be linked to anomalies in the connections of some neurocircuits (ventrolateral orbital cortex, dorsolateral/dorsomedial prefrontal cortex, anterior cingulate gyrus) and seem likely to be due to a dysregulation of glutamatergic neurotransmission in these areas (Davis et al., 2016; Jollant et al., 2011). This dysregulation seems to represent the neurobiological nucleus responsible for cognitive flexibility deficits, one of the relevant factors for the onset of psychiatric pathologies such as depression and bipolar disorder. Cognitive flexibility constitutes a crucial executive function in adaptation mechanisms to environmental changes and, therefore, in response to stress (Millan et al., 2012). Finally, a well-known drug with anti-suicidal properties is clozapine; it seems that this peculiarity is at least partly attributable to an enhancement of NMDA-mediated transmission, secondary to the ability of clozapine to inhibit glycine transport (Javitt et al., 2005; Khokhar et al., 2018).

These findings suggest that anomalies in the entire glutamate signaling process in the brain areas are responsible for cognitive tasks in close relation to self-injurious or suicidal behaviors.

1.6 Bipolar depression

Bipolar Disorder (BD) is one of the most severe chronic and often disabling psychiatric pathologies. It is characterized by a periodic alternation of depression and mania (bipolar disorder type I, although the presence of only one manic episode is sufficient for diagnostic purposes) or depression and hypomania (bipolar disorder type II).

Alongside the categorization of the DSM, some authors have hypothesized the presence of a bipolar spectrum that can group a variety of broader syndromic manifestations. According to Akiskal and Pinto, bipolar disorder can present itself as type I, type II (superimposable to the definitions of the DSM), but also as type III (hypomania associated with antidepressant therapy), type IV (hyperthymic depression), and with intermediate degrees between the various types: type I ½ (depression with protracted hypomania), type II ½ (cyclothymic depression), type III ½ (masked or unpowered bipolarity from stimulated substance use) (Akiskal and Pinto, 1999).

Some authors expand the concept of spectrum by suggesting that there is a mood spectrum. Unipolar depression and bipolar disorder are not two discrete and dichotomous entities. Since there are mood fluctuations in both conditions, they should be considered within a vision unitary psychopathology (Akiskal and Pinto, 2006; Blacker and Tsuang, 1992; Fagiolini et al., 2007; Kendler and Gardner, 1998). Furthermore, taking a more dimensional approach, a spectrum is hypothesized to group alterations afferent to anxiety, depressive, bipolar disorders, and ADHD, substance abuse, and impulse control (personality cluster B and C). In particular, in the reported clinical pictures, it is possible to find in the dimensions "fear" and "anger," opposite and coexisting poles, which do not cancel each other out. The combination of excess fear-fear deficit-excess anger-anger deficit constitutes four quadrants within a single framework, corresponding to bipolar I disorder, unipolar depression, bipolar II disorder, and ADHD (Lara et al ., 2006).

Considering the bipolar spectrum, prevalence rates approaching 4% of the adult population are recorded (Hirschfeld et al., 2003). Despite a lower prevalence than major depressive disorder and anxiety disorders, bipolar disorder is usually linked to a more marked decline in overall functioning and a more significant reduction in quality of life (Gutirrez-Rojas et al., 2008; Kessler et al., 2005; Merikangas et al., 2007; Shippee et al., 2011; Sierra et al., 2005; Solé et al., 2012).

The Collaborative Depression Study of the National Institute of Mental Health (NIMH) has shown that, in the United States, bipolar patients spend much more time with depressive symptoms (30% in type I DB, 50% in type II DB) than counterpolar symptomatology (15% in DB I and 4% in DB II) (Judd et al., 2003a, 2003b).

Other prospective studies report similar percentages: approximately 34% of the time spent in depressive phase compared to 12% with elevated/mixed mood (De Dios et al., 2010; Joffe et al., 2004; Judd et al., 2003a, 2003b; Kupka et al., 2007). There is also a gender difference in the alternation of depressive and manic/hypomanic episodes: in women, there is a higher prevalence of depressive episodes (35.6% of the time) than in men (28.7%) (Altshuler et al., 2010; Miller et al., 2014).

Various studies link periods with predominant depressive symptoms with impaired quality of life, social and occupational functioning, more markedly than manic/hypomanic or mixed phases (Bonnín et al., 2010; Gitlin et al., 2011; Judd et al., 2003a, 2003b; Kupka et al., 2007).

Given the initial polarity of the depressive type, bipolar disorder can be misdiagnosed as MDD, with disastrous consequences given the possibility of monotherapy treatments with antidepressants to generate a worsening of depressive symptoms, with the appearance of internal tension and irritability or even with a shift towards manic/hypomanic episodes in bipolar patients. Therefore, there are no substantial differences between depressive episodes in unipolar major depression and bipolar disorder, fundamental to allowing adequate and effective clinical treatments from a clinical perspective.

Compared to patients with unipolar depression, bipolar patients maintain a kind of thymic reactivity rather than a stably inflected mood. Furthermore, even during a depressive phase, "counter-polar" symptoms may frequently be present, such as accelerated motor activity, rapid speech, or delusions of magnitude, and are more likely to manifest "opposite" autonomic symptoms (especially hypersomnia, weight gain, and appetite).

In bipolar disorder, moreover, there is a marked symptomatologic seasonality, with a high probability that depressive episodes occur during the winter months (Goldberg, 2004; Rihmer and Kiss, 2002). Finally, signs and symptoms of a psychotic nature are more frequent in bipolar patients, and significant deficits in cognitive aspects have been highlighted (Borkowska and Rybakowski, 2001; Fagiolini et al., 2007; Hirschfeld, 2014).

1.7 Hints of Treatment and Treatment-Resistant Depression

The current treatments for depression are based on psychological interventions and/or therapy with antidepressant drugs. The choice of the type of intervention should be found on the subject's aptitudes and preference, especially for moderate clinical intensity and low risk for the patient. In the most severe cases, however, the guidelines recommend starting treatment as early as possible based, first of all, on the availability of possible interventions (Parikh, Quilty, Ravitz, Rosenbluth, Pavlova, Grigoriadis, Velyvis, Kennedy, Lam, MacQueen, Milev, Ravindran, Uher, et al., 2016). Some clinical pictures suggest pharmacological treatment from the first evaluation, as in the presence of psychotic manifestations, while in others psychotherapeutic interventions will be considered as the first choice, as in pregnant patients (Farahani and Correll, 2012; Huang et al., 2014; Ross et al., 2013). The most recent NICE guidelines (2018) recommend a stepped care approach: consecutive treatment steps to organize the offer of services to patients suffering from depression. In step 1 (suspected depression), support interventions, psychoeducation, and active monitoring of the clinical picture are indicated; in step 2 (persistent subthreshold depressive symptoms or mild-moderate depression) low intensity psychological and psychosocial interventions are indicated; in step 3 (mild-moderate depression that persists despite the interventions of step 2 and severe depression) combined pharmacotherapy with high-intensity psychological interventions are useful; step 4 (severe depression or complicated by non-response to multiple therapies, psychotic symptoms or major comorbidities) must make use of drug therapy, high-intensity psychosocial interventions, possibly electroconvulsive therapy, hospitalization or multi-professional combined therapies.

Psychotherapeutic treatments appear equally effective in the different depressive subtypes. However, it is helpful to associate pharmacological therapy with psychological treatment (Cuijpers et al., 2014; Driessen and Hollon, 2010; Linde et al., 2015; Simon and Perlis, 2010).

Cognitive-Behavioral Therapy (CBT) represents, among the individual psychological treatments with a good number of studies in the literature, the first line both in the acute and in the maintenance phase, given its good efficacy, and can also be helpful in patients who have not responded to drug therapy with antidepressants (Parikh, Quilty, Ravitz, Rosenbluth, Pavlova, Grigoriadis, Velyvis, Kennedy, Lam, MacQueen, Milev, Ravindran and Uher, 2016; Wiles et al., 2013). The effectiveness of CBT is comparable to that of drug treatment, and the benefits are greater the more significant the severity of the initial symptoms; there is also good evidence of efficacy for subthreshold depressive pictures (Bower et al., 2013; Cuijpers et al., 2014; DeRubeis et al., 2005; Weitz et al., 2015). Inter-Personal Therapy (IPT) and Mindfulness-Based Cognitive Therapy are also effective treatments in the acute (IPT) or maintenance (Mindfulness) phase (Galante et al., 2013; Kuyken et al., 2015; van Hees et al., 2013). However, in the meta-analyses, the differences in effectiveness remain modest between different psychological treatment types (Cuijpers et al., 2013; Linde et al., 2015). In general, psychological interventions have, almost always, a slower action than pharmacological treatments, making the latter the first choice (alone or in combination with psychotherapy) in the most serious and/or at higher risk patients (Thase et al., 2007).

Regarding drug therapy, the current antidepressant drugs on the market can be mainly divided into four classes: Selective Serotonin Reuptake Inhibitors (SSRI), Selective Norepinephrine, and Serotonin Reuptake Inhibitors (SNRI), Tricyclic Antidepressants (TCA), and Monoamine oxidase inhibitors (I-MAO).

SSRIs (such as paroxetine, sertraline, citalopram, and fluoxetine) induce a potent and selective inhibition of synaptic serotonin reuptake (much greater than that exerted on norepinephrine reuptake or $\alpha 1$, H1, or muscarinic cholinergic receptors). SNRIs (venlafaxine, duloxetine), on the other hand, show inhibitory activity also towards norepinephrine. IMAOs (such as phenelzine, isocarboxazid, and selegiline) were the first antidepressants to be discovered, although they are currently less used in clinical practice, mainly due to the increased side effects. They work by blocking the Mono-Amino-Oxidase (MAO) enzymes, responsible for the oxidative degradation of biogenic amines (serotonin, dopamine, noradrenaline, and adrenaline). Finally, TCAs

(such as amitriptyline, nortriptyline, clomipramine, and imipramine) owe their name to the typical three-ring chemical structure and act by limiting the pump for the reuptake of 5-HT, NE, and to a lesser extent also of DA (in addition to also determining a block of muscarinic cholinergic receptors, histaminergic H1, and α1 adrenergic receptors). Reboxetine is the only molecule belonging to the class of Selective Noradrenaline Reuptake Inhibitors (NRI) and acts by selectively blocking NE reuptake and increasing its synaptic availability.

A series of molecules are characterized by diversified chemical structures and mechanisms of action, which share the ability to modulate some subtypes of serotonergic and noradrenergic receptors directly. This group includes the specific noradrenergic and serotoninergic antidepressants (NASSA) such as mianserin and mirtazapine (capable of blocking the α2-adrenergic and 5-HT2 and 5-HT3 receptors), trazodone and nefazodone, which in addition to inhibiting the reuptake of serotonin (to a lesser extent than SSRIs) act as agonists on the 5-HT1A receptor and antagonists on the 5HT2A and 5HT2C and α2-adrenergic. Finally, vortioxetine and vilazodone are two antidepressant drugs with a multimodal mechanism of action capable of combining the inhibition of SERT (serotonin transporter) with a differential action on different subtypes of serotonergic receptors. Vortioxetine, in particular, inhibits SERT with a high-affinity binding, acts as a partial agonist on 5-HT1A and 5-HT1B receptors, and as an agonist on 5-HT3 5-HT1D and 5-HT7 receptors (Stahl, 2002). SSRIs and SNRIs are currently the first-choice drugs for the treatment of depression, mainly due to better safety and tolerability profiles compared to TCA and IMAO, which are considered second and third choice strategies, respectively (Gartlehner et al., 2007; Kennedy et al., 2001; Sartorius et al., 2007). In recent years, several articles have been published on the efficacy of quetiapine, a second-generation antipsychotic drug, as monotherapy to treat unipolar depression (Cutler et al., 2009; Li et al., 2016). In clinical practice, the first choice depends mainly on the clinician's assessment and factors such as tolerability, patient preference, and cost (Lam et al., 2009).

In international clinical trials, a ≥50% reduction in the score measured by specific questionnaires for depression is considered as clinical response to the therapy under study, while remission is represented by scores that fall within the non-pathological values. Antidepressant drugs are characterized by a latency period (i.e., the time between the start of treatment and the appearance of significant improvements) of about 2-4 weeks. However, several studies report how the onset of benefits may be present within the first two weeks

of treatment and that this "early" effect is usually associated with subsequent remission (Papakostas et al., 2006; Posternak and Zimmerman, 2005; Taylor et al., 2006; Wade and Friis Andersen, 2006). Conversely, for patients who, after the first two weeks, show only modest signs of improvement (≤ 20% in rating scale scores), an increase in dosage or modification of therapy may already be indicated (Lam et al., 2009).

Despite the availability of various antidepressant drugs, a significant percentage of patients with MDD do not achieve satisfactory clinical benefit. Possible therapeutic alternatives for patients who do not fully respond to treatment with an antidepressant drug are switch to a different antidepressant drug, a combination of antidepressants belonging to different drug classes, the addition of psychological therapy, or augmentation strategies with other psychotropic drugs (Shelton et al., 2010). The STAR * D study (Sequenced Treatment Alternative to Relieve Depression), conducted on 3671 patients with DDM, found that after 12 weeks of therapy with an SSRI (citalopram), only 36.8% of treated patients achieved complete symptom remission (Fava et al., 2006; Rush et al., 2006). Furthermore, from the data collected in this study, it emerges that remission and relapse are closely linked to the number of ineffective antidepressant treatments: as the number of "failed" drugs increases, relapse rates increase proportionally and remission rates decrease (Fava et al., 2006; McIntyre et al., 2014). The CO-MED (Combining Medications to Enhance Depression Outcomes) study compared the effectiveness of combining two antidepressants and monotherapy with an SSRI; evaluating the recruited patients, after 12 weeks and seven months, modest rates of remission for both strategies (37.7% - 38.9%) were reported (Rush et al., 2011).

The results of these two extensive studies suggest that about 2/3 of patients with MDD do not have complete symptom remission, defining a picture of Treatment-Resistant Depression (TRD). TRD is the failure of two or more antidepressant therapies (adjusted for dosage and duration). It represents a clinical and social phenomenon of considerable importance since it is associated with a higher frequency of medical and psychiatric comorbidities, with more significant and severe impairments of socio-occupational functioning, and with greater risks of relapses and suicidality (Fagiolini and Kupfer, 2003; Fekadu et al., 2009; Kornstein and Schneider, 2001; Luchini et al., 2014a; Malhi et al., 2005; Souery et al., 1999). Currently, the main treatment options for TRD include the combination of a psychological intervention (Parikh et al., 2009), the use of neurostimulation methods such as Electro-Convulsive Therapy or Transcranial Magnetic Stimulation

(Kennedy et al., 2009), and the continuation of drug therapy according to optimization, switching, combination or augmentation strategies. Especially in the case in which an initial partial response has occurred, it may increase the drug dosage and/or too long the time of use of the drug already taken (optimization). Switching the drug (usually to a drug of a different drug class) has the advantage of maintaining monotherapy. If, on the other hand, poly-pharmacotherapy is used, a second antidepressant drug can be added, usually of a different class or in any case with different pharmacological characteristics (combination), or the action can be enhanced with drugs that are not primarily considered antidepressants, such as lithium, thyroid hormones and atypical antipsychotics in augmentation (Lam et al., 2009; Luchini et al., 2014b; Spielmans et al., 2013).

However, it must be considered that cases of "pseudo" resistance are widespread, in which various external factors negatively influence the possible response to treatment. Among these, the most frequent seems to be poor compliance with therapy. About 30% of patients stop taking the antidepressant within the first month (more than 40% in the first three months), often following the appearance of side effects or the stigma associated with psychiatric pathology. A lack of inadequate response in terms of clinical improvement may be due to drug intake below the prescribed dose, insufficient duration of treatment, eventual comorbidities (endocrine disorders or taking drugs that can mimic depressive symptoms, such as glucocorticoids or immunosuppressants), and metabolic factors (in particular the concomitant intake of substances that increase the metabolism of the antidepressant drug), so in the initial evaluation before making a diagnosis of TRD, it is necessary to carefully search for the presence of these factors (Hodgkin et al., 2007; Luchini et al., 2014a; Olfson et al., 2006). Finally, in the evaluation of the lack of response to antidepressant therapy, particular attention must be paid to the possibility of facing the depressive polarity of a bipolar disorder: the failure to recognize a bipolar spectrum can be considered as a factor that causes a reduced efficacy of the treatment beyond which involve more frequent risks of relapse, chronicity and suicidal behaviors (Ghaemi et al., 2002; Sharma et al., 2005).

CHAPTER 2 – GLUTAMATE AND DEPRESSION

The high percentage of patients suffering from depression who show resistance to pharmacological treatments available in the market, associated with the high prevalence of depressive pathology in the general population, has pushed scientific research towards the study of antidepressant molecules that use different mechanisms of action from those based on the monoaminergic theory. The glutamate system presents considerable evidence of direct involvement in the pathogenesis of multiple psychiatric diseases, including depression. In this context, the stimulation of glutamate receptors with specific agents has provided significant responses both in the preclinical and clinical settings.

Glutamate (L-glutamic acid) is the primary excitatory neurotransmitter in the central nervous system. It is considered a sort of "master switch of the brain" due to its ability to excite and activate virtually all neurons in the central nervous system. Its presence within the CNS is ubiquitous and uniform, with a distribution involving both neuronal and glial cells. As a neurotransmitter, it is synthesized within the glia, where it also plays a role in the recycling and regeneration of most of the glutamate that is released during neurotransmission. Glutamate is the precursor of γ-aminobutyric acid (GABA), the primary inhibitory neurotransmitter of the central nervous system. The receptors that make glutamate capable of carrying out its actions within the CNS are of two types: ionotropic receptors (channel proteins) and metabotropic receptors (linked to G protein) (Stahl, 2002). A particular characteristic of glutamate is excitotoxicity, which can generate the death of neuronal cells if it is concentrated in a high manner in the extracellular space. This phenomenon seems to be important within the pathogenesis and in the maintenance of brain damage in diseases such as cerebral ischemia, convulsions, brain trauma, and neurodegenerative diseases (Moroni et al., 2004).

2.1 The glutamate receptors

As previously mentioned, the receptors belonging to the glutamate system are of two different types: ionotropic and metabotropic. The ionotropic receptors consist of a ligand-dependent ion channel, which is activated by interaction with glutamate. These receptors are classified into three groups according to the type of selective agonist capable of stimulating them, but also of intrinsic properties such as permeability and kinetics: AMPA receptors (for α-amino-3-hydroxy-5-methyl-4-isoxazole acid - propionic), NMDA receptors (for N-methyl-D-aspartate), and kainate receptors (Mayer, 2016; Moroni, 2004).

The AMPA receptors are located in the post-synaptic membrane and determine a rapid response, in the order of milliseconds, of an excitatory type (depolarization). These receptors are very permeable to Na^+ and almost impermeable to Ca^+ (although there are some exceptions capable of generating a substantial influx of calcium ions). Kainate can also interact with this receptor system, causing a prolonged but partial depolarization (Zhu and Gouaux, 2017) (Moroni, 2004). AMPA receptors seem to represent a therapeutic target for the development of new antidepressant molecules (Greger et al., 2017; Li et al., 2001).

Kainate receptors are ubiquitous in the brain, although less abundant than AMPA receptors. They appear to play a significant role in the functioning of various neural networks and brain neuroplasticity. Their activation contributes to regulating GABA release in the hypothalamic and hippocampal regions (Stahl, 2002; Moroni, 2004).

NMDA receptors are mainly located in the post-synaptic area and have relatively slow activation kinetics (hundreds of milliseconds). The channel has an interesting functioning: it opens, allowing the entry of calcium ions and the consequent cascade of events, only if three conditions co-occur. The glutamate must occupy the binding site on the NMDA receptor, glycine or D- serine must bind to the site on the NMDA receptor, and the membrane must at least partially depolarize (removing a block exerted by magnesium ions) (Stahl, 2002). Through the influx of calcium ions, NMDA receptors regulate significant neurobiological effects of a trophic nature and survival of neurons during the development phase, the modulation of essential processes for

memorization and learning, or the activation of excitotoxicity mechanisms that lead to neuronal death (Dang et al., 2014; Hansen et al., 2018).

Metabotropic glutamate receptors are part of G protein-associated receptors and are ubiquitously distributed in the central nervous system. They recognize each other at least eight subtypes of metabotropic glutamate receptors, organized into three distinct groups. Group II and III receptors are present at the presynaptic level, where they block the release of glutamate by functioning as autoreceptors. Group I receptors are mainly located at the post-synaptic level, where they seem to act as facilitators of the glutamate ionotropic receptors, enhancing excitatory transmission (Stahl, 2002). The result consists in a sort of barrier of low-intensity stimuli and an expansion of those high-intensity stimuli, able to overcome the presynaptic inhibition: the dislocation of the various receptors, therefore, allows the establishment of a sort of system of filtering capable of intensifying the signal/noise ratio of the stimuli converging on this circuit (Jong and O'Malley, 2017).

Although glutamate is ubiquitously present in the brain, some pathways of particular neuropsychopharmacological relevance are recognized:

- cortical-tronco-encephalic glutamate pathways, a set of descending pathways that project from cortical pyramidal neurons to brain stem nuclei, including raphe for serotonin, the ventral tegmental area and the substantia nigra for dopamine and the locus coeruleus for norepinephrine;
- corticostriatal pathways, which terminate on GABAergic neurons which constitute a relay station in the pale globe;
- hippocampal-striatal path, which goes from the hippocampus to the nucleus accumbens and, according to some authors, represents the main pathway related to the pathogenesis of schizophrenia;
- via thalamocortical, which carries information (often of a sensory type) from the thalamus to the cortex;
- via corticothalamic, which projects directly to the thalamus where it modulates the neuronal response to sensory information;

- direct and indirect corticocortical pathways, a complex of glutamate pathways capable of generating an excitatory (through direct inputs mediated by glutamate) or inhibitory (through indirect inputs mediated by secreting GABA interneurons) action on cortical neurons.

2.2 Therapeutic implications

Over the last few years, NMDA receptors have been extensively studied both for their particular transmission characteristics and their emerging potential in the treatment of affective and psychiatric disorders in general (Gonzalez-Burgos and Lewis, 2012; Han et al., 2014; Lally et al., 2015; Naughton et al., 2014). Numerous clinical *in vitro* and *in vivo* studies hypothesize a possible contribution of alterations in glutamate neurotransmitter modulation to the pathogenesis of mood disorders and focus on the therapeutic potential of some molecules with the ability to bind to glutamate receptors acting as specific agonists (Gerhard et al., 2016; Lener et al., 2017; Monaghan et al., 2012; Sanacora et al., 2008).

Patients with affective disorders show a lower level of glutamate in the dorsolateral prefrontal cortex, in other prefrontal cortical areas (dorsomedial and dorso-anterolateral), and anterior cingulate cortex, while in the occipital cortex, the levels of the same neurotransmitter are probably increased in proportion to the duration of the disease (Arnone et al., 2015; de Diego-Adeliño et al., 2013; Hasler et al., 2007; Salvadore and Zarate, 2010; Sanacora et al., 2012; Yildiz-Yesiloglu and Ankerst, 2006).

Two PET studies have shown a significant reduction in the density of a subtype of glutamate receptors in depressed patients, suggesting a determining role of the alteration of the signaling system of this receptor in the development of depressive pathogenesis (DeLorenzo et al., 2015; Deschwanden et al. al., 2011).

In patients with bipolar disorder, investigations on the role of glutamate transmission in the pathogenesis of the disorder are more complicated, mainly due to frequent therapy with mood-stabilizing drugs that alter brain levels of glutamate and GABA (Chitty et al., 2013; Sanacora et al., 2008). Despite these limitations, a recent study highlighted an association between the number of depressive or manic episodes and the high

levels of glutamate in the anterior cingulate cortex (during the euthymic phase) (Ehrlich et al., 2015). It seems that in patients with bipolar disorder, there is also a dysfunction of oxidative metabolism in glutamate neurons, corroborating the hypothesis of pathophysiology that intersects with the mechanisms of inflammation (Dager et al., 2004; Haroon et al., 2016).

The primary evidence of the validity of involvement of the glutamate system in depressive pathogenesis comes from numerous clinical studies investigating the preclinical and clinical responses of glutamate receptor stimulation with specific agents. Among these, the most studied is certainly ketamine, an antagonist of the NMDA receptor, which we will discuss later; the centrality of these studies is the result of the promising results obtained so far in the treatment of depressive symptoms in unipolar and bipolar patients, with rapid antidepressant action, even at subanesthetic doses, and the positive effects on suicidal ideation already in the period of a few hours (Berman et al., 2000; Mathew et al., 2012; McCloud et al., 2015; Xu et al., 2016; Zarate et al., 2006).

In addition to ketamine, many other molecules act on the glutamate system for mood disorders. Rapastinel is a modulator of the glycine site of the NMDA receptor; a randomized, double-blind study conducted on 116 patients with MDD and non-responders to previous therapy showed a significant reduction in Hamilton Depression Rating Scale (HAM-D) scores compared to placebo (Burgdorf et al., 2013; Moskal et al. ., 2005, 2014).

Lanicemine, a non-competitive NMDA receptor antagonist originally designed for stroke therapy, has been used in a clinical trial of TRD patients showing a rapid, if short-lived, antidepressant response in approximately one-third of patients (Newport et al., 2015; Sanacora et al., 2014).

Memantine, an NMDA receptor antagonist indicated for the treatment of Alzheimer's disease, has been shown to improve and maintain the antidepressant effects of ketamine in patients with bipolar depression or MDD and to prevent relapses (Anand et al., 2012; Serra, 2014; Serra et al., 2015).

Nitric oxide, a non-competitive antagonist of the NMDA receptor commonly used as an inhalation anesthetic, showed in a study on a small sample of patients with TRD a response in 20% of subjects, compared to 5% of

the placebo group, and remission in the 15% of the sample (0% in the placebo group) (Maze et al., 2008; Nagele et al., 2015).

CHAPTER 3 - KETAMINE

Ketamine is a glutamate NMDA receptor antagonist. It inhibits the receptor in the open channel conformation and mediates the release of glutamate downstream. To this action is added a weak activity on the σ1 receptors, on the norepinephrine transporter, on the μ receptors for opioids, and the serotonin transporter (Stahl, 2002). This compound was synthesized in 1963 by the pharmaceutical company Parke-Davis and administered for the first time the following year to a human subject for anesthetic purposes (Reich and Silvay, 1989).

Initially, its clinical development was part of the search for an alternative anesthetic molecule to phencyclidine due to the fewer side effects of the hallucinogenic and psychomimetic type. In 1970 the FDA (Food and Drug Administration) approved ketamine for three indications: anesthesia during diagnostic-surgical procedures that do not require relaxation of the skeletal muscles, induction of anesthesia before the administration of another drug with general anesthetic action, and in combination with low-potency anesthetics (Li and Vlisides, 2016). Different clinical uses, although off-label, include sedation in intensive care units and analgesia in the treatment of bronchospasm. It is also recommended to use ketamine to induce anesthesia before electro-convulsive therapy (ECT) in depressed patients due to its protective activity against excitotoxic damage from the glutamate increase during ECT (Hudetz and Pagel, 2010; Krystal et al., 2003; Salehi et al., 2015).

The anesthetic state induced by ketamine is characterized by a normal pharyngolaryngeal reflex and a slight increase in muscle tone, with normal cardio-respiratory function (although occasional minimal and transient respiratory depression may occur). Anesthesia for surgical procedures is generally induced with intravenous administration of ketamine at doses of approximately 1-3 mg/kg of body weight (Green and Johnson, 1990; Knox et al., 1970).

Ketamine is metabolized to two primary metabolites: norketamine, the predominant metabolite, and dihydroketamine, a nearly inactive metabolite. Norketamine is a non-competitive antagonist of the NMDA receptor and contributes to the analgesic action. After parenteral administration of ketamine, the plasma

concentration of norketamine increases while always remaining at lower levels than the plasma concentration of ketamine. After oral administration, plasma levels of norketamine are approximately four times higher than those recorded during parenteral administration.

The effect of ketamine on the monoamine system results in an inhibitory action on the transport of serotonin, norepinephrine, and dopamine. Furthermore, ketamine and its metabolites inhibit the deamination processes of monoamines and interact weakly with 5-HT3 receptors, even if this interaction does not seem to have clinical relevance (Rammes et al., 2001). Ketamine also stimulates dopamine D2 receptors at high concentrations, while at subanesthetic doses, no effect on D2 receptors or dopamine release was found (Aalto et al., 2002; Seeman et al., 2005, 2009).

The data concerning the tolerability of ketamine are mainly referred to its use in the anesthetic field. However, recent clinical trials in the psychiatric field have also investigated safety and tolerability at subanesthetic and sometimes repeated dosages. When ketamine was used to search for an antidepressant response, the most commonly reported adverse events were dissociative seizures, confusion, euphoria, visual distress, dizziness, increased blood pressure, and increased libido. These effects did not last longer than 80 minutes from the start of infusion therapy (Zarate, Singh, Carlson et al., 2006). In a sample of TRD subjects undergoing ketamine treatment, 17% presented with significant dissociative symptoms. In the same study, mean blood pressure values increased by approximately 20 mmHg for systolic pressure and ten mmHg for diastolic pressure; for two patients, it was necessary to suspend the infusion due to an excessive hemodynamic response (Murrough, Iosifescu, et al., 2013). Currently, there is insufficient data to evaluate the safety and tolerability of chronic use of ketamine, and the evidence now available is based on experiments conducted on drug addicts who use the drug for recreational purposes (therefore at uncontrolled dosages). Clinical studies conducted on ketamine users have mainly highlighted the appearance of a slowdown in responses to stimuli, anomalies in the capacity of coding information, and alterations of semantic and episodic memory (Curran and Morgan, 2000; Morgan et al., 2003, 2010; Rowland et al., 2005). However, even in the recreational use of ketamine, any effects on neurocognitive functions that occur in acute phase tend to be resolved in a short time and seem to leave no residual manifestations after a few days of ketamine administration (Curran and Morgan, 2000). The cognitive deficits highlighted among

ketamine abusers appear to depend on dose and frequency of use. In a longitudinal study on a sample of 150 subjects (healthy volunteers, former ketamine users, ketamine "abusers," occasional ketamine users, and drug addicts), the cognitive performance and memory abilities of frequent ketamine users were found to be deficient.

On the other hand, no significant alterations were found between occasional consumers and former consumers, suggesting substantial reversibility of cognitive alterations linked to chronic use of the substance (Morgan et al., 2010). Preclinical studies indicate that frequently taken high dosages of the drug lead to non-reversible neuronal damage (Olney et al., 1991). Finally, chronic ketamine abuse has also been associated with dilation of the biliary tract and cystitis onset (Chen et al., 2009; Wong et al., 2009).

In addition to intravenous infusion, ketamine can be also administered by intramuscular, intranasal, oral, sublingual, subcutaneous, transdermal, epidural, or intra-articular way. When taken orally, the drug undergoes an extensive hepatic first-pass effect which reduces its bioavailability by up to approximately 16%. Oral administration is characterized by higher blood levels of norketamine than other ways of administration. The metabolite seems to contribute to the analgesic action and to the duration of efficacy of the oral drug (it is used in resistant cases of chronic pain) (Blonk et al., 2010). Intranasal administration of ketamine has shown promising efficacy for some pediatric dental, surgical and radiological anesthetic and pre-anesthetic procedures (Roelofse et al., 2004; Weber et al., 2003). Efficacy and tolerability of the drug administered intranasally have also been evaluated in adult patients with migraine, chronic pain, and neuropathic pain, albeit on limited patient samples (Carr et al., 2004; Huge et al., 2010; Kaube et al., 2000).

Ketamine is a known substance of abuse, and in Italy, it is included among the narcotic substances in Tables I and II, Section A (Medicinal substances and compositions) of the Presidential Decree 309/90 and subsequent amendments It circulates under the slang name of special K, kit kat, vitamin K, and is often taken in search of the "out-of-body" dissociative effect. In a survey carried out at the end of 2009 among young adults (18-27 years) and published in the Mixmag Drugs Survey, a popular magazine on nightclubs in the United Kingdom, it appears that ketamine was taken in that year by 50.7% of the sample interviewed. The difficulty in the synthesis process of the molecule suggests that the ketamine sold on the illegal market comes from the

distraction of commercial pharmaceutical products (Department for drug policies, 2013; World Health Organization, 2016).

3.1 Characteristics, mechanism of action, clinical evidence

The mechanisms underlying the antidepressant effects of ketamine are still largely unknown. However, it appears evident that it is not possible to reduce them to a simple antagonistic action against the NMDA receptor. It is assumed that a cascade of events is induced, such as to lead to rapid clinical response and its maintenance even after the metabolization of the molecule (Zanos and Gould, 2018).

Low doses of ketamine induce psychomimetic effects and dissociative symptoms after about 30-40 minutes from the infusion, which disappear completely after about 80 minutes. Presumably, this time course is linked to the short half-life of ketamine (about 180 minutes). After the first phase, in which the psychomimetic effects appear, the antidepressant action of ketamine begins to appear, which is maintained for about a week after a single infusion. This means that ketamine can induce a cascade of events responsible for a rapid antidepressant effect maintained even after the molecule has been definitively metabolized and eliminated (Duman et al., 2012; Zarate et al., 2013).

In animal models, ketamine induces stimulation of the glutamate pathway at the cortical level, probably through the inhibition of GABAergic neurons and the consequent disinhibition of cortical pyramidal cells (Homayoun and Moghaddam, 2007; Moghaddam et al., 1997). Neuroimaging studies also confirm the action of low doses of ketamine at the cortical level, particularly in the prefrontal and anterior cingulate areas, thus supporting the results obtained in animal models (Covington et al., 2010; Långsjö et al., 2003, 2004; Salvadore et al., 2009, 2010).

One of the main hypotheses on the action of the drug suggests that ketamine acts as an antagonist on the NMDA receptors of GABAergic interneurons, causing their disinhibition and, therefore, the efflux of glutamate into the prefrontal cortex (Moghaddam et al., 1997). In this way, glutamate increases the AMPA receptor activation, leading to a high release of Brain Neurotrophic Factor (BDNF). In the next phase, it is hypothesized that the activation of the mTOR protein kinase (which regulates the growth, proliferation,

motility, and survival of neuronal cells, their protein synthesis, and transcription processes) initiates a cascade of events capable of inducing the translation of proteins responsible for rapid (24 hours) plastic changes of the prefrontal cortex, to generate the immediate antidepressant effect typical of ketamine (Duman et al., 2012; Dwyer et al., 2012; Li et al., 2010).

Ketamine, in addition to having its antagonistic effect on NMDA receptors, also has a binding site for AMPA receptors, inducing an increase in their activity. It seems that the antidepressant effect of ketamine cannot be separated from the binding with the AMPA receptor, so much so that animal models treated, before the administration of ketamine, with an antagonist of the AMPA receptors, did not show antidepressant effects (Autry et al., 2011; Li et al., 2010; Zhou et al., 2014)

Furthermore, ketamine induces rapid changes in the presynaptic membrane of the hippocampal region, effects that traditional antidepressants achieve only after prolonged treatment (Müller et al., 2013). The metabolites of ketamine, in particular norketamine, appear to play a longer-lasting active role than ketamine itself and, therefore, could be related to the long duration of action of the drug (Zanos et al., 2016).

The first clinical evidence of the potential antidepressant properties of ketamine dates back to 2000 when a double-blind study, conducted in eight depressed patients (seven with MDD, one with bipolar depression), compared the effects of ketamine administered intravenously at subanesthetic doses (0.5 mg/kg in 40 minutes) with those of a saline placebo. Four patients (out of 7 who completed the study) showed an antidepressant response within 4 hours of infusion (defined as at least a 50% reduction in the HAM-D score), persisting even 24, 48 and 72 hours after the infusion treatment (Berman et al., 2000). Ketamine appeared to act directly on the core aspects of depression, such as inflected mood, apathy, anhedonia, and suicidal ideation, rather than inducing a transient and nonspecific moment of euphoria (Mathew et al., 2012).

The first study was subsequently replicated in a larger sample of patients (N = 17), of which 71% showed a significant clinical response and 29% complete symptom remission within 24 hours. In this case, the therapeutic effect was maintained for at least 72 hours by 50% of the subjects and one week by 35% (Zarate et al., 2006).

The intranasal use of ketamine has been studied in DCS, bipolar disorder, and obsessive-compulsive disorder, albeit in small patient populations (Adams et al., 2017; Lapidus et al., 2014; Papolos et al., 2013). This route of administration can induce an antidepressant effect even faster than that produced by intravenous infusions and has a better level of tolerability and a lower incidence of side effects not only of dissociative and psychoticomimetic type (Opler et al., 2016)

Based on the first experimental results, it was assumed that repeated administration of ketamine represents a concrete therapeutic prospect for depressed patients resistant to standard treatments. In clinical research conducted on a sample of 10 patients with TRD, resistant to at least eight pharmacological treatments with antidepressants, the effects of repeated infusions of ketamine over two weeks were studied: subjects who presented a reduction of at least 50 % of MADRS scores following first drug administration received five additional intravenous ketamine infusions. Almost all (9 out of 10 patients) had an initial response to treatment and, therefore, were recruited for subsequent infusions. An average reduction in the MADRS score of 85% and an average relapse time of 19 days (during which the subjects did not take oral antidepressants) were observed, although with high variability. In this study, the dissociative and psychotomimetic effects were short and transient (Aan Het Rot et al., 2010). A recent study conducted by the National Institute of Mental Health showed how a single intravenous dose of ketamine (dosage of 0.5 mg/kg) could induce antidepressant effects in patients who previously unresponsive to ECT (Ibrahim et al., 2011).

The efficacy of ketamine in repeated administration has also been confirmed by other clinical studies, without any increase in side effects but, indeed, a significant attenuation of dissociative adverse events (Diamond et al., 2014; Singh, Fedgchin, EJ Daly, et al., 2016). The treatment was also tested in patients with bipolar disorder. In a depressive phase, experiencing rapid clinical effects without mood changes (mood stabilizing therapy was always maintained during treatment) (Diazgranados et al., 2010; Zarate et al., 2012). Two recent case reports have described the effects of administration, in ascending doses, of intramuscular ketamine in two patients with bipolar depression refractory to drug therapy. An initial dose of 0.5 mg/kg produced only a slight reduction in depressive symptoms after the 24-hour infusion, while higher doses (0.7 mg/kg and 1.0 mg/kg) had a better therapeutic effect. (Glue et al., 2011).

The use of ketamine could also represent a valid and fast therapeutic option for patients with suicidal ideation or a high risk of anti-conservative behavior (Murrough et al., 2015). A recent study in 14 emergency patients with significant suicidal ideation showed that a single intravenous bolus of ketamine (0.2 mg/kg over 1-2 minutes) rapidly reduced suicidal thoughts (Larkin and Beautrais, 2011). Another study in 14 patients with suicidal thoughts presents stably for at least three months evaluated the effects of increasing intravenous ketamine doses over three weeks (from 0.5 mg/kg to 0.75 mg/kg). During treatment, half of the patients showed remission of suicidal ideation (regardless of any remission of depressive symptoms). Two patients in this group maintained this effect at a 3-month follow-up (Ionescu et al., 2016). Even considering only patients with severe suicidal ideation (as defined by a score> 4 on the Scale for Suicidal Ideation), the effect of ketamine in addition to conventional antidepressant therapies compared to an active comparator (midazolam) was confirmed, regardless of the effect on depressive symptoms, within 24 hours of administration and with the maintenance of efficacy for at least six weeks (Grunebaum et al., 2018). In various studies, a rapid reduction of explicit and implicit suicidal behaviors has been highlighted through computerized tests, the Scale for Suicidal Ideation, and the evaluation of specific items of MADRS (Nock and Banaji, 2007; Price et al., 2009). Numerous studies in the literature confirm the large and significant effects of ketamine on suicidal ideation and suicide attempts (Bartoli et al., 2017; Diaz Granados et al., 2010; Thangathurai and Mogos, 2011).

3.2 S-Ketamine: clinical evidence

Ketamine is commonly administered as a racemic compound of the isomers, R-ketamine and S-ketamine (esketamine), which have different molecular characteristics. The use of Esketamine in Europe was first approved in 1998 (currently in use in Finland, Germany, Denmark, Iceland, and the Netherlands) to induce and maintain general anesthesia to enhance the efficacy of other local anesthetics and as an analgesic in emergency medicine. Esketamine has a high affinity for the NMDA receptor phencyclidine binding site (approximately 3-4 times higher than R-ketamine) (Vollenweider et al., 1997). According to recent evidence, the left-handed isomer of ketamine has a greater affinity for opioid receptors and greater potency as an ACh antagonist than the R-ketamine isomer (Mathew et al., 2012). Furthermore, in a recent pilot study on patients

with TRD, no substantial differences emerged between the racemic form and esketamine in terms of efficacy on depressive symptoms. At the same time, although there are no direct comparisons between the two substances in the literature, the latter was better tolerated than the first, as it was less associated with dissociative and psychotomimetic adverse events and a lower frequency of retrograde amnesia (Andrade, 2017; Paul et al., 2009).

A 2016 study evaluated the effect of esketamine in TRD patients with two different intravenous dosages (0.2 mg/kg and 0.4 mg/kg). Both were rapidly effective and with limited side effects (mainly transient dissociative symptoms, dizziness, dry mouth, and headache). The beneficial effect of the drug lasted for about two weeks; the lower dosage was as effective as the higher dose, but with fewer side effects (Singh, Fedgchin, E Daly, et al., 2016).

CHAPTER 4 - KETAMINE IN CLINICAL PRACTICE

Given the extensive literature supporting the use of ketamine and esketamine in the treatment of mood disorders, particularly in patients resistant to conventional treatments, in the recent years, the University of Siena Department of Molecular and Developmental Medicine has included these molecules in the range of possible therapies. Being a treatment not yet approved in Italy, this study was carried out in the context of experimental studies or off-label protocols.

4.1 Objective of the study

The objective of the study of this thesis is the evaluation of the clinical response obtained from repeated administration of intravenous ketamine and intranasal esketamine in patients with TRD. To conduct this analysis, changes in the Montgomery-Asberg Depression Rating Scale (MADRS) administered before each intake of ketamine or esketamine and according to specific subsequent endpoints, were evaluated.

4.2 Material and methods

4.2.1 S-Ketamine Protocol

The University of Siena Department of Molecular and Developmental Medicine participated as the Italian leader in a multiphase and multicentre, randomized double-blind study on the use of intranasal esketamine in addition to an oral antidepressant for the prevention of relapses in TRD ("SUSTAIN-1" and "SUSTAIN-3" ").

The purpose of the study was to evaluate the efficacy, safety, and tolerability of the combination of intranasal esketamine and oral antidepressant therapy, comparing the results with those derived from the use of an active comparator (therapy with an only oral antidepressant) associated with intranasal placebo. The timing and methods of possible relapse in patients who responded positively to treatment with intranasal esketamine in addition to oral antidepressants were also evaluated.

The inclusion criteria in the study were:

- age between 18 and 64;
- diagnosis of single episode MDD or recurrent MDD without psychotic symptoms, according to DSM criteria;
- lack of response to at least two antidepressants (but less than 5 in the current episode) administered at adequate dosages and for sufficient time (according to the criteria reported in the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire MGH-ATRQ).

The main exclusion criteria were:

- non-response to previously to ketamine, esketamine, or all possible oral therapies to be taken during the study in the current episode;
- presence of a personality disorder according to DSM criteria;
- implantation of vagus nerve stimulation or deep brain stimulation or ECT during the recent episode;
- active suicidal ideation in the six months before the start of the study;
- history of seizures (except for febrile convulsions in infancy resolved without success);
- medical conditions in the cardiovascular and pulmonary areas (including uncontrolled arterial hypertension, electrocardiographic abnormalities, OSAS), liver disease, glaucoma, uncontrolled diabetes, neoplasms, current infectious diseases;
- substance abuse (as certified by the execution of drug screens during the enrollment).

The study was divided into five phases:

1. Screening/observation phase lasting a total of 4 weeks, during which the inclusion and exclusion criteria were evaluated, with the possibility of increasing up to another three weeks the time during which to carry out a possible progressive reduction of the pre-existing oral antidepressant therapy (ineffective);

2. 4-week induction phase, during which all subjects included in the study were treated twice-weekly with esketamine (flexible-dose: 56 mg or 84 mg) in combination with a chosen oral antidepressant therapy (sertraline, escitalopram, duloxetine or venlafaxine);
3. 12-week optimization phase, to which only the subjects deemed responders to the induction phase (as defined by at least a halving of the MADRS score) had access, to reach the optimal frequency of administration (passing from 2 times a week once a week or once every two weeks depending on the severity of the depressive symptoms present) to consolidate the clinical effect;
4. A maintenance phase of variable duration, accessed by subjects who showed a stable response (MADRS reduction ≥50% from baseline) or complete remission (MADRS ≤2 in the last four weeks of the previous phase), during the which patients were randomized (double-blind) between a group receiving oral antidepressant therapy + intranasal esketamine and a group receiving oral antidepressant therapy + intranasal placebo;
5. 2-week follow-up phase (performed for each subject who received at least one dose of intranasal esketamine from the time of study exit).

During the study, the MADRS assessments were carried out through telephone interviews administered by external evaluators to minimize the risk of bias. Laboratory and ECG tests were performed both in the screening phase (to exclude the presence of pathologies reported in the exclusion criteria and to acquire reference values) and, with defined frequencies, during the course of the study.

For this work, we focused only on the induction and optimization phases, as we do not have the database for the maintenance phase. Therefore, the data analysis was conducted on all subjects belonging to the Siena clinic who received intranasal esketamine treatment for at least four weeks, in addition to oral antidepressant monotherapy.

4.2.2 Off-label use of ketamine

In recent years, starting from several studies in the literature on the efficacy and tolerability of ketamine at subanesthetic doses administered intravenously, off-label use of ketamine has been carried out in the context of mood disorders in the University of Siena Department of Molecular and Developmental Medicine. However, this is outside the regulated therapeutic indications. In particular, the use of ketamine in patients suffering from unipolar resistant depression to traditional pharmacological treatments was evaluated.

Before administering ketamine, the patients were informed of the risk/benefit ratio of the treatment and signed the relative informed consent. For each patient, the protocol was approved by the Health Department of the hospital. Before starting the treatment, an anesthetic visit, an internal visit, ECG, and test evaluation (MADRS) were carried out.

The dose of ketamine varies between 0.25 and 0.50 mg per kg of body weight, administered intravenously. The dose of 25-50 mg of ketamine was administered for approximately 50 minutes. After the first administration, patients who had a reduction of greater than or equal to 50% in the MADRS score at baseline, received five additional infusions of ketamine, distributed over two weeks, and at least one day apart. In the opinion of the clinician, the infusions were continued with the frequency of one infusion per week for a flexible time.

The ketamine infusion procedure was performed on inpatients or outpatients. Clinical and instrumental monitoring of vital signs by an anesthetist were also carried out.

Follow-up visits after the last infusion were done twice a week for the first four weeks or until relapse.

4.2.3 The Montgomery-Asberg Depression Rating Scale

The Montgomery – Asberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979) is a structured clinical interview suitable for identifying changes in depressive symptoms during drug therapy. Starting from the Comprehensive Psychopathological Rating Scale (CPRS), the MADRS is composed of ten items most sensitive to changes during treatment in the depressive picture. The severity, frequency, duration, and functional impairment related to the symptom are considered in the evaluation. The 10 items are evaluated

on a 7-point scale (score ranging from 0 = absent, to 6 = maximum severity). The total score expresses the general severity of the symptoms. The assessment takes approximately 15-20 minutes, so the scale is included among the so-called RAI (Rapid-Assessment Instruments).

Below, we reported the description of the individual items:

- Apparent sadness, understood as discouragement, depression, and despair (something more than a simple lowering of mood) that transpire from language, facial expressions, and posture. It is evaluated based on depth and the inability to act positively.
- Reported sadness: verbalization of a depressed mood, regardless of whether or not it is also manifest; it includes melancholy, discouragement, or the feeling of not being able to be helped, of being hopeless. It is assessed based on intensity, duration, and the degree to which events reportedly influence mood.
- Inner tension: feelings of ill-defined discomfort, irritability, inner agitation, nervous tension growing up to panic, terror, or anguish. It is assessed based on intensity, frequency, duration, and degree of reassurance called for.
- Reduced Sleep: understood as a reduction in the duration or depth of sleep compared to the type of sleep considered normal by the patient.
- Reduced appetite: loss of appetite compared to the usual one; it is assessed based on loss of desire to eat or the need to eat forcefully.
- Concentration difficulties: difficulty gathering ideas that can even lead to the inability to concentrate; it is evaluated based on the intensity, frequency, and degree of impairment.
- Lassitude: Difficulty starting the day or slowness and carrying out daily activities.
- Inability to feel: subjective experience of a decrease in interest in the surrounding environment or activities that generally give pleasure; impaired ability to react emotionally appropriately to circumstances or people.
- Pessimistic thoughts: ideas of guilt, inferiority, self-accusation, sinfulness, remorse, and ruin.
- Suicidal thoughts: feeling that life is not worth living, that natural death would be welcome or suicidal ideas and preparations; suicide attempts must not, in themselves, influence the assessment.

4.3 Results

Regarding the phase-III study on the use of intranasal esketamine in association with oral antidepressant monotherapy (from now on referred to as "esketamine"), 30 patients began the screening phase within the University of Siena Department of Molecular and Developmental Medicine. Of these, 11 patients successfully passed four weeks of screening and received at least one intranasal dose of esketamine. However, only nine subjects completed the induction phase (4 weeks) due to the voluntary withdrawal of 2 subjects due to difficulties in tolerating the dissociative side effects, even if mild to moderate, which occurred after the first administration. Three patients were admitted to the optimization phase, completing the following 12 weeks with flexible interval dosing.

The off-label use of intravenous ketamine (hereafter referred to as "ketamine") has been proposed to 9 patients with TRD. Of these, two patients underwent more than ten intravenous administrations in 2017. Nevertheless, the limited data available (related to using a different protocol and the inability to find medical records) did not allow us to include these patients in the evaluated sample. The remaining seven patients completed the protocol. The total sample of patients enrolled in the ketamine or esketamine protocols is therefore composed of 16 subjects.

Statistical analyzes are presented as mean and standard deviation for quantitative variables and as frequencies and percentages for qualitative variables. The pre- and post- comparisons were performed using Student's t-test on paired samples given the normal distribution of the variables (Shapiro-Wilk test). The comparison between the efficacy of the two active ingredients was performed only by qualitative comparison of the average values of the total scores at the fourth week (or 28 days) without using a statistical test due to the limitations of the sample (low number). Fisher's exact test performed the comparison of the tolerability of the two drugs. Statistical significance was set at 5% ($p < 0.05$). Analyzes were performed with STATA16 statistical software (StataCorp., College Station, TX, USA).

The detection of the scale for each sample took place according to the endpoints shown in Figure 1.

The description of the sample characteristics, the doses used, the side effects, and the single items of the MADRS were divided into two groups, esketamine and ketamine.

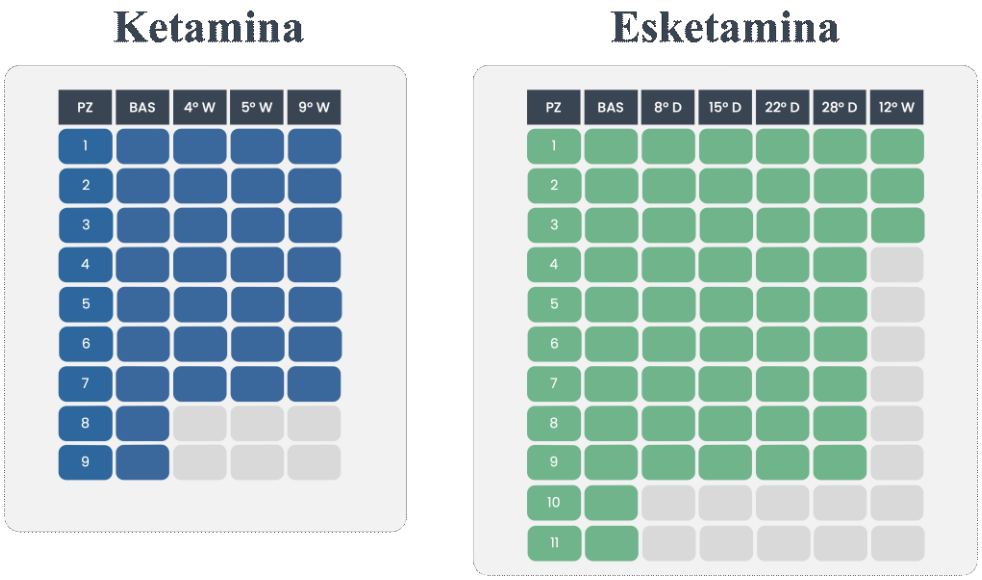


Figure 1 – Endpoints - MADRS

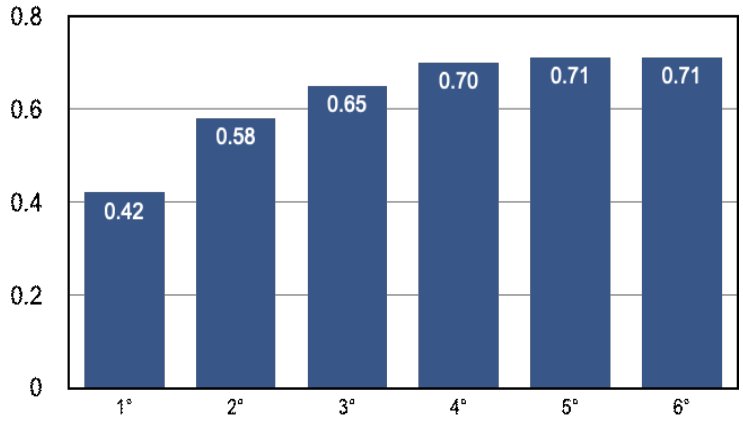
4.3.1 Intravenous ketamine

The sample subjected to ketamine was composed of 7 patients (28.6% women and 71.4% men) with a mean age of 55.3 (SD ± 5.6) years. About 71% of patients had a high school graduation, and 28.6% had a university degree. About 57% of subjects carried out a work activity.

Table 1 – Patients' characteristics (n = 7)

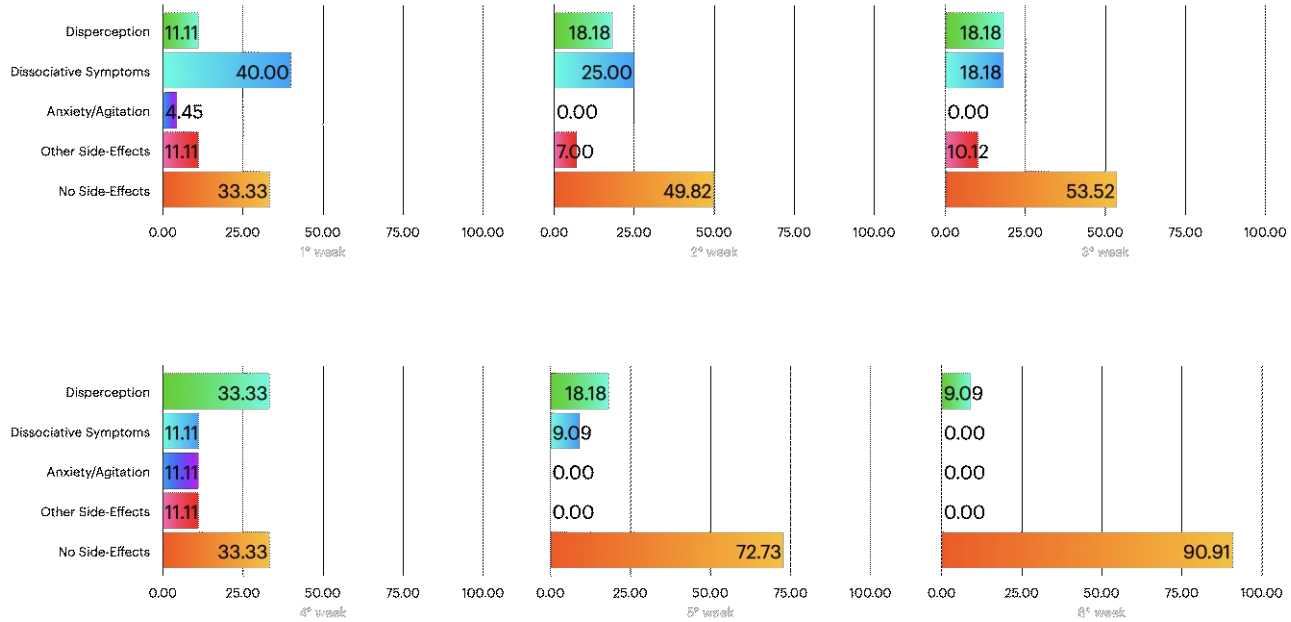
Demographic characteristics		**Educational Background**	
Gender, n(%)		**Qualification, n(%)**	
Males	5 (71.43)	High-School	5 (71.43)
Females	2 (28.57)	Degree	2 (28.57)
Age, mean (SD)	**55.3 (5.6)**	**Occupational status, n(%)**	**4 (57.14)**

The ketamine dosage was gradually increased over the weeks. In the first week, the mean dose was 0.42 (SD ± 0.10) mg/kg. At the fourth week of treatment, the dose was increased (0.70 ± 0.09 mg/kg), reaching a stable level of 0.71 (SD ± 0.10) mg/kg in the following two weeks. The full description of the dosages during the first six weeks of treatment is shown in Graph 1.



Graph 1 – Average Ketamine Dose per Week (mg/kg)

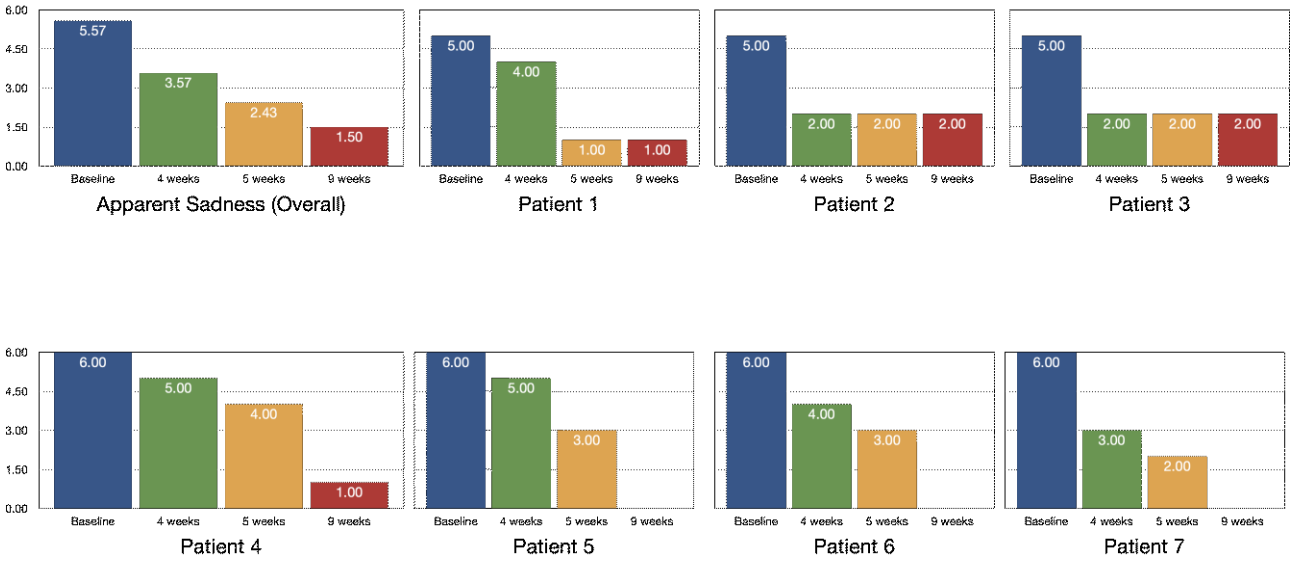
During the first six weeks of observation, there was a gradual reduction in side effects. In particular, during the first week of treatment, 40% of patients presented dissociative symptoms and 11.1% disperception; a further 11.1% had transient side effects such as nausea, headache, sedation; 4.5% experienced transient states of anxiety/agitation; 33.3% did not report any side effects. During the second week, 25% of patients presented dissociative symptoms, 18.2% reported mild distress, 7% symptoms such as nausea/sedation/headache, while 49.8% reported no side effects. This trend of decrease in side effects was also maintained during the third week. In the fourth week, there was a slight increase in patients with despair (33.3%), anxiety/agitation (11.1%), and other symptoms (11.1%). Dissociative symptoms and disperception were observed for 18.2% and 9.1% of patients, respectively, during the fifth week. Only 9.1% of patients reported disperception during the sixth week. All percentages are presented in Graph 2.



Graph 2 – Percentage of patients with side effects during the first 6 weeks

4.3.1.1 Apparent sadness

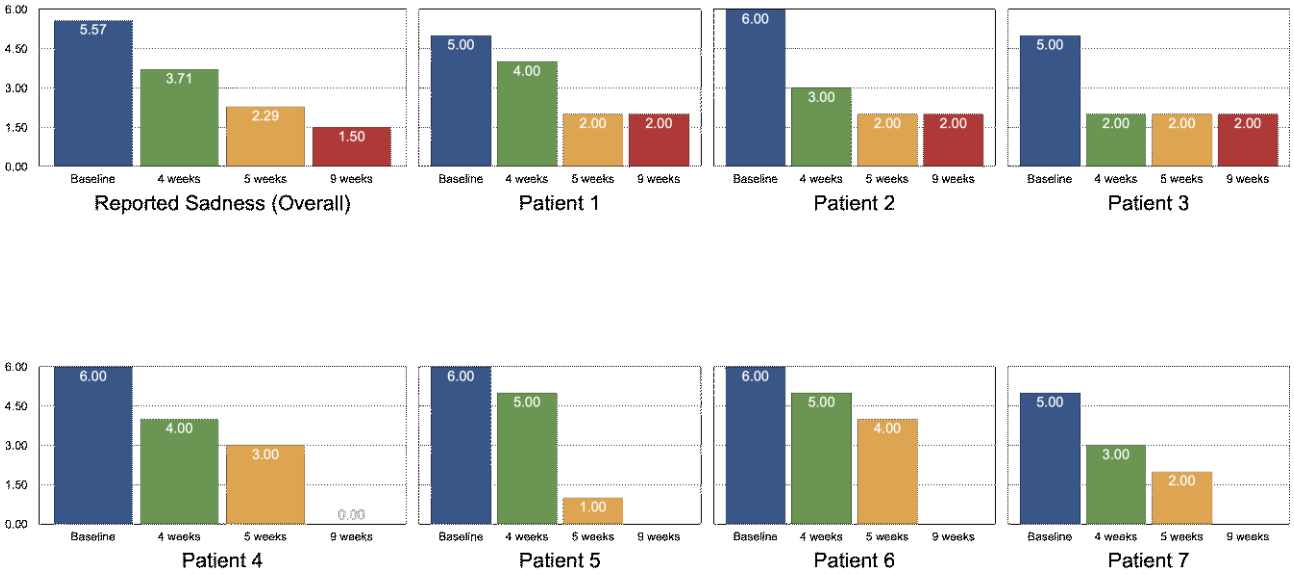
During the nine weeks of observation, there was a gradual decrease in the MADRS item values relating to apparent sadness. After four weeks of treatment, there was a significant decrease ($p < 0.05$) in the value of the item. This decreasing trend was maintained over the following weeks, again with a statistical difference of less than 0.01 in the comparisons between the baseline and the subsequent endpoints. The description of the decrease for each patient is reported together with the average in Graph 3.



Graph 3 – Apparent Sadness

4.3.1.2 Reported sadness

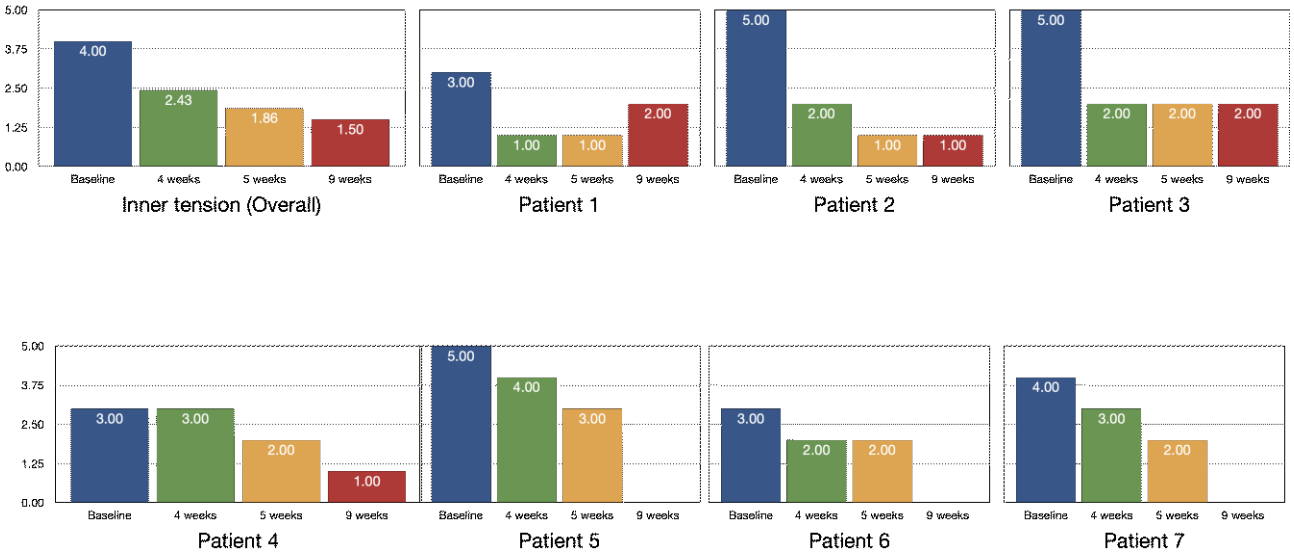
A gradual decrease was found regarding Reported Sadness over the nine weeks, with a statistically significant reduction already after four weeks ($p < 0.01$). This statistically significant difference was maintained over time in subsequent comparisons.



Graph 4 – Reported Sadness

4.3.1.3 Inner tension

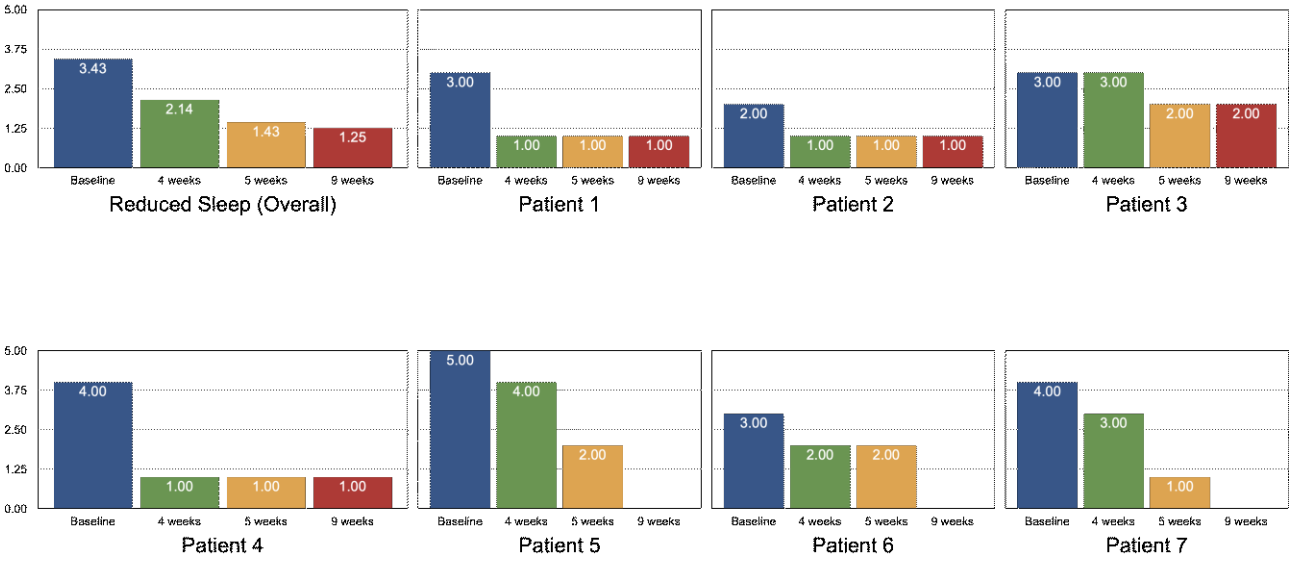
For inner tension, a gradual decrease characterized by statistical significance was found in the first comparison between baseline and four weeks ($p < 0.05$). The downward trend was confirmed in subsequent comparisons at 5 weeks ($p < 0.01$) and 9 weeks ($p < 0.05$). Only one patient experienced an increase in the score at the end of the ninth week.



Graph 5 - Inner tension

4.3.1.4 Reduced Sleep

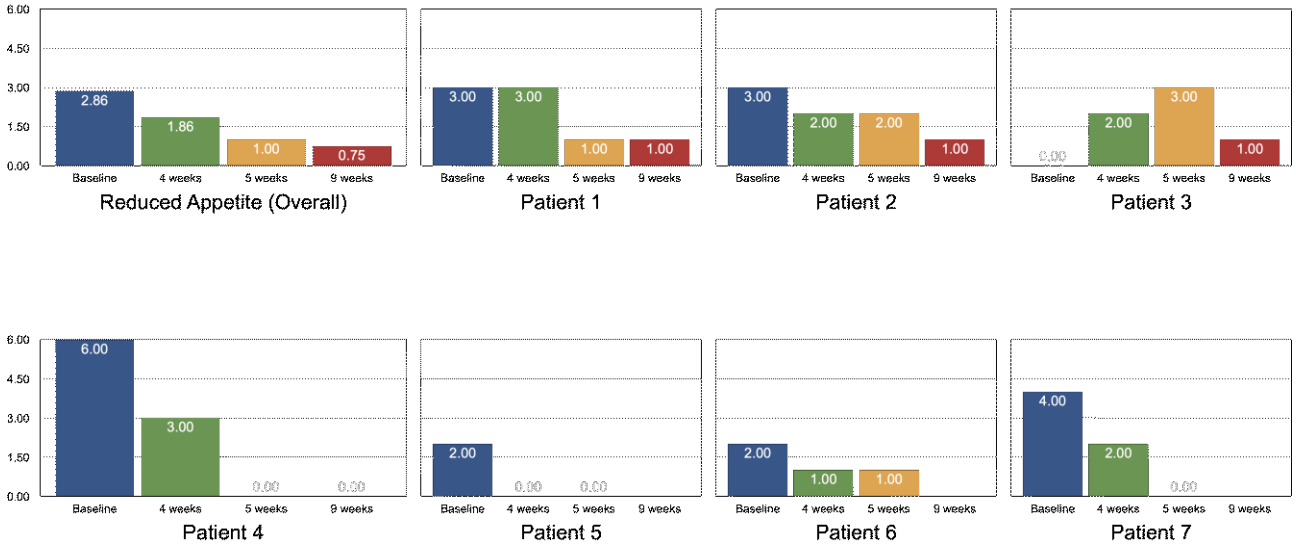
Reduced Sleep item significantly decreased after the first four weeks of treatment ($p < 0.05$). It maintained this average trend during all weeks of observation and for all patients.



Graph 6 – Reduced Sleep

4.3.1.5 Reduced Appetite

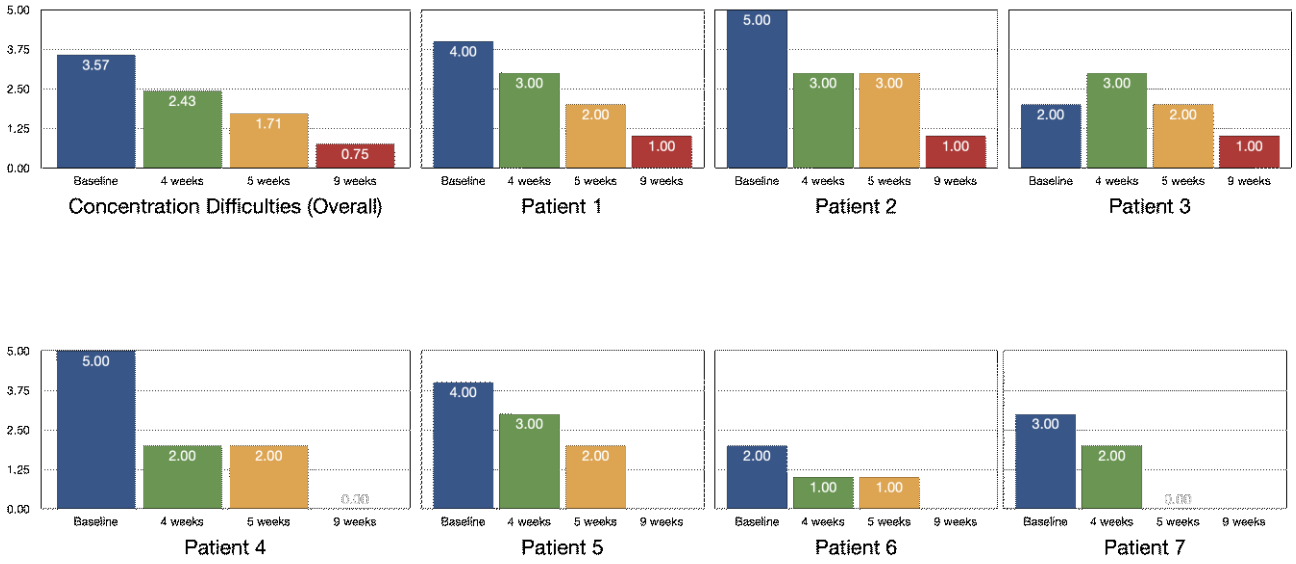
For reduced appetite, a low average score was observed already at the baseline. Over the weeks, there was a gradual reduction in value without statistical significance. Most patients experienced a continuous decrease in scores, except for one subject, for whom an initial increase in MADRS scores was observed.



Graph 7 - Appetite Reduction

4.3.1.6 Concentration difficulties

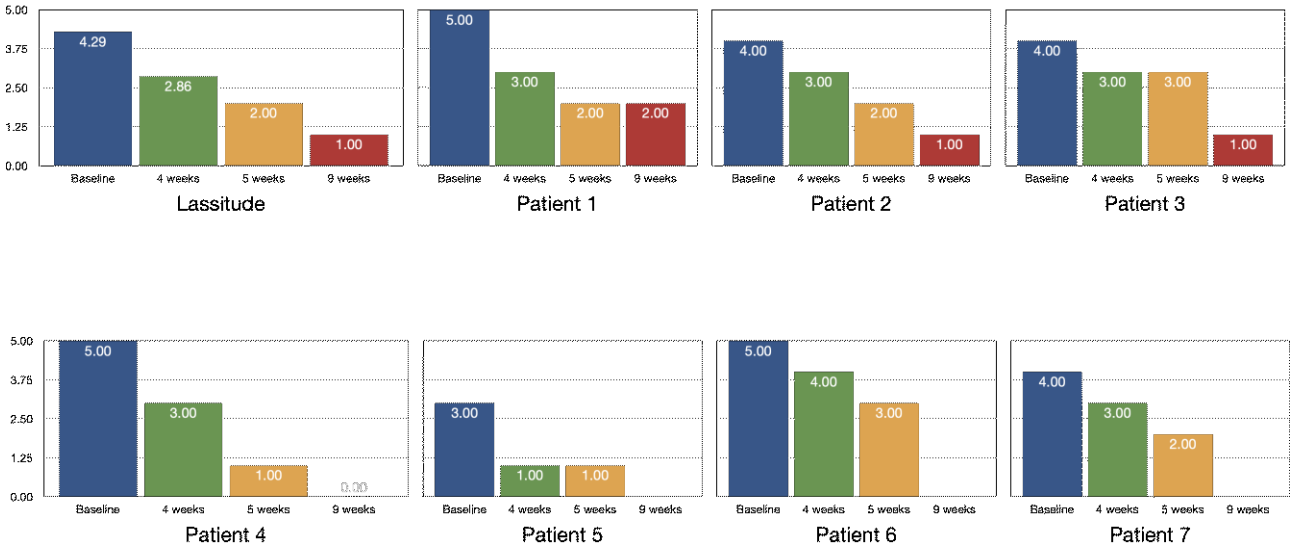
For the concentration difficulties, a statistically significant reduction was registered already at the first endpoint (4 weeks) ($p < 0.05$), with the maintenance of the trend for all subsequent weeks.



Graph 8 – Concentration difficulties

4.3.1.7 Lassitude

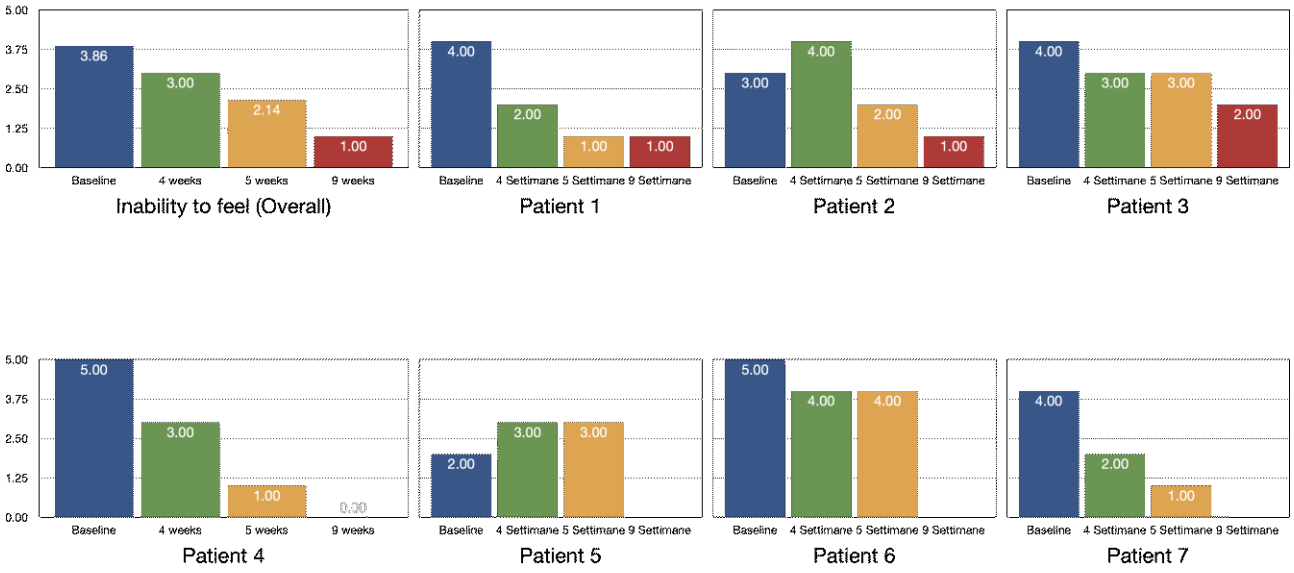
The Lassitude item showed a significant decrease from the first weeks ($p < 0.001$) and for the entire observation period.



Graph 9 - Lassitude

4.3.1.8 Inability to feel

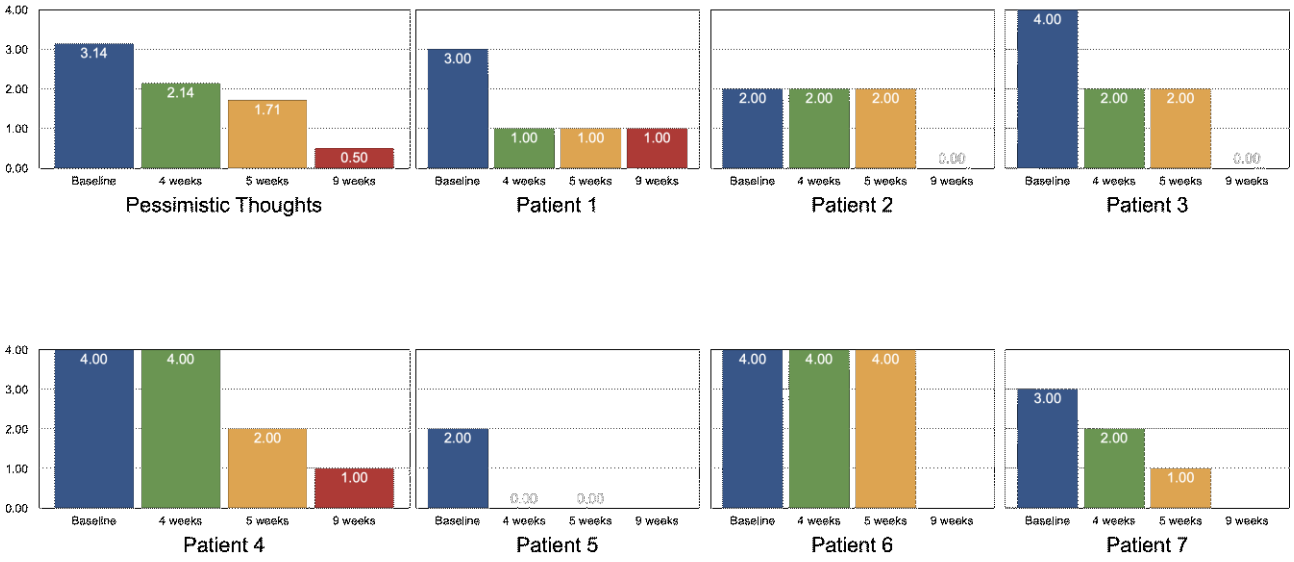
Concerning the Item MADRS Inability to feel, the trend was decreasing throughout the treatment period. Statistical differences from baseline were registered starting from the 5th week of observation ($p < 0.05$) and were maintained until the last endpoint ($p < 0.05$).



Graph 10 – Inability to feel

4.3.1.9 Pessimistic thoughts

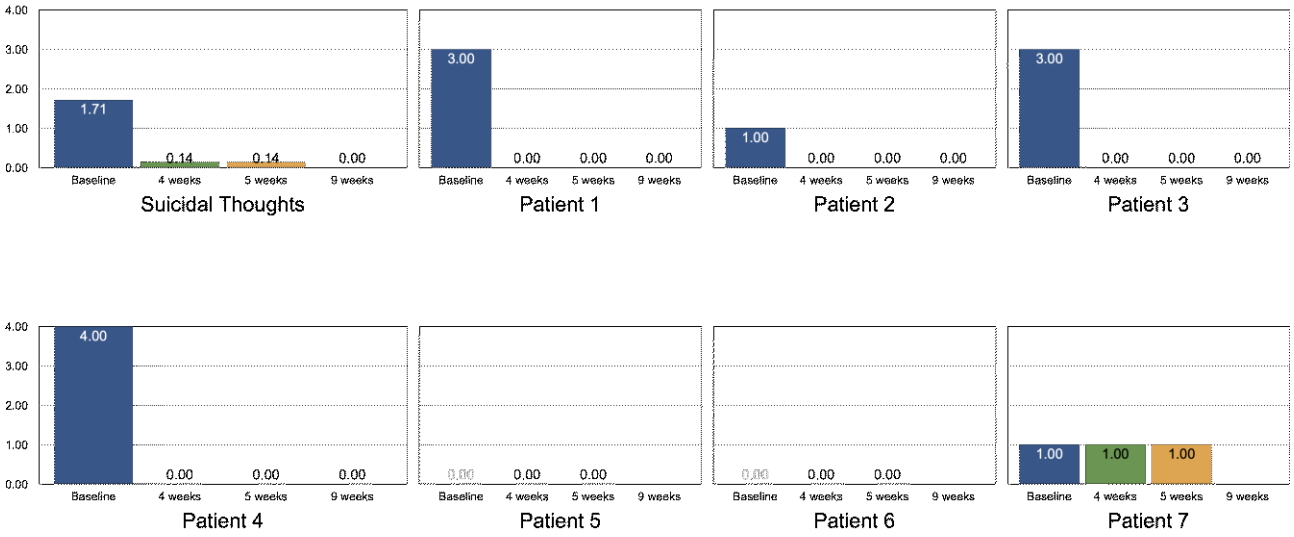
Pessimistic Thoughts reported a gradual average reduction in values. Statistical significance of less than 5% was recorded in the comparison between baseline and 4 weeks of treatment. This significance further increased in the second comparison ($p < 0.01$) and stabilized at 5% over the nine weeks of observation.



Graph 11 - Pessimistic Thoughts

4.3.1.10 Suicidal thoughts

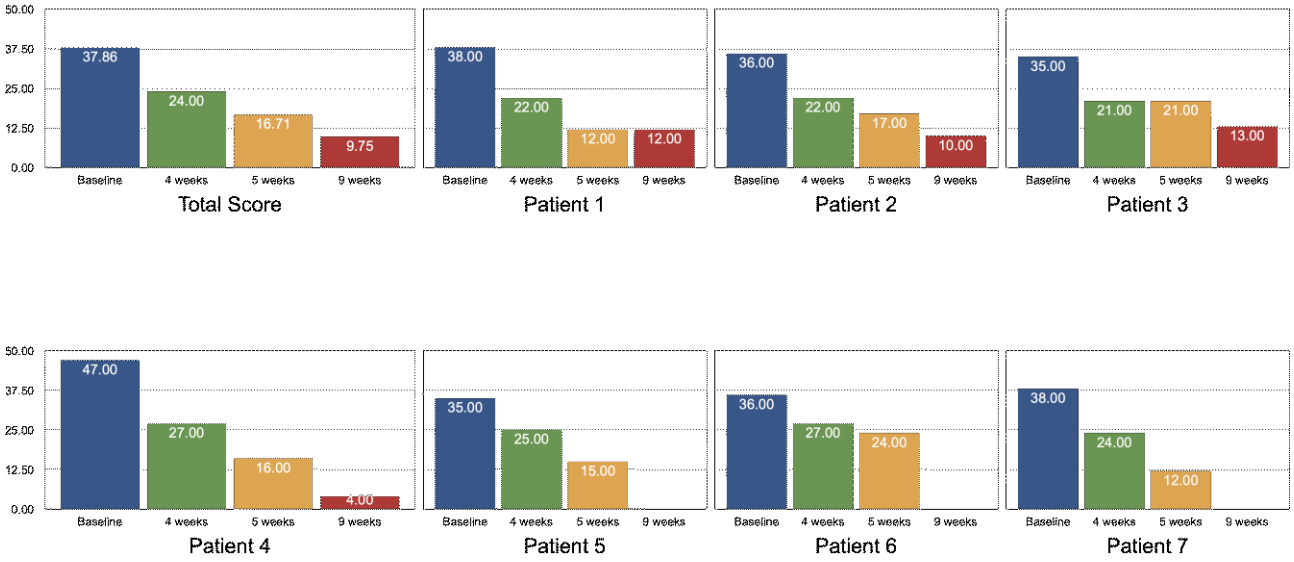
Suicidal thought has reported shallow values since the baseline. For some patients, such as patients 5 and 6, the values were always 0 throughout the treatment period. The comparison of the mean values revealed statistically significant differences at the level of 5% ($p < 0.05$) in the comparisons between baseline and the three endpoints at 4, 5, and 9 weeks of treatment.



Graph 12 - Trend of ideas of global and single patient suicide

4.3.1.11 MADRS Score

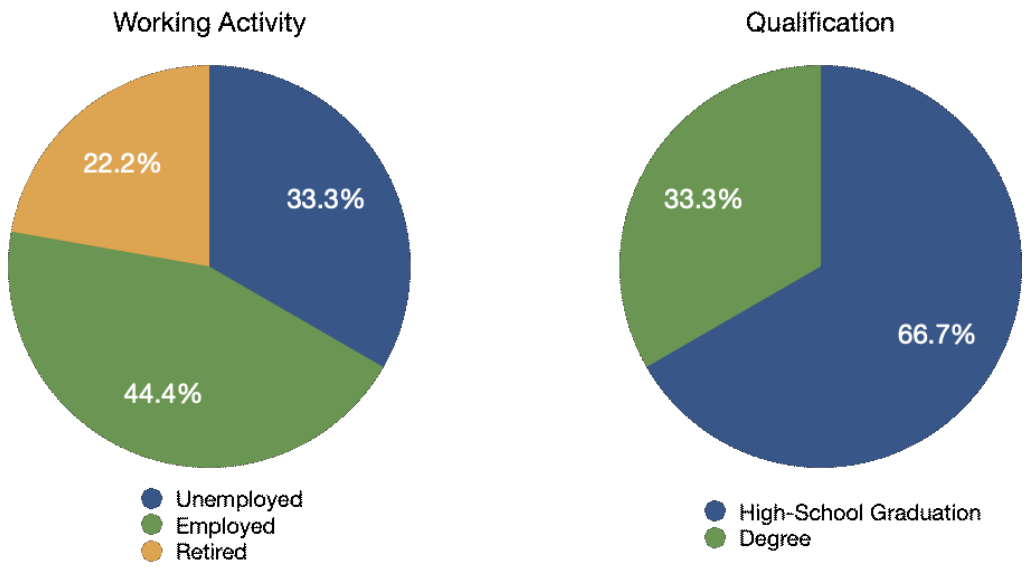
The MADRS total score recorded a sustained decrease as early as the first four weeks of treatment. Scores of all patients at baseline showed severe depression (MADRS > 34). After four weeks of treatment, mean scores decreased significantly (p <0.01), indicating moderate depression. In the fifth week, the mean values of the MADRS score fell within the parameters of mild depression (score 7-19), and finally, after nine weeks of treatment, the reduction, as well as being characterized by statistical significance (p <0.05), highlighted maintenance of mean values in the classification of mild depression. For patient 4, after nine weeks, there was a return to the normal situation and the absence of depressive symptoms.



Graph 13 – MADRS Score

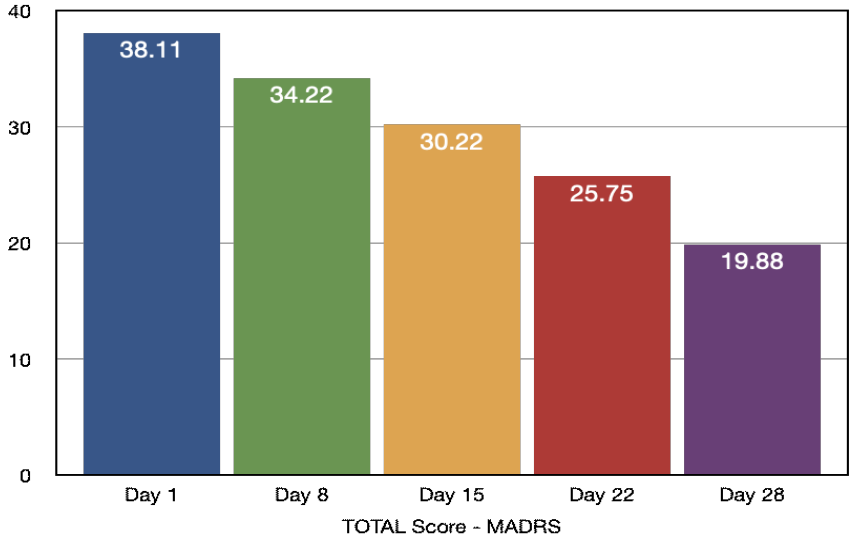
4.3.2 Intranasal esketamine

The sample was composed by 9 subjects (22.2% women; 77.8% men). The average age was 56.3 (SD ± 8.7) years. About 67% of participants had a high school graduation, and 44.4% of subjects carried out a work activity.



Graph 14 – Patients' demographic characteristics

During the first four weeks of observation (28 days), a gradual and continuous decrease in the MADRS total score was observed (Graph 15). All comparisons between the baseline (Day 1) and the following days (8, 15, 22, and 28) were characterized by a statistical significance of less than 1% ($p < 0.01$).



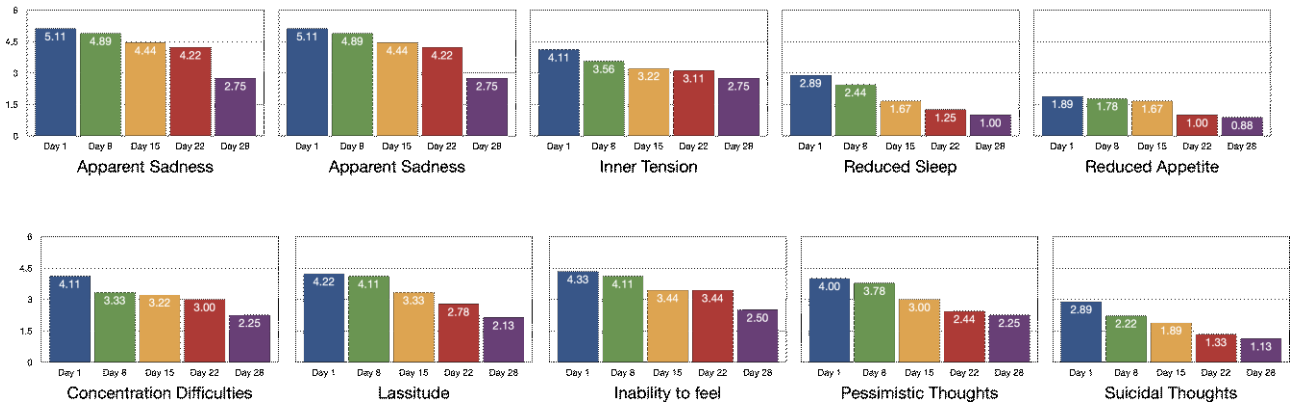
Graph 15 – MADRS score in the first 28 days of treatment

By observing the values of the individual scores per Item, it was possible to record a significant reduction after the first 8 days of treatment for the Concentration Difficulties ($p < 0.02$). In the comparison between Day 1 and Day 15, significant differences were found for the items apparent sadness ($p < 0.05$), inner tension ($p < 0.05$), reduced sleep ($p < 0.05$), lassitude ($p < 0.05$), inability to feel ($p < 0.01$) and pessimistic thoughts ($p < 0.05$).

In the comparison between Day 1 and Day 22, statistical differences were found for the items apparent sadness ($p < 0.01$), inner tension ($p < 0.05$), reduced sleep ($p < 0.01$), concentration difficulties ($p < 0.05$) , lassitude ($p < 0.05$), inability to feel ($p < 0.01$), pessimistic thoughts ($p < 0.01$) and suicidal thoughts ($p < 0.05$).

In comparing Day 1 and Day 28, all items, except inner tension, reported a statistical significance of less than 5% at the end of the four weeks of treatment. Given the reduction of the sample due to missing data on a patient, the lack of significance of the inner tension (borderline value $p = 0.0604$) could be attributable to a sample issue rather than the loss of treatment efficacy. Suicidal thoughts had a lower average initial score (2.9) than many other items. This data must be interpreted with caution, considering both the exclusion criterion for suicidal ideation and the need for an assumption of responsibility by the clinical supervisor at

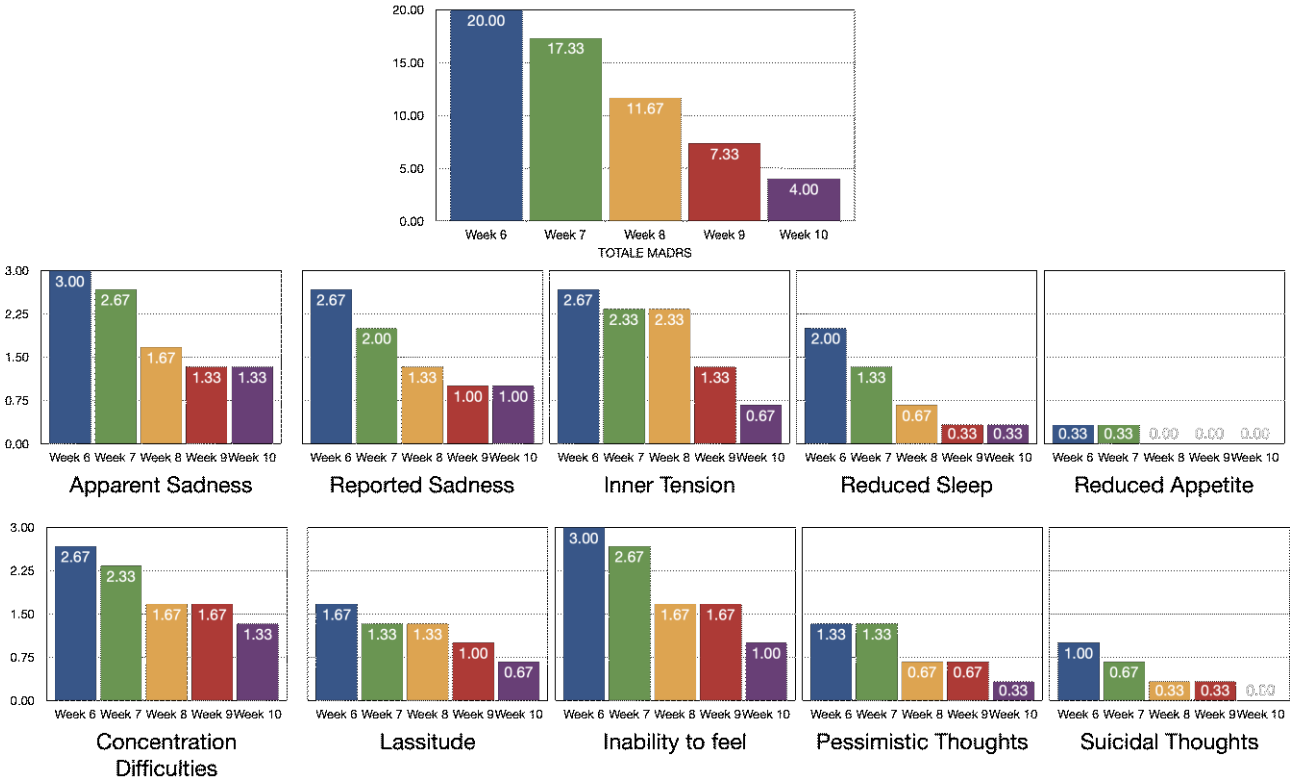
the enrollment regarding the patient's safety. This condition may have further reduced the sample included in this study.



Graph 16 – Average Item-by-Item scores in the first 28 days of treatment

The MADRS tests administered in the weeks following treatment (i.e., the sixth week from the start of treatment to the tenth week) are reported only as average values of the total score and the individual items. No comparison and, therefore, evaluation of statistical significance were performed due to the further reduction of the sample: only three of the 9 patients were admitted to the optimization phase. Also, they completed the following weeks with flexible interval administrations.

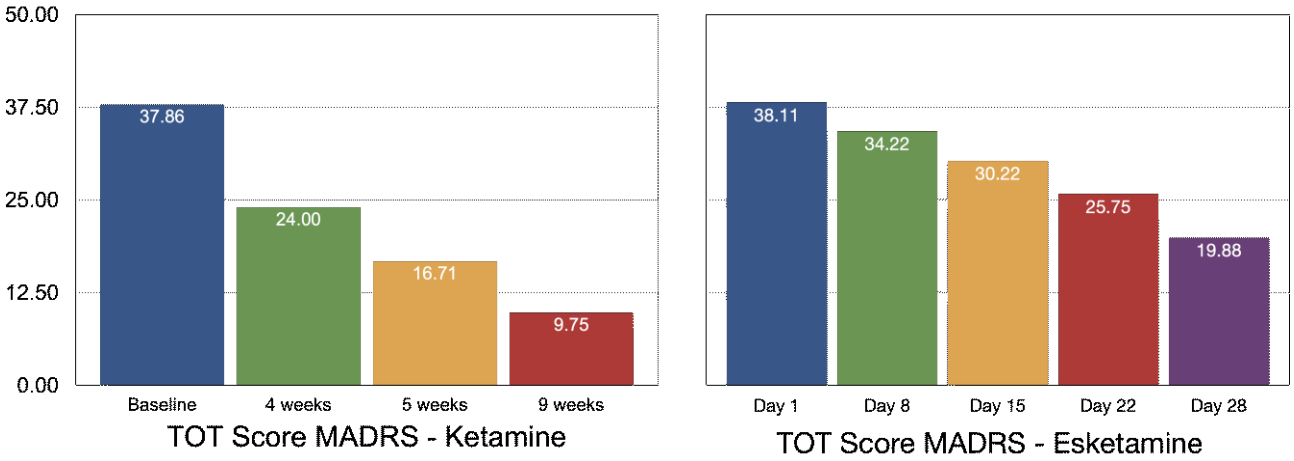
Observing the mean values of the MADRS score, there was a continuous reduction over the weeks. Most patients showed moderate depressive symptoms by the sixth week. Over the following weeks, there was a reduction in scores for all items, and the MADRS score value after ten weeks was less than 6 points (i.e., "normal": 0-6).



Graph 17 – MADRS Items scores from the 6th to the 10th week from the start of treatment

4.3.3 Comparative analysis

In the comparative analysis of the efficacy between the two treatments after 4 weeks of treatment or 28 days, it was possible to observe a more significant decrease in the score in the case of Esketamine (19.88, SD $\pm$ 9.70) compared to ketamine (24.00, SD $\pm$ 2.45).



Graph 18 – Comparison between Ketamine and Esketamine Efficacy after 4 weeks or 28 days

In the comparative analysis of the tolerability of the two treatments, a statistically significant difference emerged ($p < 0.001$). In particular, at the fourth week of treatment, the disperception was found more in the patients treated with ketamine (33.3%) than in those with Esketamine (11.1%), who in turn showed more dissociative symptoms (22.2%). The anxiety/agitation and the increase in pressure measured for both treatments reported similar incidence rates. About 44% and 33.3% of the patients treated with esketamine and ketamine, respectively, reported no side effects at the fourth week of treatment. All side effects were transient in nature. For ketamine, side effects lasted up to a maximum of approximately 40 minutes after administration; for esketamine, side effects were observed up to a maximum of 25/30 minutes.

CHAPTER 5. DISCUSSION

Over the years, ketamine has gained increasing attention from the scientific community due to its good, rapid, and long-lasting antidepressant effect.

The purpose of this work was to evaluate the efficacy and tolerability of this molecule within a stringent experimental protocol. The study performed showed that taking ketamine or esketamine generates significant and positive effects. Most patients benefited from the administration of one of the molecules from the first weeks of treatment and for a prolonged time: 15 out of 16 patients showed a reduction in the MADRS total score of at least 10 points after the last administration, corresponding to a 27% reduction in the initial score, with an average improvement of 20.9 points (from a minimum of 10 to a maximum of 37 points), corresponding to an average percentage decrease in the score between 27% and 92%.

However, after 4 weeks, only six patients were classified as responders (38% of the sample), as defined by a ≥50% reduction in MADRS score. These patients maintained their state even after about 10 weeks from the start of the administration. The result here obtained is lower than the data present in the literature, although it is necessary to underline the enormous variability (over 60%) of the response rates reported in the reference studies (aan het Rot et al., 2010; Bahr et al., 2019; Bryant et al., 2019; Murrough, Iosifescu, et al., 2013; Murrough, Perez, et al., 2013).

This low percentage can be explained in light of the small sample included in the study and the possible presence of comorbidities with pathological personality traits or personality disorders. Morbid personality alterations reduce the likelihood of responding to traditional antidepressant treatments (Bagby, Quilty, and Ryder, 2008; Shawcross and Tyrer, 1985; Shea et al., 1992). Some authors analyzed the relationship between specific personality traits and the response to stressful life events, factors involved in the pathogenesis of depression (Roberts et al., 2007). One study, in particular, showed that different personality traits present in depressed patients influence the response to CBT or specific pharmacotherapy, thus making one or the other preferable depending on the starting personological structure (Bagby, Quilty, Segal, et al., 2008). The literature showed that personality negatively influences the response to antidepressant therapy in relation

to both the personality measurement mode and the cut-off used (Mulder, 2002). In light of the results obtained, we believe that the non-exclusion of patients with morbid personality alterations in the intranasal esketamine study may have given rise to selection bias, resulting in the low percentage of complete response.

Furthermore, considering that the patients included had already presented resistance to traditional antidepressant treatments, it should be emphasized that the greater response obtained by all subjects provides a positive indication of the possibility of using the ketamine-esketamine molecules in patients who, otherwise, would not have suitable therapy to reduce symptoms.

The results show that the greatest response was obtained on the core symptoms of depression, namely sadness (apparent and reported), apathy, inability to concentrate, and fatigue. Proportionally, the response measured as a reduction in the score in the respective items appears greater than the remaining items of the MADRS, with an average decrease after 4 weeks of more than 2 points and, for patients who also received subsequent administrations, by about an additional point and half.

A particular positive effect was reported for most patients on internal tension from the early stages of administration and for both formulations of ketamine. If we consider the inner tension not only as a depressive symptom, but also as the possible first sign of an activating "side" effect expressed by antidepressant therapy (Benazzi et al., 2004), this result confirms what has already been highlighted by literature on the absence of manic/hypomanic switches treated with ketamine and also with bipolar disorder (Mathew et al., 2012).

By observing the items that evaluate circadian rhythms, the quality of sleep improves uniformly in the entire group of patients. The only exception is represented by a single patient who did not show benefits in the observation period.

Reduced appetite is the slightest present symptom in patients observed since the pre-administration phase, with a shallow baseline score.

Therapy reaches its most significant peak of efficacy within the expected 4 weeks of administration for both ketamine and esketamine. All the items of the MADRS showed a substantial improvement within the first 4

weeks; fatigue, apathy, and pessimistic thoughts reported an improvement even in the period following that of close observation.

Among the exclusion criteria from the study, active suicidal ideation was considered an element subjected to the clinician's judgment concerning the severity of the risk. This means that the evaluation of the effects of the two molecules on this specific area is reduced. The few available data indicate a very rapid response in subjects who received intravenous ketamine: after 2-5 administrations, the scores on items 9 and 10 of the MADRS (pessimistic thoughts and suicidal ideation) showed a significant reduction in values. This result confirms what has been reported in the literature about the efficacy of ketamine as an antisuicidal agent.

CONCLUSION

This work began with my direct involvement in the "SUSTAIN-1" and "SUSTAIN-3" clinical trials on esketamine.

Esketamine was approved, under the trade name Spravato, in March 2019 by the FDA in the United States, while it is being approved in Italy and other European countries with an indication of use for Treatment-Resistant Depression. The news of the approval of ketamine in the US sparked a lively debate within the scientific community, bringing ethical and scientific issues into play.

The history of depression was born with the history of humanity itself. The first traces can already be found in the written sources left by the most ancient peoples. The debate on the origin, development, and therapy of depression has involved the medical world ever since Hippocrates and Galen identified the black humor as responsible for melancholia, and the brain as the organ biochemically connected. If psychiatry initially focused on the meticulous cataloging of melancholy patients, the veil on the psychological mechanisms involved was lifted with Freud. The possibility of generating a fundamental change in the treatment of melancholia was glimpsed by acting directly on the pathogenesis of depression. Melancholy thus becomes one of the central themes of psychiatry. Genetics and neurobiology together with psychiatry describe depression as a complex disorder in which numerous hereditary, environmental, immunological, and endocrine factors interact with each other to question the categorical diagnosis and introduce the concept of the mood spectrum.

Today in the Western world, depression represents a real epidemic involving over 300 million people and with an incidence destined to rise in the coming years, despite the multiplication of therapy and prevention strategies in the field of mental health (WHO, 2017).

According to the WHO, suicide occurs in the world every 40 seconds; behind each suicide, there are, on average, 20 unsuccessful attempts. Numerous scientific tests put in close relationship mood disorders and suicidal risk; mood disorders are considered possible risk factors for such acting out, while suicide represent the second cause of death between 15 and 29 years (Hegerl, 2016; Pompili et al., 2013; Dong et al., 2018; WHO, 2017; Cao et al., 2015).

Furthermore, many patients do not respond to conventional antidepressant therapies according to a variable percentage between 10 and 60% (Fava, 2003; Rush et al., 2006). In addition to the inherent problems of depressive pathology, conventional antidepressant therapies are characterized by a latency of therapeutic action: side effects often occur before the therapeutic ones, thus generating high rates of abandonment (Ciccocioppo et al., 2018).

The presence of TRD entails a greater impact on the well-being of the individual, with a state of health inversely proportional to the degree of resistance of the depressive pathology and, consequently, a greater social cost (Johnston et al., 2019). Therefore, new treatment strategies for TRD are needed.

Introducing a new molecule such as ketamine is criticized due to ethical convictions and the contextual epidemic of opioid abuse in the USA (George, 2018). Ketamine is a known substance of abuse. In Italy, it is included among the narcotic substances. The difficulty in the synthesis process of the molecule suggests that the ketamine sold on the illegal market comes from the distraction of commercial pharmaceutical products.

Although known and subject to the scientific community's attention, these aspects must nevertheless be contextualized in a more global vision of the problem. A recent study classified a series of substances deemed abusive based on the risk of causing harm to themselves (harms to users) and causing damage to others (harms to others self). The absolute risk of ketamine is much lower than with other socially accepted substances, such as tobacco and alcohol. It is comparable to long-time commercial drugs, such as methadone or benzodiazepines (Nutt et al., 2010). The gap between perceived risk and actual risk is evident in the mainstream debate.

According to a report from the National Institute of Health about the recreational use of substances, the appetite for other molecules, used as drugs, is much higher than that shown for ketamine (Istituto Superiore di Sanità, 2011).

Some authors speculate that the antidepressant effect produced by ketamine is a passing euphoric effect. However, the comparative study of the effects of esketamine and midazolam (which may be a euphoric agent) shows much higher response rates for the first molecule (Fava et al., 2018; Murrough, Iosifescu, et al., 2013).

In clinical trials, esketamine exhibited a prolonged antidepressant effect with a reduced relapse rate than placebo (Daly et al., 2018, 2019). However, there are still no data on the long-term use of esketamine. A cost-benefit analysis, although based on a health model different from the Italian one, believes that esketamine may be the most appropriate treatment for patients with severe TRD who are non-responsive or tolerant to multiple conventional therapies. In the case of moderate symptoms or failure of only one or two antidepressant therapies, the analysis mentioned earlier recommends using psychotherapy or other oral antidepressant therapies given the lack of data on the long-term use of esketamine (CEPAC, 2019).

Besides, no data are available to date on the use of esketamine in some subpopulations, such as patients with active suicidal ideation, psychosis, bipolar disorder, substance use, or anxiety disorders.

In an overall assessment of the actual administration of ketamine, it is also necessary to consider the need for frequent psychiatric visits to monitor the patient and the limitations on the patient's life, such as not driving in the first 24 hours after administration. It follows that the relationship between the benefit of the response to TRD and the difficulty in maintaining an optimal quality of life (e.g., carrying out normal work activities) is still being evaluated.

The lack of comparative studies on the efficacy of esketamine and active comparators typically used in TRD (for example, ketamine, TMS, ECT, augmentation strategies with antipsychotic drugs) represents a limitation in identifying the potential of the drug in this area.

In our study, a significant benefit emerged on the clinical picture related to the intake of therapy with intravenous ketamine or intranasal S-ketamine, particularly on the core symptoms of depression. The positive effect does not differ between the two protocols considered. Statistical analysis has shown how the intake of ketamine or esketamine can generate significant effects, although the rate of responders obtained (≥50% improvement in the MADRS score) was lower than that reported in the literature. The symptoms on which the two molecules proved most effective were sadness, apathy, inability to concentrate, and fatigue. The greatest effects were achieved in the first 4 weeks of administration.

The main limitation of this study is the small sample size, which prevents us from expanding the results in an inferential way. Furthermore, different inclusion and exclusion criteria between the two protocols of esketamine and ketamine may have generated selection bias.

For future studies, it is considered necessary to expand the sample, uniform selection criteria, and objective evaluation of the subjects' personality traits included through the DSM-5 criteria.

In conclusion, ketamine and S-ketamine are among the few innovative and effective therapies for treating resistant depression. The criticisms leveled at their use can be overcome by stringent monitoring and the clinician's ability to identify patients eligible for treatment and the most relevant situations of TRD.

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