



Giulio Perrotta*

Psychologist sp.ing in psychotherapy with a strategic approach, Forensic Criminologist expert in sectarian cults, esoteric and security profiles, Director of the Department of Criminal and Investigative Psychology UNIFEDER, Jurist sp.ed SSPL, Lecturer, International Essayist, Italy

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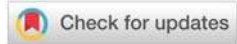
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***Corresponding author:** Dr. Giulio Perrotta, Psychologist sp.ing in psychotherapy with a strategic approach, Forensic Criminologist expert in sectarian cults, esoteric and security profiles, Director of the Department of Criminal and Investigative Psychology UNIFEDER, Jurist sp.ed SSPL, Lecturer, International Essayist, Italy, E-mail: giuliosr1984@hotmail.it

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Definitions, differential diagnosis and clinical contexts of depressive disorders

Definitional contextualization and epidemiological profiles : The term “depression” is often used, improperly, to refer to any of the various depressive disorders, categorized on a nosographic basis by the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition – (DSM-V) [1].

Depressive disorders, together with mood disorders, now represent the most frequent categories of psychopathological disorders, although recent estimates would seem to underestimate the related related problems. Certainly: << (...) Depression is a public health problem, both because of its high prevalence, and because it involves considerable disability and often manifests itself in comorbidity with chronic medical conditions and with other psychiatric disorders (Üstün TB, Sartorius N, 1995). Depression has a strong public spending impact also because depressed patients are great users of health resources (Von Korff M et al., Arch Gen Psychiatry 1992). For the World Health Organization (WHO) depression is currently the fourth cause of disability in the world, it will become the second cause in 2020, associated with chronic diseases, and

Review Article

Depressive disorders: Definitions, contexts, differential diagnosis, neural correlates and clinical strategies

Abstract

Starting from the categorical definitions of “depressive disorders”, we proceeded to list the individual forms provided by the DSM-V, with a particular focus on historical, clinical, neurobiological and therapeutic profiles, concluding the analysis of the possible strategies to be used to finalize the resolutions to problems arising from the disorder in question.

the first in 2030, resulting in a substantial loss of productivity per day of illness and increased mortality. In other words, depressed patients will have a higher work and social disability than diseases such as hypertension, diabetes, arthritis and low back pain (Murray CJL, Lopez AD, Lancet 1997; WHO, 2004) (...)>> [2].

According to the WHO, in the world: <<(…) over 350 million people suffer from depression, with a prevalence that varies widely between different countries (Weissman MM et al., JAMA 1996) if the average prevalence calculated in 60 countries involved is 3.2% for subjects without physical comorbidities, and varies from 9.3% to 23% in subjects with chronic pathologies, in the American population the prevalence at 12 months is equal to 8.3%, while in Italy it was estimated at 3% (Moussavi S, Lancet 2007; Kessler RC, Bromet EJ, Annu Rev Public Health 2013). More recent studies report a risk of depression during life between 10 and 15%, in this percentage the “unipolar” forms are very common (Lepine JP, Briley M, Neuropsychiatr Dis Treat 2011), with a prevalence double in women, higher in the young than in the elderly – if we consider subjects without chronic physical comorbidities – and in high-income countries compared to poor countries. For some authors, this risk rises to 20% of the population, while the point incidence is estimated at around 2-4%. Epidemiological studies also suggest that the presence of sub-threshold disorders, ie disorders that do not fully meet the diagnostic criteria, may constitute problems of clinical relevance. Individuals with sub-threshold depression, of facts, show disability and reduced social function. This depressive form presents deficits, use of health services and psychotropic drugs that are similar or even greater than formal affective disorders (Johnson J et al., J Am Medical Ass 1992) (...)>> [2]. Estimates, however, even in the writer’s opinion,

underestimate the problem, especially in western and highly industrialized countries [3].

Profili storici e classificatori

In ancient times, the Greek physician Hippocrates of Cos described the condition of melancholia (in Greek μελαγχολία) as a distinct disease with particular mental and physical symptoms, characterizing all the “fears and discouragement, if they last long” as symptomatic of this particular disease [4]. This description among other things is very similar to the modern concept, albeit with a different content spectrum, including symptoms of sadness, discouragement and discouragement, often fear, anger, delusions and obsessions [5].

The term “depression” comes from the Latin verb “deprimere”, which means “press down” [6] and was used since the 14th century, even by great authors of English literature [7]. A first use instead as a reference to a psychiatric symptom was made by the French psychiatrist Louis Delasiauve in 1856; from that moment, and particularly from 1860, the term began to appear in medical dictionaries as a reference to a lowering of emotional function with pathological features [8]. Even though “melancholy” remained the predominant term in diagnostics, the term “depression” grew from the studies of the German psychiatrist Emil Kraepelin who used it as a general term to refer to the different types of depressive melancholy [9]. Sigmund Freud then compared the state of melancholy to mourning, in his paper “Lutto e melanconia” (1917), theorizing the loss of an “object” (eg the loss of a relationship due to death or interruption of a loving relationship), in relation to the loss of the “subject”: in essence, the depressed individual, according to the author, identifies with the object of affection, according to an unconscious process of narcissistic matrix (called “libidinal investment”) ego “). The result of this loss involves severe melancholic symptoms deeper than mourning, not only is the outside world seen negatively, but the ego itself is compromised [10]. The patient’s decline in self-perception is revealed in the conviction of his guilt and his inferiority and unworthiness [11], exactly as it happens in the first life experiences, which then will mark us for the whole existence [12].

More recently, the first version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-I, 1952) spoke of “depressive reaction”, while DSM-II (1968) of “depressive neurosis”, defined as an overreaction to internal conflict or an identifiable event. It also included manic-depressive psychosis among the major affective disorders [12]. In the mid-twentieth century, researchers hypothesized that depression was caused by a chemical imbalance in brain neurotransmitters: a theory based on observations made in the 1950s on the effects of reserpine and isoniazid in modifying the levels of family neurotransmitters of monoamines concerning depressive symptoms [13].

The term “major depressive disorder” was instead introduced by a group of US doctors in the mid-1970s as part of the proposed diagnostic criteria based on symptom patterns

(called “Research Diagnostic Criteria”, structured on the basis of previous “criteria”). Feighner “) [14], which then formed the DSM-III of 1980 [15]. To maintain consistency, the ICD-10 uses the same criteria, with only minor changes [15,16]. Indeed, the ICD-10, simplifying the previous ICD-9, lists the depressive episode, persistent mood disorders (dysthymia), other mood disorders and unspecified disorders; similar to the previous version, it distinguishes different subclasses of depressive episode: the mild and moderate form of depression, the severe depressive episode without or with psychotic symptoms, atypical depression and “masked” depression, and again the unspecified depressive episode (Table 1).

Table 1: ICD-9 and ICD-10: all diagnoses of depressive disorders.

ICD-9	ICD-10
1. Major depression, single or recurrent episode (endogenous depression, monopolar depression, psychotic depression, involutionary melancholia, depressive psychosis)	1. Depressive episode (single episode, atypical depression and disguised depression)
2. Atypical depressive disorder	2. Recurrent depressive disorder
3. Dysthymic disorder (anxious depression, reactive depression, depressive reaction, neurotic depressive state)	3. Persistent mood disorders (dysthymia)
4. Chronic depressive personality disorder	4. Other mood disorders (recurrent mood disorders and short repeated depressive episodes)
5. Disorder of adaptation with depressed mood (mourning reaction)	5. Joint anxiety-depressive disorder
6. Prolonged depressive reaction	
7. Depressive disorder not otherwise specified	

<<(…) As you can see, there are some differences between the Diagnostic and Statistical Manual of Mental Disorders and the ICD. In the ICD-9, for example, the “chronic depressive personality disorder” was recognized (later eliminated in the most recent version), while it is not mentioned either in the DSM-IV or in the DSM-V. In the ICD-10 the so-called “mixed anxiety depressive disorder” is recognized as a separate nosographic entity (diagnosis absent in the previous version); in the DSM-IV the “mixed anxious depressive disorder” was inserted in the research appendix, a diagnosis then eliminated in the subsequent DSM-V as it was assessed as not sufficiently reliable. (...)>> [2].

Below we will instead focus on the contents of the DSM-IV (1994) and DSM-V (2013).

Clinical contention and categorical classifications

There are several clinical “forms” on a depressive basis, categorized according to the symptoms; for this it is necessary to demarcate the boundaries in a reliable way, so as to be able to deal with the theme “depressions” in a more correct manner, always bearing in mind that not all people who experience depressive symptoms actually suffer from a pathological form [3].



From one extreme to the other of the “depressive continuum”, understood as the presence of depressive symptoms in a continuum growing from sub-clinical forms of paucisymptomatic to full-blown clinical forms of increasing gravity, we could place the “depressive temper” (Rovai L et al., Eur Rev Med Pharmacol Sci 2013), which expresses the fundamental and characteristic affective disposition of each person; is a basic predisposition that precedes the experience. Depressive temperament is characterized by a tendency to sadness, low self-esteem, pessimism, isolation: the subject appears predominantly gloomy, introverted, solitary and incapable of having fun, tending to brooding. He has concerns about his own inadequacies and failures, presenting an ease in feeling guilty [2].

In the second place of the imaginary scale we find the “physiological depressive reactions”: the “sadness”, the “blues” and the “mourning”. Sadness is one of the primary emotions and consists of a universal response to adversity, which in the ethological meaning of the term demonstrates its important adaptive function. By blues (bad mood) we mean short-term transitory forms of depression consisting of reactions to specific stressful events: we distinguish for example. the holiday blues (the sadness that appears when you return from vacation); maternity or baby blues (also called third day syndrome; typically emerges 2–3 days after birth and disappears within about ten days), not to be confused with the much more severe postpartum depression; we also mention the anniversary blues (melancholy states in relation to certain recurrences) and the premenstrual blues. Mourning is an “emotional” state that appears in relation to loss experiences (death, divorce, emotional detachments, emigration, wars, etc.) [2]. As reported in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) (APA, 2013), bereavement can present the same symptoms as a major depressive episode, such as feelings of intense sadness, rumination on loss, insomnia, poor appetite and weight loss, but there are some elements that make it possible to distinguish the two phenomena: in mourning, first of all the experiences and negative thoughts appear strictly in relation to the deceased; reactivity to external stimuli is maintained, the psychomotor slowdown typical of major depression is not present, as are ideas of self-depreciation and excessive guilt or other psychotic symptoms and suicidal ideation is rare. The reaction of mourning also differs for other psychopathological signs such as “mummification” (keeping the objects of the deceased as they were before death) and serious “anniversary” reactions [2].

Still in the depressive continuum, in third place, it is possible to highlight the forms that define the “threshold” between “physiological reactions” and “real depressive disorders” [2]; let us say, to simplify, the “typical and atypical forms of depressive disorders” [1]. << (...) First of all, a pathological condition determines alterations of the functioning and an interference with the social adaptation; is an experience qualitatively different from mourning, representing a fracture with respect to the pre-morbid characteristics. In the category of depressive disorders we find a series of pathologies that

share a primary disorder of emotions and feelings at different levels of severity. Mood alteration includes pessimistic arousal, hypersensitivity to unpleasant events, reduced sensitivity to pleasant events, reduced anticipatory and consummatory pleasure, emotional flattening, apathy and affective depersonalization. A cognitive dimension and a somatic, vegetative and psychomotor dimension can be identified in the symptomatological nucleus: the former include feelings of self-depreciation, self-accusation and guilt, the idea of loss, low self-esteem, helplessness and impotence. ‘Hopelessness (despair) (Beck AT, Arch gen psychiatry 1963), holotimic delusions, diminished ability to think and recurrent thoughts of death, ideation or suicidal attempts. The second part includes changes in weight and appetite, reduction or increase in the rate of sleep and alterations in the structure of the same (eg reduction of sleep δ , increase in REM activity and REM latency reduction) agitation or psychomotor slowdown (such as pseudodementia or stupor) and extreme fatigue. (...)>> [2].

The following are the categorized forms of depressive disorders of DSM-IV (1994) and DSM-V (2013): << (...) are (here) reported the depressive disorders cataloged in the two main systems of classification of diseases, the DSM of the American Psychiatric Association and the International Classification of Diseases of the WHO (WHO, 2007), comparing the two most recent versions. To demonstrate the growing attention that global health has focused on the problem, the DSM-V revolutionizes the chapter dedicated to new depressive disorders compared to the previous DSM-IV and conceptualizes differently the chronic forms of depression, trying to favor a better diagnostic process. The most recent DSM-V maintains the gravity specifications and the specifications regarding the melancholic, atypical, psychotic (congruous and incongruous mood) characteristics, the catatonia or mixed characteristics, the onset (peripartum), and the seasonal trend; instead introduces the specification for the possible presence of associated anxiety. (...) >> [2] (Table 2).

Focusing attention on the DSM-V categorization (latest version), we find the following forms [1]:

1. *Disruptive mood dysregulation disorder*. It is a disorder

Table 2: DSM-IV and DSM-V: all diagnoses of depressive disorders.

DSM-IV	DSM-V
1. Major depressive disorder (single and recurrent episode)	1. Disruptive mood dysregulation disorder
2. Dysthymic disorder	2. Major depressive disorder
3. Depressive disorder not otherwise specified (premenstrual dysphoric disorder, minor depressive disorder, short recurrent depressive disorder, post-psychotic depressive disorder, ...)	3. Persistent depressive disorder (or dysthymia)
4. Disorder of adaptation with depressed mood	4. Premenstrual dysphoric disorder
	5. Disorder of adaptation with depressed mood
	6. Depressive disorder induced by substances and drugs
	7. Depressive disorder due to another medical condition
	8. Depressive disorder with other specification
	9. Depressive disorder without other specification

that appears before the age of 18 (with first onset between 6 and 10 years) and is characterized by persistent irritability, which involves frequent anger and aggression (at least 3 times a week). It often evolves, in adolescence or early adulthood, into an anxiety disorder or major depression. It is quite common to find this disorder in children who have ADHD or anxiety disorders in developmental age.

2. *Major depressive disorder or unipolar depressive or endogenous depression.* It is a depression not linked to particular events (eg grief, loss, stressful situations) and the main symptoms related to mood, vital drive, thoughts and ability to concentrate. It is characterized by depressed mood episodes mainly accompanied by low self-esteem and loss of interest or pleasure in normally pleasant activities (c.d. anhedonia). A clinical investigation is suggested first to exclude physical pathologies capable of favoring this condition (eg hormonal dysfunctions, systemic infectious conditions, use of drugs or drugs).

For the diagnosis of major depression, 5 or more of the following symptoms must have been present almost every day during the same 2-week period, and one of them must be a depressed mood or a loss of interest or pleasure (criterion A):

- Depressed mood for most of the day;
- Marked decrease in interest or pleasure for all or almost all activities for most of the day;
- Significant (> 5%) increase or loss of weight or decrease or increase in appetite;
- Insomnia (often maintenance insomnia [central]) or hypersomnia;
- Agitation or psychomotor slowing observed by others (not self-reported);
- Asthenia or energy loss;
- Excessive or inappropriate feelings of self-depreciation or guilt;
- Decreased ability to think or concentrate or indecision;
- Recurring thoughts of death or suicide, a suicide attempt, or a specific plan to carry it out.

Furthermore: the symptoms cause clinically significant distress and impairment of functioning in the social, work or other important areas (criterion B); the episode is not attributable to the physiological effects of a substance or to another medical condition (criterion C); the occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder or schizophrenia spectrum disorder and other psychotic disorders with other specification or without specification (criterion D); there has never been a manic or hypomanic episode. Note. This exclusion does not apply if all the manic-like or hypomanic-like episodes are induced by a substance or are attributable to the physiological effects of another medical condition (criterion E).

Other important considerations concerning the following data:

- ✓ The A-C criteria constitute a major depressive episode.
- ✓ Responses to a significant loss (eg, mourning, financial meltdown, losses resulting from a natural disaster, serious medical illness or disability) may include feelings of intense sadness, rumination on loss, insomnia, poor appetite and weight loss, noted in Criterion A, which may resemble a depressive episode. Although these symptoms may be understandable or considered appropriate for loss, the presence of a major depressive episode in addition to the normal response to a significant loss should be carefully considered. This decision inevitably requires a clinical evaluation based on the history of the individual and on the cultural norms for the expression of discomfort in the context of loss.
- ✓ A manic episode (at least a week) or hypo-manic (lasting up to 4 days) can be understood as the exact opposite of a depressive crisis, it is in fact a short period of time in which the subject appears extremely more active and energetic with respect to his usual course, to the point of risking putting himself in danger, suffering from insomnia or taking on intrusive behavior towards others. il DSM-5 distingue la “*depressione maggiore*” nelle seguenti forme: lieve; moderata; grave con o senza manifestazioni psicotiche; in remissione parziale o totale; cronica; con manifestazioni catatoniche o melanconiche o atipiche; con esordio nel post-partum.
- ✓ These classifications refer to the previous ones listed in DSM-IV which distinguished 5 subtypes of major depressive disorder:
 - *Melancholic depression* is characterized by a loss of pleasure in all or almost all activities, a lack of reactivity to pleasant stimuli, a depressed mood more pronounced than that of pain or loss, a worsening of symptoms in the morning, early morning waking, psychomotor retardation, excessive weight loss (not to be confused with anorexia nervosa), or excessive guilt.
 - *Ica Atypical depression* is characterized by mood reactivity (paradoxical anhedonia) and positivity, significant weight gain or increased appetite, excessive sleep or drowsiness (hypersomnia), a feeling of heaviness in the limbs known as “lead paralysis” and significant reduction in social value, as a result of hypersensitivity to perceived interpersonal refusal.
 - *Catatonic depression* is a rare and severe form of major depression involving motor behavior disorders and other symptoms. The individual appears dumb and almost deaf, remains motionless or shows movements without a purpose or even bizarre. Catatonic symptoms also occur in schizophrenia or during manic episodes or may be caused by neuroleptic malignant syndrome.

- *Post-partum depression disorders or those associated with the puerperium, not classified elsewhere.* This refers to the intense prolonged and sometimes disabling depression experienced by women after childbirth. Postpartum depression has an incidence rate of 10–15% among new mothers. The DSM-IV establishes that, in order to qualify it as a post-partum depression, the onset must occur within a month of the birth. It has been determined that postpartum depression can last up to three months.

- *Stagionale Seasonal Affective Disorder (SAD)* is a form of depression in which depressive episodes become acute in autumn or winter and then resolve in the spring. The diagnosis is made if at least two episodes occurred in the cold months, with none at other times, for a period of two or more years.

3. *Persistent depressive disorder or dysthymic disorder or dysthymia.* It is a disorder characterized by a chronic depressed mood, which occurs almost every day for at least 2 years. Periods may occur in which the mood is “normal” but tend to last only a few days or a few weeks. Generally, this type of disorder is difficult to detect as the main symptoms are not as severe as major depressive disorder. The symptoms of dysthymia are:

- Poor or excessive appetite;
- Insomnia or hypersomnia;
- Low energy and constant sense of fatigue;
- Low self-esteem;
- Decline in concentration and difficulty in making decisions;
- Feeling of being “hopeless”.

To be able to make a diagnosis it is necessary to have at least 2 symptoms listed above for a duration of at least 2 years.

- a) “Major depression” and “persistent or dysthymic depressive disorder” may include one or more specifiers describing additional manifestations during a depressive episode:
- b) **Anxiety:** patients feel tense and unusually restless; they have difficulty concentrating, because they worry or fear that something terrible might happen, or they feel that they could lose control of themselves.
- c) **Mixed characteristics:** patients also present 3 or more manic or hypomanic symptoms (eg, elevated mood, grandeur, greater talkative than usual, flight of ideas, decreased sleep). Patients who have this type of depression are at risk of developing a bipolar disorder.
- d) **Melancholy:** patients no longer feel pleasure for almost all activities or do not respond to stimuli that are usually pleasant. They may feel despondent or desperate,

feel excessive or inappropriate guilt, or have early awakenings in the early morning, marked psychomotor slowing or agitation, and significant anorexia or weight loss.

- e) **Atypia:** patients’ mood lights up momentarily in response to positive events (eg, a visit by children). They also have 2 or more of the following: excessive reactions to perceived criticism or waste, feeling of paralysis (a sense of heaviness or fatigue, usually in the extremities), weight gain or appetite and hypersomnia.
- f) **Psychosis:** patients have delusions and/or hallucinations. Delusions often concern having committed sins or unforgivable crimes, having incurable diseases or unspeakable defects or being persecuted. Hallucinations can be auditory (eg, accusatory or condemning voices) or visual. If only the items are described, particular attention should be paid to determining whether these items represent true hallucinations.
- g) **Catatonia:** patients have severe psychomotor retardation, devote themselves to excessive a finalistic activity, and / or withdrawal; some patients make faces and repeat words (echolalia) or movements (echopraxia).
- h) **Onset in the peripartum:** the onset is in pregnancy or within the first 4 weeks after the birth. Psychotic features may be present; Infanticide is often associated with psychotic episodes involving imperative hallucinations that incite to kill the newborn or delusions that the child is possessed.
- i) **Seasonal model:** episodes occur at a certain time of the year, most often autumn or winter.

4. *Premenstrual dysphoric disorder.* It was first introduced in DSM-V and is diagnosed when at least 5 of the following symptoms are present in most of the premenstrual phases:

- marked emotional lability (profound fluctuations in mood);
- Irritability or anger or increased interpersonal conflicts;
- Significantly low mood, feelings of despair and self-critical thoughts;
- marked anxiety, tension or feeling of having nerves on the surface;
- Reduction of interest in normal activities;
- Difficulty concentrating;
- Sense of fatigue and energy loss;
- Changes in appetite;
- Sense of loss of control of one’s life;
- Physical symptoms such as breast soreness, joint or muscle pain, swelling and weight gain.

5. *Adaptation disorder with depressed mood.* In DSM-V, adaptation disorders are defined as “clinically significant emotional or behavioral symptoms” that develop “in response to one or more identifiable psychosocial stressors”. Symptoms must occur within 3 months of the start of the stressful factor. The reaction must be disproportionate to the nature of the stress or there must be a significant impairment of social or work functioning. No diagnosis of adaptation disorder should be made if the reaction meets the criteria for another specific anxiety or mood disorder. The symptoms of the disorder usually resolve within 6 months, although they may last longer if they are produced by a chronic stressor or have persistent consequences. Therefore, adaptation disorders are short-term maladaptive reactions to what can be experienced as a personal calamity, but which in psychiatric terms is defined as a stressor. Personality organization helps to determine the disproportionate responses to stressors. Difficulties in an interfamily relationship can cause an adaptation disorder that involves the entire family system; specific stages of development – such as the start of school, the abandonment of the home, marriage, the birth of a child, failure to reach work goals, leaving the home of the last child and retirement – they are often associated with an adjustment disorder. Crucial to understanding adaptation disorder is the knowledge of three factors: the nature of the stressor, the conscious and unconscious meanings of the stressor and the patient’s pre-existing vulnerability. The DSM lists several types of adaptation disorders; in the case in question, we are interested in the form “with depressed mood”, precisely because of this point of contact with depressive disorder: it is in fact characterized by a marked negative bending of the mood.

6. *Depressive disorder with other specification.* In this category fall:

- a) *Depressive episodes with short-lived hypomania.* It is a sub-category of depressive disorders characterized by short-lived hypomanic episodes contemporaneous with episodic depressive manifestations. Recently, SIP (the Italian company of psychiatry) has compiled a list of 8 subtypes of depression, just because it is considered a sub-classification of depressive disorder with other specification.
- b) *The single depressive episode.* An episode can start quickly in a few days or slowly for several weeks and generally lasts for several weeks and months. In order to talk about a depressive episode, different depressive symptoms must be present permanently for at least 2 weeks. Most people who have a depressive episode will have further episodes in their life (recurrent depressive disorder). The risk of recurrence of the disorder can be reduced with appropriate treatment. When depressive episodes repeat themselves we speak of recurrent or major or unipolar depressive disorder.
- c) *Postpartum depressive disorder.* Becoming a mother is a complex psychological process, which can offer the opportunity to review one’s own childhood bonds, reworking past conflicts and prefiguring a new mature

and integrated identity, but it can also deconstruct a fragile personality, exposing it to the risk of psychopathologies. If the relationship with one’s mother has been positive, the pregnant woman can identify herself with an image of fertility and protection and at the same time with herself as a child, remembering the need for affection that she showed and the confidence that she would be satisfied, thus succeeding to descend into the role of mother and to understand the needs of the child; instead, if the relationship with her mother was conflictual, the woman re-experiences with her child the painful fusion experienced as a child with her mother, feeling that she has failed in her process of individuation and reducing her willingness to care for her child if not is sustained and has unsolved psychological conflicts, the intense effort of psychological, physiological and social adaptation required by motherhood can expose her to the risk of clinical pictures, especially depressive, of different intensity and severity. The first and mildest of the post-partum depressive clinical pictures is the baby-blues or maternity blues, a mild transient emotional disorder that affects more than half of Western women and that occurs in the days immediately following childbirth. The “blues” is a moment of lowering the mood, with a feeling of tiredness, of sadness and distrust, crying crying, which is accentuated around the fourth or fifth day after the birth, that is, in correspondence with the milky whipping, it lasts some hours or a few days and then resolves spontaneously. However, if it persists and worsens, it can become a real post-partum depression and, in some extreme cases, become a puerperal psychosis. The DSM reports a specific post-partum depression, with symptoms such as depressed mood for most of the day, sleep disorders such as insomnia or hypersomnia, agitation or psychomotor slowing, feeling of exhaustion due to lack of energy, feelings of self-depreciation or excessive and inappropriate guilt, sharp reduction in the ability to think, concentrate or make decisions. Puerperal psychosis, on the other hand, is the most serious post-partum depressive condition, since it involves a destructuring of psychic functions, an impairment of the reality test and the onset of psychotic symptoms such as delusions and hallucinations. Postpartum depression is not only a state of discomfort for the mother, but also affects the health of the child, with modalities and outcomes that cannot be accurately predicted, since the depression itself involves a fluctuation of the maternal mood and the modalities of interaction with the child. The interactive style of depressed mothers is not uniform, however Cohn and Tronick (1989) have detected 4 main patterns:

- a) *Intrusive mother style.* The style of these mothers is intrusive, as it does not respect the child’s rhythms, but tends to force them, intervening even when the child manifests the need to withdraw from interaction to regain energy. The stimulation is excessive and inopportune, it is accomplished with an irritated tone of voice, agitated and awkward maneuvers of care that arouse anger and hostility in the child;

b) *Withdrawn maternal style*. These mothers show themselves unavailable to interaction, so attempts by children to engage with them generally fail, generating a sense of incompetence in the children themselves, who develop a negative affective core, dominated by sadness and resignation;

c) *Positive maternal style*. These mothers resemble the non-depressed ones, since they are sufficiently responsive and involved in interaction, allowing the child to develop a predominantly positive affective nucleus. However, they differ from non-depressed mothers in the quantity and frequency of interactive exchanges, which is significantly lower;

d) *Mixed maternal style*. These mothers oscillate between an intrusive, withdrawn style and a positive style, based on changes in mood and contingent situations. Even in children, there is an analogous oscillation with a risk of emotional disorganization, since I cannot foresee the mother's response with stability.

The maternal depressive symptomatic picture reproduces in the child, who experiences a micro-depression, with psychomotor retardation, prevalence of melancholy moods, facial and postural inexpressiveness. In this regard, Stern (1995) identified 4 types of subjective experience of the child with a depressed mother:

a) *Microdepression*. The child fails to involve the mother, so try to get in touch with her through identification and imitation. Imitation involves taking on expressions and behaviors similar to those observed in the mother: since the maternal face is inexpressive and sad, her voice has a low tone and her posture seems soft, even the child will reproduce this configuration, becoming silent and expressionless. Then, through identification, he models his state of mind on that of his mother, feeling the same feelings of suffering, loss and distrust;

b) *Resuscitation of the mother*. The child who does not receive a response from his mother to his invitations, activates strategies that capture his attention, for example, raises his eyebrows, opens his mouth, vocalises more frequently and in a higher tone. Often, by intensifying the efforts to involve the mother, the child gets an answer, since the mother realizes her emotional unavailability and changes her attitude, approaching her son and interacting with him;

c) *Search for self-stimulation*. If the child does not receive a reply from his mother, despite his efforts, he desists from "reviving her" and relies on the search for stimulation and gratification in the external environment;

d) *False stimulation*. When mothers notice that they have not offered stimulation to the child, they try to repair, resorting to intense and forced stimulation, which is intrusive and inappropriate. However, being the only stimulation available, the child accepts it, being content.

Si assiste, quindi, ad un'interazione forzata, dove la madre attua una falsa stimolazione e il bambino risponde con un falso sé compiacente, stando al gioco, pur di soddisfare il suo bisogno di interazione.

d) The *complicated persistent mourning*. It occurs when the person is in mourning and presents a series of disabling symptoms for a period exceeding 12 months. Already in the DSM-IV-TR the mourning had been placed among the so-called "conditions that can be object of clinical attention", just to indicate how, in the normal process of elaboration consequent to such event, could be such difficulties to render the condition of the pathological survivor. However, the manual provided for the possibility of turning towards a diagnosis of a major depressive episode if the symptoms and functional impairment persisted for more than 2 months, thus allowing the consequences of failure to mourn to be included in a more properly depressive situation. The DSM-V therefore proposed the diagnosis of persistent and complicated mourning disorder to indicate precisely those conditions in which the acute manifestations of mourning, with negative experiences, of sadness, guilt, envy, anger, associated with persistent ruminations related to The causes, circumstances and consequences of the loss remain if at least 12 months have passed since the death of someone with whom the grieving individual had a close relationship, considering this period of time as a discriminating factor between normal and pathological mourning. The diagnostic criteria of persistent and complicated mourning disorder are:

a) The individual experienced the death of someone with whom he had a close relationship.

b) Since the time of death, at least one of the following symptoms has been present for a number of days longer than that in which it was not present and at a clinically significant severity level, and has persisted in adults at least 12 months and in children for at least 6 months after mourning:

1. A persistent desire / nostalgia for the deceased person. In small children, desire can be expressed in play and behavior even through behaviors that reflect being separated from, and even reunited with, a caregiver or another figure that is the object of attachment.

2. Sadness and intense emotional pain following death.

3. Concern for the deceased.

4. Concern for the circumstances of death. In children, this concern for the deceased can be expressed through the contents of the game and the behavior can extend to concern about the possible death of other close people.

c) Since the time of death, at least 6 of the following symptoms have been present for a number of days longer than those in which they were not present and at a clinically significant severity level, and have persisted in adults at least 12 months and in children at least 6 months after mourning:

1) Suffering related to death:

- Marked difficulty in accepting death. In children, this difficulty depends on the ability to understand the meaning and finality of death.

- Feel disbelief or emotional numbness about the loss.
- Difficulty to abandon oneself to positive memories concerning the deceased.
- Bitterness or anger in relation to the loss.
- Negative self-assessment in relation to the deceased or death (eg sense of self-guilt).
- Excessive avoidance of memories of the loss (eg avoidance of persons, places or situations associated with the deceased; in children this may include avoidance of thoughts and feelings regarding the deceased).

2) Social and identity disorder.

3) Desire to die to be close to the deceased.

4) From the moment of death, difficulty in trusting others.

5) From the moment of death, feeling of being alone or detached from others.

6) Feeling that life is empty or meaningless without the deceased, or thought not to succeed without the deceased.

7) Confusion about one's role in life, or diminished sense of one's own identity (eg a part of oneself is diminished along with the deceased).

8) From the moment of loss, difficulty or reluctance to pursue one's own interests or to make plans for the future (eg friendships, activities).

d) The disorder causes clinically significant distress or impairment in social, occupational or other important areas.

e) The bereavement reaction is disproportionate or inconsistent with cultural or religious or age-appropriate norms.

e) *Psychotic depression*. A specific form of depressive episode is psychotic or delusional depression. Psychotic depression is characterized by false ideas and beliefs (delusions) and sometimes even by hallucinations. The disappointments are typically focused on grossly exaggerated feelings of guilt (eg "I am just a burden to my family" or "I made a terrible mistake"), on the fear of complete financial ruin (disappointment of poverty) or on the exaggerated fear of a serious incurable disease (hypochondriac disappointment). The disappointments usually remain even if proof of the contrary is available (for example, having enough money). Patients with psychotic depression almost always need psychiatric treatment due to the severity of this disorder and the high risk of suicide. Psychotic depression can occur in both unipolar and bipolar depression.

f) *Atypical depression*. Patients with this type of depression have the same depressive symptoms as those with typical depression with two exceptions: whereas in patients with typical depression there is lack of appetite (often with weight loss) and difficulty falling asleep, patients with atypical depression show excessive food and sleep intake. This type of depression can occur in unipolar and bipolar depression.

7) *Substance / drug-induced depressive disorder*. All symptoms of major depression appear and such symptoms persist beyond the expected duration of the effects of drug or drug intoxication or the period of abstinence.

8) *Depressive disorder due to medical condition*. It is a depressive picture as a direct result of another disease; ex: stroke, Huntington's disease, traumatic brain injury, Parkinson's disease, hypothyroidism, ...;

9) *Depressive disorder with no other specification*. It is a residual category that embraces all those depressive morbid conditions that create a clinically significant discomfort and predominate in the subject's psychological framework but do not fully meet the criteria for one of the categorized depressive disorders.

Cross-sectional profiles between depressive disorder and bipolar disorder. Differential diagnosis

Bipolar affective disorders (manic-depressive disorder) are less frequent than unipolar disorders (or depressive and / or manic), but are more serious. We distinguish 2 forms: bipolar I and bipolar II. Type I bipolar patients suffer from both depressive episodes and manic episodes. Manic episodes may occur suddenly after several depressive episodes and, if present, the original diagnosis of unipolar depression must be changed to bipolar affective disorder. This change in mood can occur very quickly (overnight) after a depressive episode or after months and years of healthy mood. The manic phases are characterized by an excessive mood, associated with hyperactivity, restlessness, irritability, talkativeness and reduced need for sleep. Mania influences thought, judgment and social behavior causing serious problems and difficulties. When an individual is in a manic phase he can take indiscriminate or unsafe sexual practices or imprudent decisions or impulsive economic decisions. The best way to describe this "tumult of emotions" that alternates is "going from being on top of the world to the depths of despair". Type II bipolar patients, on the other hand, have a different characteristic from the previous version: the manic symptoms are less pronounced and do not lead to serious psychosocial problems, speaking of hypomanicity (and not manic). Therefore, if a patient suffers from both depressive episodes and hypomanic episodes, a bipolar II disorder is diagnosed. However, from these 2 forms the residual hypothesis of the hypomanic episode that occurs immediately after the end of a depressive episode must be distinguished: in this case, we will speak only of a depressive episode with episodic hypomanicity. [1]

<<(…) From a transversal perspective, a Major Depressive Episode appears phenomenologically similar to Major Depressive Disorder and Bipolar Disorder. In the clinical reality, however, some elements combined together can help the clinician distinguish between the two conditions (Vöhringer & Perlis, *Psychiatr Clin N Am* 2016). It is of fundamental importance, in fact, to recognize the belonging of the depressive condition to one or the other of the longitudinal clinical conditions since the choice of treatment and the prognostic meaning are different; in the first case an antidepressant therapy is indicated, which will be maintained for about 1 year (in the absence of elements

indicating the need to continue with a prophylactic treatment, such as at least 3 lifetime depressive episodes or 2 episodes interspersed with a free period of duration less than 5 years). In the case of bipolar depression, on the other hand, the first-choice treatment consists of a mood-stabilizing drug, which will be maintained in the long term (usually for life) with the aim of preventing affective recurrences of both polarities. The correct differential diagnosis is not always easy for the clinician, especially if he is not a specialist in psychiatry, for two substantial reasons: first of all, a significant proportion of patients with a subsequent diagnosis of DB presents an EDM as a first affective lifetime episode, which will therefore necessarily be considered as unipolar (a recent meta-analysis has estimated that 22.5% of subjects with DDM followed for 12–18 months will subsequently develop a counterstrike episode – Ratheesh et al., *Acta Psychiatr Scand* 2017; the conversion risk is maximal in the first year, and then decreases – Kessing et al., *Bipolar Disord* 2017); secondly, patients, especially in the case of a Type II DB, will report recurrent EDM in their medical histories while they will tend to consider the short hypomanic phases as physiological well-being periods, especially when accompanied by symptoms such as mild euphoria and increased energy and activities aimed at, thus denying its belonging to the sphere of the disorder and thus preventing a correct longitudinal diagnosis. It is therefore necessary to recall the importance of an adequate longitudinal anamnesis, conducted where possible with the help of family members (...): the recent literature evidences, in fact, underline the relationship between the number of affective episodes and the increase in the risk of subsequent recurrence, the reduction of the probability of response / remission of the episode, the severity of subsequent episodes, the reduction of the threshold for the development of subsequent affective episodes (initially associated with stressful events and subsequently independent of them), and finally the progression towards a cognitive impairment (Kapczinski et al., *Expert Rev Neurother* 2017). Beyond the possible use of assessment scales and / or self-administered questionnaires (such as: Mood Disorders Questionnaire, Bipolar Spectrum Diagnostic Scale, Bipolar Disorder Screening Scale, Hypomania Checklist) that can help identify bipolar depression, the only really effective strategy consists in focusing attention on the longitudinal dimension of the disease (we return to the kraepelinian teachings), thus avoiding to base the diagnosis exclusively on the transversal approach. A correct and innovative approach to the diagnosis of bipolar depression consists in considering a cumulative risk index that derives from the sum of the genetic risk (familiarity for DB) with intraepisode or longitudinal clinical elements that are mainly associated with bipolar depression. (...) A useful tool, expression of the same probabilistic approach and which represents a summation of many of the bipolar predictor clinical elements already mentioned, is the Bipolarity Index, proposed by Sachs in 2004, which recently confirmed its predictive ability with high sensitivity and specificity (Aiken et al., *J Affect Disord* 2017) (...)>> [17].

A useful summary scheme of the main aspects is reported by the Australian and New Zealand guidelines for the treatment of affective disorders (Malhi et al., *Aust N Z J Psychiatry* 2015) (Table 3).

Table 3: Distinctive Criteria Between Depression and Bipolar Disorders.

Features	Bipolarity	Depressive monopoly (Depression)
Family history	Familiarity with the bipolarity and use of drugs / alcohol	Less familiar with the
Onset of the disease	20-25 years	bipolarity and substance use
Beginning / End of the episode	Sudden / fast	16-20 / 25-30 years
Comorbidity	Most frequent ADHD	Gradual / slow
Duration of the episode	Less than 6 months	ADHD less frequent
Number of previous episodes	multiple	More than 6 months
Affective symptoms	Liability of mood and symptoms	Rare
Psychomotor symptoms	Manic	Deflected mood and little energy
Sleep disorders	Less frequent slowdown	More frequent slowdown
Appetite changes	Hypersomnia / Diurnal sleepiness	Initial insomnia and reduced sleep
Other symptoms	Hyperphagia / Weight gain	Loss of appetite and weight

<<(…) Regarding the efficacy of antidepressants in bipolar depression, the topic is a source of debate and basically there are two opposing schools of thought: one that deems antidepressants to be harmful, the other that considers appropriate the use of antidepressants in combination to stabilizers in certain circumstances. The open questions regarding the use of antidepressants in bipolar depression, issues on which the ongoing debate on their possible use is based, concern their effectiveness, the fact that the aforementioned phenomenon of tolerance may occur, especially in the long term, but above all the risk of switch in counter-episode, the risk of induction of mixed states and the risk of acceleration of the cycle / induction of rapid cyclicity. Regarding the efficacy of antidepressants in bipolar depression, 2 recent randomized controlled clinical trials have shown that the addition of agomelatine or citalopram to stabilizers does not have any advantage in terms of acute or prophylactic efficacy. A recent meta-analysis that includes the two aforementioned RCTs and others still being published, concludes, however, that second-generation antidepressants have a statistically significant but modest effect as regards depressive symptomatology (Standardized Mean Difference 0.165), while they do not differ compared to the addition of placebo for response and remission rates (McGirr et al., *Lancet Psychiatry* 2016). It is therefore likely that only some patients will benefit from the addition of an antidepressant. The same authors also conclude that the use of antidepressants is not associated with a significant increase in the risk of manic switch in the short term, while the 52-week increase in risk is significant (long-term destabilization); the practical clinical conclusion that can be drawn from this is that if employed, antidepressants in bipolar depression should always be used in association with mood stabilizers (never as monotherapy), and should be discontinued after a few weeks. The use of antidepressants in bipolar depression, beyond the efficacy or less acute, can in some cases determine

the appearance of mixed aspects, consequently leading to an increase in the suicide risk generally greater in the case of mixity (Koukopoulos et al., *Acta Psychiatr Scand* 2014; Sani et al., *Psychother Psychosom* 2014; Tortorella et al., *J Psychopathol* 2015). From a clinical point of view, it can be concluded that the use of antidepressants should provide particular attention to the detection of counter-symptoms within the EDM, whether already framed in a longitudinal diagnosis of DB (in this case in association with a stabilizer) which is not yet identified as belonging to the bipolar spectrum (in this case monotherapy); above all psychomotor agitation and anxiety understood as internal tension (sometimes accompanied by ideological acceleration) should lead to particular attention if not to the exclusion of the option of the use of antidepressants. In the case of inhibited / anergic depressions, with an important ideomotor slowdown, the use of antidepressants can be useful (Salvi et al., *J Clin Psychiatry* 2008; Pacchiarotti et al., *Am J Psychiatry* 2013). Beyond the use of antidepressants, and despite divergences between the various international guidelines, the treatment of bipolar depression sees first-line drugs as monotherapy: lithium, valproic acid, lamotrigine, quetiapine (quetiapine XR), with the addition according to some guidelines, of olanzapine and lurasidone (for a comparison between the various guidelines see Parker et al., *Acta Psychiatr Scand* 2017). Various non-pharmacological strategies such as group or individual psychoeducation, interpersonal therapy and social rhythms (IPSRT) and cognitive behavioral therapy (CBT) are variously indicated (in acute and / or maintenance) for the treatment of bipolar depression: in acute the effect on the depressive symptomatology is of small entity although clinically meaningful for some typologies of intervention (above all and less IPSRT), while the effect of the addition of psychoeducational and / or cognitive-behavioral interventions is significant (initiated in patients depressed or eutymic) on the prevention of recurrences (Oud et al., *Br J Psychiatry* 2016). (...)>>. [17]

Correlation between depressive disorders and suicide

The theme of suicidio, in depressive disorders, is of central importance: a therapist (of psychological and non-medical training) who finds himself in front of a patient with obvious suicidal symptoms, should immediately send it to the attention of a psychiatrist, to favor the correct psychopharmacological classification. Suicidal behavior does not seem to be an intrinsic dimension of any psychiatric disorder “and therefore deserves a place of its own in the new DSM as a” separate diagnosis “. At the present time it configures this behavioral symptom only within the framework of the criteria to be evaluated, identifying it in the category “suicidal behavior disorder” [1].

<<(...) The World Health Organization (WHO) estimates that around 880,000 people die each year from suicide worldwide (World Health Organization, 2014). In Italy, there are over 4,000 deaths from suicide each year. These broad estimates indicate a death by suicide every 40 seconds and a suicide attempt every 3 seconds. Suicide attempts, in fact, are 10 to 20 times higher than the number of completed suicides. This necessary premise, makes us reflect on how suicide is a

widespread phenomenon in the population, to the point of being considered the second main cause of death in an age between 14 and 29 years, and also one of the main causes of death between 18 and 44 years, in both sexes. A mistake dictated by the logic of common sense is that of associating, in terms of causal relationship, the major depressive disorder and the risk of suicide. The vision that today seems to do justice to the complexity of the phenomenon lies in considering depression as an important but not exclusive contributing factor in determining the risk of suicide. This led to the conclusion that suicide is more related to a vulnerability acquired during development and puts the individual in danger when adverse events and psychiatric disorders break into an individual's life. For years, literature has critically cited the study by Guze and Robins (*Br J Psychiatry*, 1970) which states that 15% of depressed patients die by suicide. More recent studies have recognized the existence of a hierarchy in the risk of suicide in patients with psychiatric disorders. Bostwick and Pankratz (*Am J Psychiatry*, 2000), in their studies estimate that the prevalence of lifetime suicide risk in patients hospitalized for suicide risk is 8.6%. For affective disorders in hospitalized patients without specific suicide risk, lifetime prevalence is 4.0%. The lifetime prevalence for patients with affective disorder in outpatient treatment is 2.2%, and for the general population without affective disorder it is less than 0.5%. An interesting study (Kessing, *Br J Psychiatry*, 2004) considered the risk of suicide in relation to the severity of the depressive episode. In this study a very large sample of patients at their first discharge - of which 1,103 with an ICD-10 diagnosis of mild depressive episode; 3,182 with a diagnosis of moderate depressive episode and 2,914 with a diagnosis of severe depressive episode - shows significant differences due to the risk of suicide and relapse of the disease, which increases in relation to mild → moderate → severe depressive disorder. (...) Suicide is the result of an inner dialogue. The mind reviews all the possible options that can calm mental pain, when the idea of suicide emerges, the mind refuses it and continues to verify the options. If, however, a satisfactory solution to the resolution of pain is not found, suicide arises again, until the mind accepts suicide as a solution, identifies it as the only answer, the only option available, and therefore plans it. The individual experiences a state of psychological constriction, a tunnel vision. The dichotomous thought emerges, that is the narrowing of the range to only two options (very few for a range): to have a specific and total solution (almost magical) or the end (suicide). Suicide is better understood not as a desire for death, but as a cessation of the flow of ideas, or the complete cessation of one's state of consciousness and therefore the resolution of unbearable psychological pain. (...) Working on mental pain, also means making use of the help of specific pharmacological treatments. The literature shows that an untreated or unsuccessfully treated major depressive episode constitutes the main cause of suicide attempts and proper suicide (Rihmer et al., *J Affect Disord*, 2006). The importance of using antidepressants to prevent suicide has been consolidated for many years. In patients with major depression who receive long-term drug treatment (antidepressants and / or mood stabilizers), the risk of committing suicide or attempting it is

reduced by 53% -93% compared to patients who do not take any type of therapy (Guzzetta et al., J Clin Psychiatry 2007). It is of fundamental importance, however, to monitor patients who have received antidepressant treatment over time as the risk of suicidal behavior in depressed patients who take antidepressants is relatively more frequent in the first 10-14 days of treatment, or in the days preceding the initiation of antidepressant action (Simon et al., Am J Psychiatry 2007). Antidepressants have been subjected to considerable investigations into their impact on suicide risk. Although they were considered the main aids for reducing the risk of suicide, some research showed that they could play a role in increasing this risk. The literature has therefore been enriched with articles that accuse or exonerate these drugs, specifically the selective serotonin re-uptake inhibitors (SSRIs). Over time it has been clarified that in many circumstances the use of the antidepressant is contraindicated if improperly prescribed to subjects suffering from bipolar disorder in the depressive phase or in subjects at risk of suicide because it worsens precisely those symptoms most feared as agitation, insomnia and in general a sense of internal restlessness. Moreover, in the juvenile population the risks seem to be much greater than in the other age groups and much emphasis is now placed precisely on the wise use of these drugs in relation to the age and the psychic state of the subject. The use of the antidepressant should be avoided in the acute phases of suicide risk where everything is unstable and susceptible to sudden changes, especially in conditions that could imply a mixed or dysphoric state. The appearance of some signs and symptoms should guide the use or discontinuation of the antidepressant drug in the monitoring of suicide risk. These are the conditions in which agitation, anxiety, insomnia, dysphoric-irritable states, anger, the appearance of new symptoms not previously ascertained occur. The doctor must therefore evaluate an alternative therapy until the suspension. Antidepressant therapy can then be started at a later stage of greater stability. Lithium deserves a separate discussion. Its proven antisuicidal action makes it a drug of first use even in major depression with the risk of suicide (Guzzetta et al., J Clin Psychiatry 2007). It is interesting to note the beneficial effect that the use of lithium has in those patients with mood disorder hospitalized for a major depressive episode. In this regard, a study conducted in 2001 highlighted how, by dividing patients into three groups - those with excellent responses, those with a medium response and those with poor responses - the action of lithium in reducing the risk of suicide is not expressed only in those who respond well to therapy but also to those who, while struggling with depressive symptoms, have a decreased risk of suicide (Ahrens B, Muller-Oerlinghausen B. Pharmacopsychiatry 2001). Lithium decreases recurrence of depressive illness both in major depression and in bipolar disorder, confirming in this latter case the properties against the risk of suicide. A possible action of lithium that can explain the antisuicidal effect is the enhancement of cerebral serotonergic function at the limbic prefrontal level. This effect could compensate for the well-known serotonergic reduction often identified in subjects at risk of suicide or in those who die by suicide (Pompili et al., The prevention of suicide, 2013). To increase the efficacy of

therapies, the current perspective introduced by nutraceuticals makes it possible to use formulations that combine the principles of nutrition and those of pharmacology. As a result, this combination enhances antidepressant drug therapy. In fact, a large number of factors can make the action of drugs difficult; nutraceuticals can restructure physiological mechanisms allowing better pharmacological metabolism. Among the many examples that see the use of N-Acetyl Cysteine (NAC) in enhancing the therapy of mood disorders, we cite the case of NAC in the reduction of suicidal ideation in patients with bipolar depression and compared with patients with characteristics similar treated with placebo (Waterdrinker et al., J Clin Psychiatry, 2015). Psychotherapy also plays a crucial role in managing suicide risk in depressed patients. In addition to having the benefit of increasing adherence and increasing the effectiveness of pharmacotherapy (Fountoulakis et al., Can J Psychiatry 2009), psychotherapy offers itself as a space for reflection and containment to support those who need to speak, to be understood above all in the most difficult moments. It is not uncommon for patients, especially those who live in the uniqueness of their own pain and inability to want to be helped, do not trust the psychotherapy intervention. Faced with the arduous task of opening up the uniqueness of individual pain, the therapist is called to intervene through the implementation of an empathic listening. (...)>> [18].

The DSM-V also encodes the hypothesis of *non-suicidal self-harm* [1]. The self-injuring act performs different functions: the most reliable relate to a strategy of emotional regulation, a form of "learned" self-punishment due to a debilitating life context, and again, an attempt to exit dissociative states. In DSM-IV, self-injury is included among the symptoms of borderline personality disorder: "recurrent threats, gestures, suicidal behavior or self-mutilating behavior". However, although some research has confirmed the existence of a strong relationship between self-injury and this personality disorder, even patients receiving other diagnoses appear to be intentionally and deliberately injured. In particular, subjects suffering from major depression, anxiety disorders, substance abuse, eating disorders, post-traumatic stress disorder, schizophrenia and other serious personality disorders. In addition, recent studies have investigated the existence or absence of an association between intentional self-injury and para-suicidal and suicidal gestures. It was initially hypothesized that these behaviors could be located along a continuum. However, non-suicidal self-injurious gestures and para-suicidal gestures would seem to differ for some important points, including the use of different methods, different physical severity outcomes (greater for para-suicidal and suicidal gestures) and different intentionality (non-suicidal self-harm is frequently implemented in the absence of suicidal ideation). This distinction turns out to be the starting point for the proposal put forward in the current diagnostic manual (DSM-V): non-suicidal self-harm could be conceived as a diagnostic category in its own right. The criteria proposed in the current diagnostic manual indeed include:

a) In the last year, in five or more days, the individual has intentionally inflicted damage of some kind on the body

surface capable of inducing bleeding, bruising or pain (for example, cutting himself, burning himself, stabbing himself, hitting himself, rubbing excessively), with the expectation that the injury leads to only minor or moderate physical damage (there is no suicidal intention).

b) The individual is involved in self-injuring activities with one or more of the following expectations:

1. Get relief from a negative feeling or cognitive state;
2. Solving an interpersonal difficulty;
3. Induce a positive feeling.

c) Self-harm is associated with at least one of the following symptoms:

1. Interpersonal difficulties or negative feelings or thoughts, such as depression, anxiety, tension, anger, generalized discomfort, self-criticism, which occur in the period immediately preceding the self-injurious act;

2. Before making the gesture, there is a period of concern that is difficult to control with regard to the gesture that the individual intends to make;

3. Thoughts of self-harm frequently, even when the behavior is not implemented.

Correlation between depressive disorder and anxiety [19]

<<(…) Depression and anxiety are two very common disorders and represent the most frequently diagnosed psychiatric nosographic categories. They appear inextricably connected to each other both in clinical psychiatric and non-specialist clinical practice. We commonly hear of “anxious depression” or “anxiety-depressive syndrome”, but what is really the relationship between these two psychopathological conditions?

To try to give an answer to this question let's start with some literature data: 350 million people in the world suffer from depression and 265 million suffer from anxiety, with a prevalence calculated on the entire population of 4.4% and 3.6%. These data vary widely in different countries, especially depending on the socioeconomic level: anxiety and depression are more frequent in high-income countries than in developing countries and the risk of manifesting an anxious or depressive disorder is lower in eastern and greater countries in countries at war. Like depression, anxiety disorders also affect predominantly women (4.6% vs 3.6%), and young people (WHO, 2017; Kessler RC, Bromet EJ, Rev Public Health 2013; Baxter AJ et al., Psychol Med 2013). The comorbidity between anxiety and depression is very frequent, and can occur at any age, from childhood to adulthood (Moller HJ et al., Eur Arch Psychiatry Clin Neurosci 2016): several epidemiological studies have shown that over 50% of patients with a depressive disorder during their lifetime develop an anxiety disorder, especially generalized anxiety disorder and panic disorder; 85% of depressed patients manifest anxious symptoms, such as

alertness, panic attacks, free or somatized anxiety and phobias. 90% of subjects with an anxiety disorder experience depressive symptoms or a major depressive disorder in comorbidity (Lenze EJ et al., Am J Psychiatry 2000 May; Gorman JM, Depress Anxiety 1996-1997), with a risk during life between 50% and 65% in patients with a panic disorder, between 8% and 39% in patients with a generalized anxiety disorder and between 34% and 70% in patients with social phobia. In 31% of the cases the anxiety disorder precedes the depressive episode, with an onset between one and ten years before (17.6% Social phobia, 7.8% Phobia, 6.7% Generalized anxiety disorder, 3.1 % Panic disorder), representing the strongest predictor of a secondary depressive disorder (Kessler RC et al., Br J Psychiatry 1996).

These data account for the considerable socio-economic impact, as well as the important consequences in terms of “loss of health” caused by these disorders. It has been estimated that currently depression is the fourth cause of disability in the world; according to the projections it will rise to second place in 2020 and the first in 2030. Anxiety disorders represent the sixth global cause of non-fatal health loss (non-fatal health loss) and appear in the ranking of the ten causes of YLD (years of life lived with disability; the YLD is calculated by multiplying the prevalence of a disease or injury and its main disabling consequences by its weighted severity level). Anxiety and depression are even more disabling when they occur simultaneously. The prognosis, and its impact on global functioning, seem to worsen in cases where there is comorbidity; the overlap of anxious symptoms, or of an anxiety disorder, accelerates, worsens, and lengthens the course of the depressive episode (Menza M et al., J Clin Psychiatry 2003), determining:

a) a greater severity of depressive symptoms, as demonstrated by the results of psychometric tests such as the Hamilton Rating Scale for Depression (HAM-D), the Beck Depression Inventory (BDI);

b) Longer duration of the episode with increased risk of chronic illness;

c) A greater suicidal risk;

d) A greater abuse of alcohol or drugs;

e) Lower working and social functioning;

f) Less response to short and long term drug treatments;

g) Greater access to health services (Tiller JWG, MJA 2012).

(…) The anxious symptoms also frequently remain as residual symptoms of the depressive episode (39.9% of cases; Cuffel BJ et al., J Clin Psychiatry 2003), hesitating in a worse prognosis. The somatic effects of anxiety and depression should also not be forgotten: these two conditions in fact alter the main regulatory systems of our body, such as the hormonal, endocrine and immune systems, determining metabolic, cardiovascular, somatosensory / emotional, cognitive and neuronal disreactivity and immune through the activity of cytokines, cortisol, ACTH, neurotransmitters and other

substances. Anxiety and depression are predictive factors for the onset of chronic organic diseases and often occur in comorbidity with them (eg cardiovascular diseases, autoimmune diseases, obstructive pulmonary syndromes, infections, chronic pain, insulin resistance, inflammatory bowel diseases and cancer), worsening the course and increasing mortality.

(...) It is likely that the relationship between anxiety, depression and psychobiological changes is bidirectional or even more complex. Neurobiological and phenomenological evidence suggests that depression and anxiety could represent different manifestations of a similar vulnerability, linked to a common “stressor” (Das-Munshi J et al., *Br J Psychiatry* 2008). Genetic studies have shown a heritability of depression equal to 37% and an inheritance of anxiety disorders equal to 30%; studies on families, twins and adoptive children have shown that this heritability cannot be attributed to a single gene, and that depression and anxiety are pathologies with complex genetic characteristics. Among the genes studied, the serotonin transporter (5-HTT), the tryptophan hydroxylase (TPH) gene and the BDNF gene are particularly important in depression. It is interesting to note that in scientific studies the 5-HTT knockout mice showed, in addition to depressive behaviors, also a state of excessive anxiety (Belmaker RH, Agam G, *N Engl J Med* 2008). Kendler and colleagues postulated the genetic correspondence theory of the mixed anxiety disorder in 1992, providing evidence on the same genetic origin of anxiety and depression for shared genetic factors expressed in vulnerable patients (Kendler KS et al., *Arch Gen Psychiatry* 1992). The possible evolution from an anxiety disorder to a depressive disorder and vice versa was observed in a longitudinal perspective (Rhebergen D et al., *Acta Psychiatr Scand* 2011). It was therefore suggested that the two conditions could be the extremes of a continuum (Nutt DJ, *J Clin Psychiatry* 1999) with a shared diathesis, represented by a non-specific “negative effect”. Observing that the most recent classes of antidepressants were effective in anxiety disorders was an important finding in support of these hypotheses, providing further evidence to support previous interpretations of psychiatric symptoms as a manifestation of specific independent neurochemical changes to clinical diagnosis and the concept of Freyhan’s target symptoms, according to which psychotropic drugs act on symptoms and not on disorders. This is especially true for selective serotonin reuptake inhibitors (SSRIs) whose effectiveness in anxiety and depressive disorders has been traced back to their agonistic action on the serotonin-1A (5-HT_{1A}) receptor subtype: the difference between their effect antidepressant and anxiolytic may depend on their action on pre-synaptic (anxiolytic) or post-synaptic (antidepressant) 5-HT_{1A} receptors. Recent research on the activity of the cerebral cortex (pattern of inhibition and activation) in the high-density areas of serotonergic receptors support the continuum theory, providing a biological model. Epidemiological studies have shown that about half of patients suffering from ICD-10 mixed anxiety disorder (MADD) according to ICD-10 criteria (with sub-threshold symptoms that do not fully meet the criteria for anxiety or depressive disorder) develop a disorder within a year psychiatric “full”. It has therefore been suggested by some authors that MADD may constitute a prodromal stage of another psychiatric disorder, and should therefore be classified

based on this disorder and not as an independent diagnostic entity (Batelaan NM et al., *J Nerv Ment Dis* 2012).

(...) A recent literature review (Ionescu DF et al., *CNS Spec* 2013) compared the different definitions and classifications of the disorder using the DSM criteria, ICD criteria, dimensional and syndromic approach in relation to the 5 Feighner domains required to establish diagnostic validity in psychiatric illness. The authors concluded that dimensional diagnosis is probably the best approach to distinguish depressive anxiety syndrome from other forms of depressive and anxiety disorder, identifying a more serious clinical picture than that outlined by other diagnostic criteria proposed in official classification.

(...) Since the birth of psychiatric nosography, at the end of the nineteenth century, up to the seventies of the last century, anxiety and depression were widely accepted by the non-psychoanalytic psychiatric community as several manifestations of an affective spectrum disorder. In fact, the first two editions of the DSM (APA, 2013), published respectively in 1952 and 1968, included these two disorders within the same chapter (in “psychoneurotic disorders” in DSM I, later called “neurosis” in the DSM II). The birth of psychopharmacology since the 1950s has led to the development of drugs with specific antidepressant effects (eg tricyclic antidepressants) and anxiolytics (eg benzodiazepines), effectively supporting the separation between depression and anxiety. The DSM III, published in 1980, represented a strong break with the past, distinguishing the category of “affective disorders” from “anxiety disorders”. A contribution of this historic division was the presence of two separate consultation committees assigned to the drafting of the relative sections. Simultaneously with the DSM, from 1948 to today there have been several versions of the International Classification of Diseases (ICD, WHO 2007): in 1990 the World Health Organization (WHO) approved the ICD-10 which, unlike its predecessor ICD-9, published in 1978, included the mixed anxiety-depressive disorder in its section on anxiety disorders. According to the ICD criteria, the diagnosis of mixed anxiety-depressive disorder can be placed when the symptoms of anxiety and depression are both present, but neither of them are clearly predominant, nor are they so marked as to justify a diagnosis if considered separately. When both the depressive and the anxious syndrome are so serious as to justify an individual diagnosis, a diagnosis of both disorders should be made and this category should not be used. The DSM-IV, published in 1994, in the wake of the growing interest of literature or perhaps in response to the ICD, included the diagnosis of mixed anxiety-depressive disorder in the research appendix, a diagnosis then eliminated in the subsequent DSM-V (2013), as assessed as not sufficiently reliable. At present, the DSM-V allows to add the specification “with anxiety” to any type of depressive disorder. Patients presenting with comorbid, subsyndromic anxiety and depressive symptoms, equally important, can be diagnosed with a “Depressive disorder with other specification with anxiety”. In the DSM-V and ICD-10 the category of “Adaptation disorders” is also classified, in which the possibility of a combination of anxious and depressive symptoms is envisaged.

(...) Beyond the official nosographic systems, some authors have tried to define anxiety-depressive disorder with different conceptualizations. Clark and Watson (Clark LA, Watson D, J Abnorm Psychol 1991) proposed a tripartite model of affective disorders consisting of a general stressor, physiological hyperarousal (specific to anxiety) and anhedonia (specific to depression). Moffitt and colleagues (Moffitt TE et al., Arch Gen Psychiatry 2007) have suggested the all-inclusive term “distress disorders” to indicate both anxiety and depressive syndromes. Peter Tyrer in 1989 coined the term “cotimia” to define a coaxial diagnosis in its own right, which provides for the co-presence of anxiety (generalized or evolved in panic) and depressive symptoms for a minimum of four weeks, for most of the day all the days. The author also suggests the term “general neurotic syndrome” to indicate a syndrome constituted by a core of neurotic elements, such as anxious, depressive syndromes and passive-aggressive or anancastic personality traits, and invites the scientific community to perfect the concept of comorbidity, since the high% in the psychiatric clinic would represent nothing but the demonstration of the failure of the classification systems. Strong supporter of the validity and clinical utility of the diagnosis of cotimia, as proven by genetic, neurobiological, epidemiological evidence, by pharmacological studies and by “outcome” and characterized by a significantly worse prognosis than the diagnoses considered separately, Tyrer provocatively states that the motivations to favor of the separation of the various neurotic disorders are to be found only in the economic interests of the pharmaceutical industry and researchers (Tyrer P et al., J Pers Disord 2003), deeming the motivations provided by the scientific world to be inconsistent (Tyrer P, Br J Psychiatry 2001). The same author, together with Shorter (Shorter E, Tyrer P, BMJ 2003) states how the inadequate separation of depression and anxiety has led to a slowdown in the discovery of new effective pharmacological treatments, demonstrating an inverse relationship between the number of new diagnoses and the number of new drugs on the market since 1980. According to the authors, this situation occurred due to the impossibility of developing drugs for “natural” pathologies, since the FDA only accepts targeted pharmacological treatments for the diagnostic categories indicated in the DSM, which, however, would be artifacts. At present, the most effective drugs available in the anxiety-depressive syndrome are the serotonergic and noradrenergic double-acting antidepressants belonging to the SNRI class, such as duloxetine and venlafaxine. It is hypothesized that drugs with an exclusive serotonergic action are effective due to the important involvement of noradrenergic systems in the genesis of anxiety symptoms.

Depressive disorders in children and adolescents [20-25]

<<(...) The basic manifestations of depressive disorders in children and adolescents are similar to those of adults but are associated with concerns typical of children, such as homework and play. Children may not be able to explain feelings or internal experiences. Depression must be considered when a young person, who first behaved adequately, starts going wrong at school, isolates himself or commits delinquent

actions. In some children with a major depressive disorder, the predominant mood is irritability rather than sadness (an important difference between infantile form and adult forms). The irritability associated with childhood depression can manifest itself as hyperactivity and aggressive, antisocial behavior. In children with intellectual disabilities, depression or other mood disorders may manifest as somatic symptoms and behavioral disorders.

(...) *Disruptive mood dysregulation disorder* results in persistent irritability and frequent episodes of behavior that is very out of control, with onset at 6 years to 10 years. Many children also have other disorders, particular oppositional defiant disorder, attention deficit / hyperactivity disorder, or anxiety disorder. Diagnosis is not made before 6 years or after 18 years. As adults, patients may develop unipolar (rather than bipolar) depression or anxiety disorder. The events include the presence of the following for ≥ 12 months (without any period ≥ 3 months without all of them):

- a) Serious outbursts of recurrent anger (eg, verbal anger and / or physical assault against persons or property) that are grossly disproportionate to the situation and that occur on average ≥ 3 times / week;
- b) Outbreaks of anger that are not consistent with the level of development;
- c) An irritable state of mind, angry present every day for most of the day and observed by others (eg, parents, teachers, peers).

Anger outbursts and angry moods must occur in 2 of the 3 living environments (at home or at school, with peers).

(...) *Major depressive disorder* is a discrete depressive episode lasting ≥ 2 weeks. It is found in 2% of children and in 5% of adolescents. Major depressive disorder can occur at any age but is more common after puberty. If left untreated, major depression can regress spontaneously in 6-12 months. The risk of recurrence is greater in patients who have severe episodes, who are younger, or who have had more episodes. The persistence of depressive symptoms, even mild during remission is a strong predictor of recurrence. For the diagnosis, 1 or both of the following criteria must be present for most of the day almost every day during the same 2-week period:

- a) Sensation of sadness or state of sadness (eg, in tears) or irritability observed by others;
- b) Loss of interest or absence of pleasure in almost all activities (often expressed as deep boredom)

In addition, 4 or more of the following criteria must be present:

- a) Weight loss (in children, inability to achieve expected weight gain) or decreased or increased appetite;
- b) Insomnia or hypersomnia;
- c) Agitation or psychomotor slowing observed by others (not self-reported);

d) Asthenia or energy loss;

e) Decreased ability to think, to concentrate, and to make choices;

f) Recurrent thoughts of death (not just fear of dying) and / or suicidal ideation or plans;

g) Feelings of worthlessness (that is, feeling rejected and unloved) or excessive or inappropriate guilt.

Severe adolescent depression is a risk factor for failures in schooling, drug abuse, and suicidal behavior. In the period in which children and adolescents present a depressive state, these tend to lag far behind in studies and lose important relationships with peers.

(...) Dysthymia is a depressed or irritable persistent mood that lasts for most of the day for several days, not for 1 year or more, over 2 or more of the following:

a) Poor appetite or hyperphagia;

b) Insomnia or hypersomnia;

c) Low energy or fatigue;

d) Low self-esteem;

e) Poor concentration;

f) Feelings of despair

The symptoms may be more or less intense than those of a major depressive disorder.

A major depressive episode may occur before or during the first year (ie, before the duration criterion is satisfied for persistent depressive disorder).

(...) As for adults, relapses and recurrences are frequent. Children and adolescents must remain in treatment for at least 1 year from symptom regression. Most experts recommend that children who have experienced a number of episodes of major depressive disorder equal to 2 or more must be treated permanently. (...)>>.

<<(…) The phenomenological expressiveness of adolescent depressive pictures varies according to age group and clinical phenotype. A peculiar phenotype is atypical depression, characterized by the frequent inversion of some typical behavioral and psychopathological patterns (reverse diurnal alternation, hyperphagia and hypersomnia) and by the presence of a psychopathological nucleus with high interpersonal sensitivity and sensitivity to rejection. This cognitive-affective distortion often leads to histrionic and demonstrative behaviors, explicitly expressed (on social networks, diaries) concerning suicidal or self-harming threats that can often also be acted upon. Considering also the frequent comorbidity with multiple anxiety disorders, impulse control disorders, bipolar spectrum disorders II, diagnostic misunderstanding of this phenotype increases the risk of lethality. The most serious picture of depression in adolescence is depression

with psychotic symptoms characterized by disproportional phenomena such as auditory hallucinations (voices of blame or induction to suicide) or visual (threatening or disparaging images) and holotimic delusions more often at fault, shame, persecutors. In these cases, a correct differential diagnosis is essential with early-onset schizophrenia or with other serious psychotic disorders related to neurodevelopment for the purpose of a prognosis and specific treatment. Depression with psychotic symptoms is also an important risk factor for developing a bipolar I disorder; such picture implies greater gravity and suicidal risk, more frequent spontaneous or induced manic switch and need for treatment with antipsychotics and timoregolatori. Another clinical phenotype, in the unipolar context, is Persistent Depressive Disorder (15% of cases) characterized by a permanently depressed or irritable mood, chronic course for at least one year without free intervals longer than two months. The onset is insidious with less severe symptoms than DDM but chronic and pervasive (average disease duration of two to three years) such as to seriously interfere with the personality in training (Masi G et al., *Psychopathology* 2001). In adolescence the sad mood is associated with anger, irritability, low self-esteem, vegetative symptoms, social withdrawal, behavioral disorders or marked academic difficulties and concentration. At least half of the subjects experience a more acute episode, a major depressive episode, which overlaps with Persistent Depressive Disorder, resulting in a clinical condition called “Double Depression” with greater severity and functional impairment (Birmaher B et al., *Acad Child Adolesc Psychiatry* 2007).

(...) The average duration of a depressive episode is a few months. One-year cure rates are around 75% and after 90 years about 90% (Birmaher B et al., *Acad Child Adolesc Psychiatry* 2007). Depression is a phasic disease and can often recur: long-term follow-up studies report a recurrence of the disorder in 40% of subjects within two years, and in 70% within five years. Factors able to increase the risk of relapse or chronic condition are: negative socio-environmental conditions, very early onset, severity of previous episodes, poor compliance with treatment, presence of psychotic symptoms, comorbidity, psychiatric familiarity, premorbid state, low IQ (Birmaher B et al., *Acad Child Adolesc Psychiatry* 2007). The continuity between the depression of the developmental age and that of the adult is still discussed. 50% of depressed adults report onset of symptoms before the age of 18 (Birmaher B et al., *Acad Child Adolesc Psychiatry* 2007); the recurrence of episodes persists into adulthood in more than 50% of subjects. Comorbidity in DDM is very high. Anxiety disorders (separation anxiety, generalized anxiety, social phobia, panic) and obsessive compulsive disorder are present in 30 to 60% of depressed adolescents; their early and associated onset may indicate a possible bipolar evolution (Masi G et al., *J Clin Psychiatry* 2012). ADHD is found in about 30% of children and 15% of adolescents with acute or chronic depression. It is discussed whether the impulsive dimension of ADHD may increase the suicidal risk of depressed adolescents particularly in the acute phase (Chronis-Tuscano A et al., *Arch Gen Psychiatry* 2010; Patros CH et al., *J Clin Psychology* 2013). Behavioral disorders such as oppositional defiant and conduct disorder are present

in 20–30% of depressed adolescents and can persist even after improvement in depressive symptoms, affecting prognosis and psychosocial adaptation, increasing the risk of substance use and of self-injuring impulsive behavior, in the form of suicide attempts or deaths from dangerous and impulsive conduct. Among children and adolescents with DDM approximately 1/5 is at risk of developing a bipolar disorder, particularly in the more early-onset forms (Geller B et al., *Am J Psychiatry* 2001). Other risk factors are the family history of bipolar disorder, the presence of psychomotor slowing, psychotic symptoms and the appearance of iatrogenic hypomanic switches (Birmaher B et al., *Am J Psychiatry* 2009).

(...) The most devastating consequence of a depressive disorder is attempted or completed suicides (Meltzer H et al., Office National Statistics 2001). Suicidal behavior is characterized by a more or less explicit desire to die. In this sense it should be distinguished from those self-injurious behaviors (cuts, scratches, etc.) that do not have a direct intentionality and purpose to kill themselves. The “concept of suicidal behavior” is different from that of “expression of suicide”, which includes not only suicidal behavior but also the ideation. This aspect is situated in a continuum that starts from sporadic suicidal ideations, reactive to the context or activated by more intense stress situations not associated with self-injurious planning, to arrive at persistent and pervasive ideas with specific planning and worse prognosis. In turn, suicide attempts can be devoid of medical implications (eg low dose drug intake), with more or less serious implications or even a complete suicide. These different levels of suicidality have different prevalence in the general population: sporadic suicidal ideations in up to 10% of adolescents; suicide rate in Italy is about 4 in 100,000. There are wide differences, particularly in the suicide rate, depending on the geographical areas, both in European countries (much higher rates in the Nordic countries) and in Italy (higher incidence in the North). Other psychiatric conditions that increase the risk of suicide, in particular if in combination, are: bipolar disorder, schizophrenia, schizoaffective disorder, borderline personality disorder, post-traumatic stress disorder. The best prevention of suicidal risk is the early recognition in the patient of risk factors such as previous suicide attempts, psychotic symptoms, bipolar depression in the mixed phase, borderline personality disorder, conduct disorder, familiarity with suicide attempts, violence or impulsiveness in the family context, substance use, school drop-out (Brent DA et al., *J Am Acad Child Adolesc Psychiatry* 1999). (...) >> [26,27].

The neural correlates in depressive disorders [28]

<<(...) The study of the neurobiological bases of depression began in the 1950s when Bernard Brodie observed in the laboratories of the National Institute of Health in Bethesda that reserpine, an antihypertensive and antipsychotic molecule capable of inducing a depressive syndrome in humans, produced in the rat almost complete depletion of cerebral serotonin. Subsequently, Arvid Carlsson showed that reserpine also depleted the brain levels of Noradrenaline and Dopamine, suggesting, for the first time, that these monoamines

could be involved in the control of the affective sphere and that the reduction of their brain levels could be the main triggering cause depressive pathology. These fascinating and extraordinary results motivated the pharmaceutical industries to activate lines of research in order to develop molecules capable of increasing the levels of monoamines, presumably reduced in some areas of the brains of depressed subjects. Brodie’s important discovery thus gave rise to a research that continues today after more than sixty years and represents one of the most fascinating stories in the field of knowledge of the physiology and pathology of the human brain.

(...) The monoaminergic hypothesis of depression constituted a crucial and still valid biological basis for the pharmacotherapy of depressive pathology when it was shown that all antidepressant drugs induced a marked increase in serotonin and / or norepinephrine brain levels in a few hours. More than 60 years later, the drug therapy of this disease still uses molecules capable of increasing synaptic levels of serotonin and / or norepinephrine. The development of these molecules not only made it possible to obtain effective drugs and with fewer and fewer side effects, but also gave a fundamental contribution to understanding the molecular and cellular mechanisms involved in the etiopathogenesis of affective, emotional and cognitive disorders.

The monoaminergic hypothesis of depression (the antidepressant in a few hours increases the levels of monoamines in the synapses) has been in apparent contrast to the clinical evidence for over 40 years which shows that the improvement of symptoms does not occur before 4–6 weeks from the beginning of the treatment. This paradox has only recently found a convincing explanation both from basic and clinical research with the demonstration that a 4–6 week treatment with antidepressants, useful for obtaining a significant improvement in symptoms was also necessary to stimulate the molecular mechanisms that modulate the function of specific genes involved in the expression and synthesis of different trophic factors. In fact, through this mechanism antidepressant drugs are able over time (weeks / months) to improve the altered function of neurons, making them less sensitive to stressful events through a partial recovery of their trophism with the consequent partial or total recovery, over a period of months / years, of the volumes of some important brain areas involved in the modulation of the affective, emotional and cognitive sphere. Therefore, at the end of the nineties, the discovery that drugs synthesized and developed to rapidly increase (hours) the monoamine synaptic concentrations were also able to modify the function of specific genes capable of expressing molecules at longer times (weeks). Neurotrophic action suggested to add the neurotrophic hypothesis to the monoaminergic hypothesis.

(...) Depression is a chronic, progressive and recurrent disease whose etiopathogenetic bases are associated not only with a monoaminergic transmission dysfunction but also with a progressive loss of neuronal trophism with consequent reduction of plastic properties and therefore the inability of neuronal subpopulations of specific areas cerebral, involved in

the control of the emotional, affective, physical and cognitive functions, to be able to adapt to negative environmental stimuli.

Alterations in the levels of neurotransmitters, in the activity of signal transduction systems and in the expression of specific genes are the basis of the phenomenon known as cellular plasticity, ie the ability of neurons to know how to adapt both to morphological and functional levels to environmental stimuli, endocrine and pharmacological, and to the same stressful insults. Experimental studies have indeed shown that the plastic properties of neurons are associated with changes in cell morphology that can determine an increase or decrease in the formation of synapses and dendritic spines, as well as in an extension or retraction of dendrites. The changes in neuronal plasticity are associated with different modes of learning and memorization and are in turn stimulated by the enriched environment (ie from an optimal condition that provides the individual with a greater quantity and variety of positive stimuli), physical exercise and from long-term treatment with psychotropic drugs, while they are inhibited by psychosocial stress and by the state of depression, anxiety, psychosis. Taken together, these data have more recently directed research to understand the complex mechanisms of tropism regulation and neuronal plasticity giving rise to what is defined as the neurotrophic hypothesis of depression.

The neurotrophic hypothesis of depression originated between the late nineties and the beginning of the new century when experimental research first and clinical research immediately showed that brain neurons following stressful events of various nature and long duration go encountering a loss of trophism. Experimental research has shown unequivocally that brain neurons of rats subjected to chronic stress lose trophism and show a reduction in both dendritic arborization and dendritic spike density. In parallel to these evidences, clinical research has shown that the volume of some brain areas (hippocampus, prefrontal cortex, nucleus accubens) of subjects with severe depression, not treated pharmacologically or who have suffered severe psychological trauma is significantly reduced compared to the range of values of healthy subjects.

The experimental and clinical discovery that treatment with antidepressant drugs significantly reverts experimentally induced neuronal hypotrophism from chronic stress as well as the reduction in volume of some brain areas present in depressive pathology suggested that these drugs were born, as reported in the previous paragraph, to restore the reduced levels of serotonin and / or norepinephrine also have the ability to restore at least in part the neuronal hypotrophism and the consequent functional alterations of the affective, emotional and cognitive sphere associated with it. The evidence that all antidepressant drugs have the ability to activate, even if in a totally non-specific way, different genes capable of expressing both trophic factors and immune system molecules capable of modulating the regulatory mechanisms of neuronal trophism, has brought new knowledge on the mechanisms etiopathogenetics of depressive pathology. In particular, these studies have shown that the trophic factors of neuronal (BDNF)

and glial (GDNF) origin play a crucial role in mediating the effects of antidepressant drugs on neuronal trophism. These results have stimulated in recent years numerous researches for the development of both trophic molecules capable of overcoming the blood brain barrier and having a direct action on neurons, both of molecules and through epigenetic mechanisms can modulate the function of specific genes capable of expressing molecules trophic and / or immune system. In particular, molecules capable of modulating the expression of specific clusters of genes may in the near future represent a new class of more selective and effective antidepressant drugs.

(...) The evidence that BDNF and other trophic molecules play a crucial role in the mechanism of differentiation and proliferation of new cells, a phenomenon that occurs in physiological conditions in the human brain from childhood, adolescence to old age and is crucial in control of adaptive mechanisms to stressful events, pathological insults, pharmacological treatments, suggests that neurogenesis is a phenomenon closely related to the neurotrophic hypothesis. In fact, the functional integrity of the metabolic pathways that lead to the synthesis of trophic factors and the proliferation of new cells is considered crucial to guarantee the best and most immediate adaptive responses to the adult and newly formed cells. On the contrary, the reduced gene expression of the trophic factors and of the process of neurogenesis due to prolonged stress or to particular genetic factors (polymorphisms) is thought to have a crucial role in increasing the threshold of vulnerability to mood disorders and / or in reducing resilience in depressed subjects. Neurogenesis (differentiation and proliferation of new neurons) is a well-documented biological process in the brain of mammals, from rodents to primates, including humans. This phenomenon is very intense in childhood and adolescence, is significantly reduced in the adult brain and is still present in the brain of the elderly. Important and very recent studies have shown that this fascinating mechanism of brain renewal through the expression of new neurons is markedly enhanced by favorable environmental conditions such as the enriched environment, learning, a balanced diet, physical activity and above all by a adequate number of hours of restful sleep. It is no coincidence that melatonin significantly strengthens the differentiation of stem cells and the proliferation of neurons, while sleep deprivation, as well as other stressful stimuli, an inadequate diet, a sedentary life and the lack of social interactions and motivations inhibit this phenomenon. It is important to emphasize that alcohol and many substances of abuse inhibit the differentiation of stem cells and the proliferation of neurons and glial cells, significantly reducing the process of neurogenesis, especially in the brains of children and adolescents. In contrast, all antidepressant drugs enhance neurogenesis by promoting differentiation and proliferation of neurons. It is interesting to note that neurogenesis appears to be associated with the ability of the brain of mammals, including humans, to memorize recent memories, a phenomenon that is significantly reduced in the aging brain in which the process of neurogenesis is greatly reduced.

(...) One of the most important problems of experimental

and clinical neurobiology of affective disorders is to understand how a depressive disorder is capable, if not treated in a timely and adequate manner (appropriate and prolonged dosage) of altering the homeostasis of the neurons, particularly in brain areas such as the hippocampus, the amygdala and the cingulate cortex whose morphology and function are altered by this pathology. In depressed subjects, in whom the treatment is not continued for long enough, the number of relapses in the months following the cessation of therapy is always markedly higher than that of patients treated for at least 2 years. Furthermore, in patients with repeated relapses, the hippocampal volume is significantly reduced compared to the values obtained in the same patients at the beginning of therapy. These results suggest that timely treatment is needed to protect the depressed brain and adequate dosages and times that go far beyond simple remission of symptoms. The extraordinary images obtained, at an experimental level, with high-resolution supermicroscopes and at the clinical level through the studies of "Brain Imaging", have allowed us to demonstrate that a chronic stress in animals and depressive pathology in humans determine a reduction in capacity functional neurons associated with a loss of trophism, a phenomenon partially reversed by antidepressant drugs.

Consistent with this conclusion, recent studies have shown that treatment with antidepressants can restore hippocampal volume reduction in patients with depressive pathology. In this regard, the evidence that morphological alterations represent the consequence of an inadequately treated pathology is of great importance. This observation has a significant clinical significance because it suggests that, since the morphological modifications are not present at the first depressive episode, there is a time frame in which one can and must intervene to prevent, or at least slow down, the hypotrophic process associated with depressive pathology. If this does not happen, the risk that the patient may experience atrophy of specific neurons during his lifetime is very high and the subsequent treatments will be less effective. Recurrence is in fact a very heavy insult to neurons, which lose trophism and become less sensitive to therapy and are unable to recover, if not partially, their functional potential.

Taken together, current clinical and experimental data suggest that patients with multiple depressive episodes have a great risk of experiencing changes in the morphology of selective neuronal populations, a phenomenon that could make complete remission more difficult. Early treatment in the first episode is crucial to limit or abolish the risk of hypotrophism in specific brain areas and ensure adequate functional recovery of neurons. When this occurs, the remission phenomenon is longer lasting over time and the risk of recurrence is reduced. (...)>>.

Clinical strategies for the management of the pathological conditions

Pharmacological therapies: <<(…) Depression, in its various forms, is the most widespread mental disorder on a global level. It is a chronic recurrent pathology that manifests itself with somatic, affective and vegetative symptoms and has a greater prevalence in women and in the elderly population.

Depression is characterized by a very high comorbidity with other psychiatric disorders, including anxiety disorder, substance abuse, and impulse control disorder. Until the 1950s it was thought to be an exclusive pathology of the psychic sphere and, as such, had to be treated with psychotherapy and psychoanalysis. The discovery of the antidepressant action of some drugs arises by chance with the use of the isoniazid that in 1952 Hoffmann-La Roche, introduced into the market as an antibiotic for the treatment of tuberculosis. In 1953, a similar analogue, iproniazid, was developed for the same purpose. However, its use was associated with numerous unexpected effects, including euphoria, psychostimulant action, increased appetite and improved sleep. These observations led to the hyproniazide becoming a widely used drug for the treatment of major depression in just a few years. Subsequently it was discovered that the action of this molecule depended on its ability to inhibit the Mono-Amino-Oxidase (MAO), the main enzyme system responsible for the degradation of catecholamines (noradrenaline, dopamine and serotonin). Another historic step in the development of antidepressants was the discovery of tricycle compounds. The first drug of this class to be introduced into therapy was imipramine. Also in this case the discovery was causal since, being a chlorpromazine analogue, it was developed as an antipsychotic. As a neuroleptic it proved to be of modest efficacy while a remarkable ability to improve symptoms of depression was observed. Imipramine also demonstrated less adverse effects than the MAO inhibitor iproniazide. In the following years numerous other tricyclic molecules were developed and it was discovered that the main mechanism of their action was the blocking of catecholamine reuptake with the consequent increase in synaptic availability. The observation of the ability of reserpine (an anti-hypertensive catecholamine importer) to cause depressive symptoms and the discovery of the mechanisms of action of tricyclics and MAO inhibitors represented the founding elements of the catecholaminergic hypothesis according to which the symptoms of the disease are caused from low levels of noradrenergic, serotonergic and central dopaminergic transmission. On the basis of this neurobiological principle an intense activity of drug development was started that around the beginning of the 70s of the last century led to the discovery of fluoxetine, the first selective serotonin reuptake inhibitor (SSRI). Several antidepressants with an atypical mechanism followed, including: bupropion (dopamine reuptake inhibitor), selective serotonin and noradrenaline reuptake inhibitors (SNRIs) such as venlafaxine and duloxetine, selective norepinephrine reuptake inhibitors (NRIs) such as maprotiline and reboxetine, and drugs active on serotonergic receptors (mirtazapine, trazodone, mianserine). In 2013 the American Food and Drug Administration (FDA) authorized the registration of vortioxetine, the most recent and currently marketed antidepressant drug.

(…) MAO is an enzyme responsible for the oxidative degradation of biogenic amines (serotonin, dopamine, noradrenaline and adrenaline) and sympathomimetic amines (tyramine, benzylamine, etc.). It is present in two isoforms, respectively named MAO-A and MAO-B. The MAO-A enzyme is mainly responsible for the degradation of serotonin,

noradrenaline and adrenaline, while MAO-B has a prevalent action on phenethylamines and benzylamines; both isoforms degrade dopamine. MAOs are located in the presynaptic terminal where they are responsible for the degradation of biogenic amines. Their inhibition causes a marked increase in monoamine concentrations in the presynaptic terminal, making them readily available for release when action potentials reach the nerve terminal. The first MAO inhibitory drugs developed acted by irreversibly and non-selectively inhibiting both isoenzymes, resulting in marked hepatic toxicity, excessive accumulation of peripheral catecholamines and risk of even severe hypertensive crisis. This risk is amplified by the intake of cheese (cheese effect) or other fermented foods which, containing high amounts of tyramine, in the presence of MAO inhibition cause a marked accumulation of catecholamines. The safety and handling profile of this class of drugs has been improved with the development of reversible molecules such as phenelzine and tranylcypromine and even more with the creation of drugs with reversible action and selective MAO-A (RIMA) as moclobemide, clorgiline, toloxatone, brofaromine. The main side effects of this class of molecules remain the risk of hypertension and serotonergic syndrome. These adverse manifestations are particularly frequent when MAO inhibitors are administered in combination with other drugs that increase catecholaminergic transmission (eg other antidepressants; nasal decongestants, etc.).

(...) Unlike most other antidepressants that are classified according to their mechanism of action, *tricyclics* (TCAs) are named according to their chemical structure to three condensed benzene rings. TCAs, to which molecules such as imipramine, chlorimipramine, amitriptyline, trimipramine, nortriptyline belong have a complex pharmacological profile characterized by at least three main actions: 1) they inhibit the noradrenaline transporter, serotonin and dopamine, increasing their synaptic availability and therefore favoring catecholaminergic transmission; 2) produce postsynaptic α_1 and α_2 adrenergic receptor blockade; 3) antagonize postsynaptic muscarinic receptors and blocking histamine H1 receptors. Inhibition of noradrenaline and serotonin reuptake are responsible for the therapeutic effects of TCAs, while inhibition of α_1 and α_2 adrenergic receptors, muscarinics and H1s are responsible for the classic undesirable actions of these drugs including: orthostatic hypotension, increase heart rate, xerostomia, difficulty adjusting vision, dryness of the skin and mucous membranes, constipation, urinary sedation retention, cognitive impairment, increased appetite and increased body weight. TCAs are also indicated for the treatment of some forms of anxiety (which makes them useful in the treatment of mixed forms of depression and anxiety), in neuropathic pain and in some forms of migraine. They are contraindicated in patients with prostatic hypertrophy, glaucoma, cardiovascular diseases.

(...) In 1987, the FDA approved fluoxetine, the first drug belonging to the class of SSRIs (*selective serotonin reuptake inhibitors*), for the treatment of depression. Many other SSRIs have been developed in the coming years; among these are sertraline, citalopram, escitalopram, paroxetine, fluvoxamine. SSRIs are up to 1500 times more selective towards the serotonin

transporter than that of noradrenaline or dopamine whereas they have negligible affinity for postsynaptic adrenergic receptors such as α_1 , α_2 and β , for histamine H1 receptors and for muscarinic receptors. Some SSRIs have a direct but very weak pharmacological action on postsynaptic serotonin receptors (eg 5-HT_{1A}, 5-HT_{2A} and 5-HT_{2C}). The potentiation of the serotonergic transmission produced by these drugs is therefore attributable to the increased concentrations of the endogenous neurotransmitter in the synaptic space produced by the inhibition of its re-uptake. The absence of binding with adrenergic, muscarinic and histaminergic receptors means that the profile of undesired events related to their use is decidedly lower than that of TCAs. For SSRIs the most frequently reported adverse events are: nausea and consequent decrease in appetite; insomnia and alterations in the sexual sphere (erectile dysfunction, decreased libido and anorgasmia). In addition to the major depression, SSRIs are effective in the treatment of obsessive compulsive disorder (they are first choice drugs), generalized anxiety and prophylaxis of panic attacks. SSRIs also seem to have beneficial effects in the treatment of premature ejaculation, so that one of them, desipramine, has been approved by the EMA for such use

(...) Venlafaxine, introduced in therapy in the first half of the 1990s, was the first antidepressant drug belonging to the class of SNRIs (*selective serotonin and norepinephrine reuptake inhibitors*). Its mechanism of action is somewhat different from that of SSRIs and TCAs as it selectively blocks the reuptake of serotonin and noradrenaline (in this order). After the approval of venlafaxine, other SNRIs were developed, for example duloxetine and milnacipran (in the USA). Unlike TCAs, SNRIs have minimal or zero effects on adrenergic (α_1 , α_2 and β), histamine (H1), muscarinic, dopaminergic or postsynaptic serotonin receptors. SNRIs would seem to have a therapeutic efficacy equivalent to that of SSRIs. The clinical tolerability and prevalence of sexual dysfunction in SNRIs are also comparable to those described for SSRIs.

(...) Reboxetine is the only molecule attributable to the class of NRI (*selective norepinephrine reuptake inhibitors*). It acts by selectively blocking noradrenaline re-uptake, increasing its synaptic availability. Its antidepressant efficacy has been demonstrated in various clinical studies. However, meta-analysis data would seem to demonstrate an efficacy profile comparable to that of other antidepressants but a higher incidence of undesirable effects. Among these: cardiovascular disorders, excessive sedation, difficulty in adjusting vision, taste changes, sexual dysfunction, disorders in the urinary tract.

(...) Then, there are a number of molecules that act on *serotonin and noradrenaline receptors*. It is a series of rather diversified molecules, but which share the ability to directly modulate some subtypes of serotonergic and noradrenergic receptors. Specific heterogeneous and serotonergic antidepressants (NASSA) can be attributed to this heterogeneous group, such as mianserin and mirtazapine which act by blocking the serotonin α_2 -adrenergic and 5-HT_{2A} and 5-HT_{2C} receptors. Then there are the trazodone and the nefazodone that besides inhibiting the

reuptake of serotonin (but to a lesser extent than the SSRIs) act as agonists on the 5-HT_{1A} receptor and antagonists on the 5HT_{2A} and 5HT_{2C} and α 2-adrenergic. The use of these drugs is usually accompanied by sedation. They find utility in inducing or improving sleep in patients whose depressive state is accompanied by difficulty sleeping.

(...) Newly discovered are *multimodal antidepressants*. Clinical studies have suggested that in patients with reduced adherence to treatment, treatment with two antidepressants with different mechanisms of action can often be more effective than association with other classes of drugs. Indeed, by combining two molecules capable of modulating different molecular “targets” (receptors, transport mechanisms, etc.) it is possible to obtain a better adherence to the therapy.

The new system of classification of psychotropic drugs proposed by the Task Force of the European College Neuropsychopharmacology has recently suggested that vortioxetine and vilazidone (...) are two antidepressants with multimodal mechanism of action as they are able to combine the inhibition of SERT (serotonin transporter) with a differential action on different serotonergic receptor subtypes. Vortioxetine inhibits the SERT with a high affinity bond, acts as a partial agonist on the 5-HT_{1A} and 5-HT_{1B} receptors and as an agonist on the 5-HT₃, 5-HT_{1D} and 5-HT₇ receptors. (...)>> [29].

The recommended doses of drugs recommended for depressive disorders, according to the indications of the World Health Organization and the research carried out in the last decades [30,31], vary from therapy to therapy (Table 4).

Non-pharmacological therapies. Psychosocial and psychological [32]

<<(...) The risk of developing major depression is increased by numerous psychosocial factors, such as a low socio-economic level, poverty, unemployment, the presence of a disabling physical disorder and low levels of education (APA, 2010). About half of the patients have more than one episode of illness during their lifetime and the risk of recurrence of depressive episodes is 35%. Patients who have presented at least three depressive episodes during their lifetime, in the absence of preventive treatment, have a risk of falling back by 100%. The presence of a major depressive disorder is associated with high personal and social costs, and a significant reduction in the quality of life, similarly to what happens for many chronic physical pathologies, such as diabetes mellitus, asthma, myocardial infarction and arterial hypertension (Kessler et al, Psychol Med 2003). In most cases, following symptom remission, the psychosocial functioning of patients with major depression returns to premorbid levels, although in 35% of patients subthreshold depressive symptoms may persist, contributing to the disability associated with the disease. Furthermore, the psychosocial functioning of these patients is influenced by the presence of numerous comorbid physical pathologies, above all cardiovascular, metabolic and infectious. Considering the prevalence, the risk of relapse

Table 4:

Antidepressant	Mechanism	Dosing range (mg)
First line		
	MT1/MT2 agonist; 5-HT 2 antagonist	
	NDRI	
Agomelatine	SSRI	25-50
Bupropion	SNRI	150-300
Citalopram	SNRI	20-40
Desvenlafaxine	SSRI	50-100
Duloxetine	SSRI	60
Escitalopram		10-20
Fluoxetine	Adrenergic Agonist Alfa2; 5-HT 2 antagonist	20-60
Fluvoxamine	SNRI	100-300
Mianserin	Adrenergic Agonist Alfa2; 5-HT 2 antagonist	60-120
Milnacipran	antagonist	100
Mirtazapine	SSRI	15-45
Paroxetine		20-50
		(25-62,5 fot version RC)
Sertraline	SSRI	50-200
Venlafaxine	SNRI	75-225
Vortioxetine	Serotonin reuptake inhibitor; 5-HT 1A agonist; 5- HT 1B partial agonist; 5- HT 3A antagonist; 5- HT 1D antagonist; 5- HT 7 antagonist.	10-20
Second line		
Amitriptyline / Clomipramine (and other)	TCA	---
Levomilnacipran	SNRI	40-120
Moclobemide	Reversible MAO-A inhibitor	300-600
quetiapine	Atypical antipsychotic	150-300
Transdermal selegiline	Reversible MAO-B inhibitor	6-12
Trazodone	Serotonin reuptake inhibitor; 5-HT 2 antagonist	150-300
Vilazodone	Serotonin reuptake inhibitor; 5-HT 1A partial agonist	20-40
Third line		
Phenelzine	Irreversible MAO inhibitor	45-90
Tranlycypromine	Irreversible MAO inhibitor	20-60
Reboxetine	Norepinephrine reuptake inhibitor	8-10

and the high levels of disability associated with this disease, considerable efforts have been made in recent years to improve the long-term treatment of depression (NICE, 2010; American Psychiatric Association, 2010; Cleare et al ., J Psychopharmacol 2015; Kennedy et al., Can J Psychiatry 2009). The main international guidelines agree on the need to customize treatments based on the socio-demographic, clinical and psychological characteristics of individual patients, as well as on the need to adopt an integrated approach that includes, in addition to antidepressant drugs at appropriate dosages and for a duration adequate, the use of psychological and psychosocial interventions that can contribute to the symptomatic, functional and personal remission of patients (Gelenberg, J Clin Psychiatry 2010). In this paper we will briefly review the psychological and psychosocial interventions that have proven effective for the treatment of major depression and which are currently recommended by the main international guidelines.

(...) The use of psychotherapy in patients with depression is currently strongly recommended by the main international guidelines. Psychotherapy is indicated as an exclusive treatment in mild or moderate depression, while it is recommended in association with pharmacological treatment in severe depression, especially when suicidal ideation is present. The elements that can guide the clinician in the choice of psychotherapeutic treatment, alone or in association with pharmacological treatment, are the following: 1) stressful psychosocial factors; 2) intrapsychic conflicts; 3) interpersonal difficulties; 4) comorbidities with personality disorders. Furthermore, the choice of the type of psychotherapy to be adopted depends on other factors, such as the goals of the therapy, the response obtained to previous psychotherapies, the availability of therapists trained in the use of specific psychotherapeutic techniques and the patient's requests. Psychotherapy should be the first-line treatment when depression occurs during pregnancy, or in women who have a pregnancy planned, and during breast-feeding. The duration and frequency of the appointments that characterize an effective treatment has not been the subject of rigorous studies. Most of the available evidence lays down for a minimum duration of 16–18 weeks of treatment, with weekly appointments. The efficacy of psychotherapy in patients suffering from depression, both as monotherapy and as an adjunct to the pharmacological treatment, has been confirmed by numerous randomized controlled studies (Cuijpers et al., *Depress Anxiety* 2014), especially with regard to the reduction of depressive symptoms, improving quality of life, improving psychosocial functioning and reducing relapses (Cuijpers et al., *Depress Anxiety* 2014). At the moment the psychotherapeutic approaches that have received the greatest scientific evidence in the treatment of major depression are cognitive behavioral therapy (TCC) and interpersonal psychotherapy (Interpersonal therapy - IPT) [33]. Other approaches, including psychoanalytic-derived therapy, group therapies and family-systemic ones, although widely used in clinical practice, have not at this time achieved the same level of efficacy in randomized controlled trials (APA, 2010).

In the last decade, however, the short strategic therapies seem to be able to make a positive contribution to the management and resolution of the depressive problem: in fact, already from the first session, the therapist with a strategic approach tends to identify, through a carefully designed progression of questions occurrence (Nardone and Salvini, 2004), the type of depression that afflicts the patient; later, it will use all the techniques and strategies recognized by that approach to optimize the results, reaching a positive outcome between 70% and 80% in a maximum of 10 sessions (Muriana et al., 2006). The Brief Strategic Therapy Model (by Nardone, Italian therapist linked to the school of Palo Alto) [34], is based on the idea that pathologies originate from failed or attempted solutions to problems that the environment can recognize on the subject and therefore this must correct to come back into harmony with it; always this model also has the merit of having defined what are the characteristics that unite people who, entering the psychologist's office, call themselves "depressed":

1) *Giving up*: the feeling of incapacity that progressively creeps into every area of life can lead to throwing down your arms, giving up reacting and fighting. Renunciation often derives from the inevitability of events to which there is no solution (deaths or separations) or to which apparently we cannot find a way out (other psychological discomforts). "Renunciation is a daily suicide", Honoré de Balzac.

2) *Complaining*: complaining is a natural human reaction. It is necessary for survival because the lament activates the attention of others and spurs them to offer us the care we need. Just imagine how many alarm bells light up in a mother when she hears her baby crying. The problem arises when the complaining becomes continuous and constant, because the more we ask for help, the greater will be our feeling of incapacity, in fact if we were able on our own we would not have complained. Moreover, complaining constantly, we will become less and less credible in the eyes of others and our subsequent requests for help will lose value. "The complaints are anchors in the sand that prevent us from taking off."

3) *Delegate (or demand)*: a direct consequence of giving up, letting others do there and then makes us feel better, but then it comes back to us like a boomerang because the reality we are building is: "I can't do it myself!", thus increasing our conviction of incapacity and our depressive state. "We build the reality that we then suffer".

Therapies in case of resistance to treatment [35]

<<(…) A depressive condition that does not reach sufficient remission after adequate treatment is considered resistant to treatment (Fava M, *Biol Psychiatry* 2003). It is estimated that DRT occurs in a percentage between 30% and 40% of adequately treated depressive episodes with the first choice antidepressant therapy. The DRT results in personal suffering, disproportionate burdens and health costs. While it is evident that DRT is a common and fundamental issue in the treatment of major depressive episodes, there is no consensus however on its definition.

The Guidelines define a patient as resistant to treatment "when a consecutive treatment with two drugs of different classes, used for a sufficient period of time at an adequate dose, fails to induce an acceptable effect". However, "sufficient time" and "adequate dose" are not defined. Furthermore, the concept of "class" corresponds to the mechanism of action of the drug (Gelenberg AJ et al., APA 2010; Lam RW et al., CANMAT 2016). There is substantial evidence that most patients with DDM do not receive adequate treatment. Some studies have found that only about 50% of patients meet the minimum criteria, so many patients who seem resistant to treatment are actually "pseudoresistant".

In general, there are 4 characteristics that determine the adequacy of antidepressant treatment and the judgment that the patient did not respond to an adequate treatment study: dose assessment, duration of treatment, adherence to therapy and clinical outcome (Sackeim HA, *J Clin Psychiatry* 2001).

Various models of DRT staging are proposed (Thase & Rush, 1997; Souery et al., 1999; Fava, 2003). The validity of these models is essential in order to develop adequate operational guidelines (Ruhé HG et al., J Affect Disord 2012).

(...) Numerous studies have been carried out to identify the predictive factors of the response to antidepressant treatment (Nierenberg AA, Psychiatr Clin North Am 2003). Some risk factors for non-response to a single antidepressant treatment have been proposed. These factors mainly concern the characteristics of the episode, psychiatric and somatic comorbidities, family history and psychosocial factors. The strategies to adopt in case of resistant depression are many: they consist in the substitution with another antidepressant drug (or combinations of two or more drugs), in the strengthening with other classes of psychotropic drugs (second generation antipsychotics, nutraceuticals-folate, methionine, vitamins of group B, vitamin E, vitamin C, zinc, calcium, N-acetyl-cysteine- [36], omega-3/6/9 fatty acids), in the beginning of a psychotherapeutic therapy and the use of somatic therapies and neuro-modulator. If classically psychotherapy has always had an importance in view of a treatment that is the most integrated to pharmacotherapy, the somatic DDM therapies play a prominent role in those cases in which the Depression is resistant to pharmacological treatment (Cusin C and Dougherty DD, Biol Mood Anxiety Disord 2012) (Table 5).

Table 5: Comparison of the characteristics of the available somatic therapies.

	Method and technique of intervention	Effectiveness in DRT	Side effects
TEC	Convulsive (with patient under anesthesia)	60%	Typical of anesthesia, headache, muscle pain, amnesia, cognitive disorders
	Non convulsive (patient awake)		Headache, potential convulsions, induction of manias
rTMS	Non convulsive (patient awake)	38%	Itching, burning, temporary headaches, redness
tDCS		dubious	Cough, hoarseness, alteration of the voice, reversible bradycardia, infections
VNS	Surgical (moderately invasive and under general anesthesia)	dubious	typical of the operation, hemorrhage, stroke, infections
DBS	Surgery (invasive and under anesthesia)	dubious	risk of ablation of the wrong area
MRgFUS	Surgery (invasive and under anesthesia)	dubious	potential hypomania and activation of the autonomic nervous system
Fototerapia	Non-invasive surgery	dubious	
	Non-invasive		

Pharmacogenetics and Depression [37]

<<(...) The use of antidepressant drugs, in moderate and severe forms of depression, is to be considered a first-line treatment and is a therapeutic option to be taken into consideration, together with other types of interventions, even in mild cases (Kennedy SH et al., Can J Psychiatry Rev Can Psychiatr 2016). However, despite the numerous molecules currently available on the market, the response rate to antidepressant drugs remains not optimal, reaching around

50% (Papakostas GI et al., J Clin Psychiatry 2009), and their use is burdened by an incidence of side effects that can reach 55% (Papakostas GI, J Clin Psychiatry 2008).

The results of one of the largest studies on the treatment of major depressive disorder, the Sequenced Treatment Alternatives to Relieve Depression (STAR * D), show that only 30% of patients manifest a clinically appreciable response to the first pharmacological intervention, while the cumulative rate of remission, given the different sequential interventions, stood at 67% (Sinyor M et al., Can J Psychiatry Rev Can Psychiatr 2010).

Although several factors may be crucial in determining a patient's response to a given drug, such as the severity of the disease being considered, the diet or the interaction with other active ingredients taken at the same time, an individual's genetics plays a fundamental role in determining variations in the metabolization of a substance or in the interaction of a molecule with its target (Hamburg MA & Collins FS, N Engl J Med 2010).

Pharmacogenetics, a term coined in 1959 by Friederich Vogel, studies the interaction between the genetics of an individual and his response to drugs and has as its main objective the personalization of the treatment, ie the identification of the best drug therapy for each individual, particular individual (Vogel F, Ergebnisse der Inneren Medizin und Kinderheilkunde 1959).

Pharmacogenetic research has found its broadest expression in oncology, where direct therapies based on genetic information are now considered fundamental as a standard of care in numerous neoplastic diseases (Gonzalez de Castro D et al., Clin Pharmacol Ther 2013).

As for the treatment with antidepressant drugs, genetic factors seem to contribute considerably to inter-individual variability (42-50%) in the response to drug therapy and in the onset of side effects (Crisafulli C et al., Front Pharmacol 2011; Tansey KE et al., Biol Psychiatry 2013). This variability can be attributed to both pharmacokinetic and pharmacodynamic elements. With regard to the pharmacokinetic side, cytochrome P450 isoforms 2D6, 2C19, 2C9, 1A2, 3A4 / 3A5 and 2B6 seem to be involved in antidepressant metabolism although with significant differences from one antidepressant molecule to another (Wu-Chou AI et al., Melatonin, Neuroprotective Agents and Antidepressant Therapy 2016). In fact, the allelic variations of the CYP 2D6 and CYP 2C19 isoforms would seem to lead to the most significant modifications of the metabolism profile of antidepressant molecules with evident clinical implications (Wu-Chou AI et al., Melatonin, Neuroprotective Agents and Antidepressant Therapy 2016; Kirchheiner J et al., Mol Psychiatry 2004) (Table 6):

(...) Although research in the pharmacogenetic field has developed above all in the pharmacokinetic sense, given the lower number of genes involved in determining phenotypic variations with detectable clinical implications, in the pharmacogenetics of antidepressants also the

Table 6: CYP450 isoforms involved in the metabolism of antidepressants and related substrates.

2D6	2C19	2C9	1A2
Paroxetine Venlafaxine Fluoxetine Citalopram	Sertraline Citalopram Escitalopram Moclobemide	Fluoxetine Tricyclic antidepressants Venlafaxine Mirtazapine	Paroxetine Fluvoxamine Escitalopram Agomelatine
Mirtazapine Tricyclic antidepressants	Tricyclic antidepressants		

pharmacodynamic component has a certain relevance, especially considering allelic variations of coding genes the Brain-Derived Neurotrophic Factor polypeptide (BDNF; Niitsu T et al., *Prog Neuropsychopharmacol Biol Psychiatry* 2013).

Given the amount of evidence found and reported in the literature, there is a strong biological rationale in considering the integration of pharmacogenetic information into one's clinical practice (Mrazek DA et al., *JAMA* 2011).

With the progress of IT and technological developments, genetic analyzes are, with the passing of the years, seeing a significant reduction in the prices of realization. This has led to the development of several genetic tests, available for clinical use, also sold directly to professionals. The use of these instruments is experiencing increasing use: the number of pharmacogenetic tests carried out doubled between 2012 and 2014 and it is estimated that it doubled again in 2015 (Gardner KR et al., *Psychiatry J* 2014). The evidence on the clinical utility of pharmacogenetic investigations in psychiatric clinical practice, in particular as regards the pharmacological treatment of major depressive disorder and the use of antidepressant drugs more generally, is now abundant (Bousman CA et al., *BMC Psychiatry* 2017). Although there are still no guidelines on the indications and appropriateness of use in the daily clinical practice of pharmacogenetic tests specific for antidepressant drugs, the recent scientific literature has begun to provide practical advice for the use of the currently commercially available tests (Bousman CA et al., *Lancet Psychiatry* 2016).

However, a recent systematic review has analyzed all clinical trials and cost-benefit studies conducted on pharmacogenetic tests in the treatment of major depressive disorder, highlighting some critical issues (Rosenblat JD et al., *J Clin Psychiatry* 2017).

Although most clinical trials show promising results, many of them present considerable limitations. Most of them do not have an appropriate control group, were not blinded or did not present appropriate randomization. Furthermore, these are studies funded by the test companies, and the authors are subjected to conflicts of interest that undermine the scientific objectivity of the results.

As for the studies focused on the cost-benefit ratio, the results are quite conflicting, also based on the differences in the economic level and health expenditure of the different countries taken into consideration (Olgati P et al., *Prog Neuropsychopharmacol Biol Psychiatry* 2012).

Furthermore, while some studies show that pharmacogenetic tests may not be convenient (Hornberger J et al., *Am J Manag Care* 2015), technological development and cost reduction of these procedures is constantly updated: in a few years the price of a previously very expensive analysis could be considerably reduced, making a relatively recent cost-benefit evaluation obsolete.

Among the studies related to the efficacy of pharmacogenetic tests, one in particular (Brennan FX et al., *Prim Care Companion CNS Disord* 2015) is effectively valid, being randomized, controlled and conducted in double blind. The study showed a statistically significant increase in clinical remissions in the group of patients undergoing pharmacokinetic pharmacogenetic investigation. However, although all patients were treated with antidepressant drugs, not all were affected by major depressive disorders, however, as some were subjected to drug treatment with antidepressant drugs for an anxiety disorder. Two other randomized controlled trials on the use of pharmacogenetic tests in the treatment of major depressive disorder confirmed a statistically significant improvement in the intervention group, ie one in which the prescribed drug choice was guided by pharmacogenetic information, compared to controls. However, both of these studies were monocentric and conducted on small samples, respectively of 51 (Winner JG et al., *Discov Med* 2013) and 148 (Singh AB, *Clin Psychopharmacol Neurosci off Sci J Korean Coll Neuropsychopharmacol* 2015).

An even more recent study (Pérez V et al., *BMC Psychiatry* 2017), not included in the aforementioned systematic review, also randomized, controlled and double-blind, showed a significantly higher response rate at twelve weeks patients suffering from major depressive disorder in which the choice of the drug was guided by a latest generation pharmacogenetic test (47.8% vs 36.1%, $p = 0.048$; OR = 1.62 [95% CI 1.00-2.61]). Furthermore, the frequency of onset and severity of side effects were also lower in the intervention group (68.5% vs 51.4%, $p = 0.026$; OR = 2.06 [95% CI 1.09-3.89]). Considering the large sample of patients included (N = 316) and the completeness of the pharmacogenetic test used based on pharmacokinetic and pharmacodynamic principles (Neurofarmagen®, AB-Biotics SA, Barcelona, Spain), this study is certainly to be considered as one of the most informative with respect to the use of pharmacogenetic tests designed for the evaluation of the treatment of major depressive disorder.

Conclusions

Depressive disorders are now widely known in the academic and clinical world, as the most widespread category of mental disorders. And despite the fact that the nature and presence of depressive symptoms is widely recognized in medicine, the diagnostic revisions of the last decades support the need for a process that aims to further identify clinical pictures in an increasingly valid and reliable way.

The best treatment to date is the one combined between psychotherapy and targeted drug therapy, supplemented by somatic and nutritional therapies.

The identifying profile of the pathology is also fundamental, to then find the most suitable targeted therapy; an identifying error would de facto annul the possibility of recovery and management of the disease, as in the case of an erroneous diagnosis of bipolar disorder or personality disorders, and vice versa.

In the neurobiological field, recent research shows the crucial role of reduced neuronal plasticity in the etiology of depressive pathology, and suggests that a drug therapy, especially if combined with a valid psychosocial or psychoeducational support, can guarantee a better adherence of the patient to the treatment. In fact, drug therapy can only benefit from the association with non-pharmacological practices capable of favoring mechanisms that modulate trophism and brain plasticity. The consolidated neurobiological evidences show that the depressed subject's neurons present a loss of trophism and neuronal plasticity that limit their best adaptation to negative environmental stimuli. The same evidences show how antidepressants activate, although with non-specific mechanisms, the function of genes involved in the synthesis of trophic factors. The profile linked to pharmacogenetics and drug-resistance deserves great attention. Neurostimulation is still an expanding field aimed at improving the efficacy, safety and tolerability of DRT treatments.

Major Depressive Disorder (MDD) is one of the most common but also the most debilitating mental disorders; however, its etiology remains unclear, seeking it in both neurobiological and environmental factors [38]. In recent years, several genetic and genotypic components have been found that predispose to depression; predisposition which is not in itself triggering the pathology but which would be triggered in the presence of other elements, such as environmental stress-causing and physiopathological hormones. Genetic expression would therefore predispose but would not be a trigger. Other factors related to the triadial alterations of the serotonin-dopamine-norepinephrine transmitters, but in recent years the patient has not completely recovered; the neurotrophic and neuroplastic factors, and also the sudden changes of sex hormones, cortisone and catecholamine, and the immune aspects treated and cytokines. Still, other profiles concern the inflammatory profiles found in the presence of increased levels of histamine and interleukin-1 and -6 (related to the increase in hunger) and interleukin-4 (linked to the decrease in hunger) [39].

Future research perspectives must be clearly oriented in the hypothesis of correlating all these analysis profiles, reconstructing the psycho-bio-pathological path of a disorder still with an etiology that is not completely explained.

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