DEPRESSION : IS IT A CURSE OR WORTH FIGHTING?

APRNworld®

Disclaimer

The Nursing Continuing Professional Education materials produced by APRNWORLD® are made as an integrated review of current evidence available from multiple sources. The bulk of the information is taken from major scientific journals and other relevant publications. APRNWORLD® made every reasonable effort to cite these resources appropriately however, may have omissions made inadvertently due to the vast and generic nature of the scientific information available. APRNWORLD® does not hold copyright of any of such information. The copyright of such information belongs to the specific author/ publisher or their legal designee. Even though we made every reasonable effort in ensuring the quality and correctness of information, APRNWORLD® does not bear the responsibility of the accuracy of the information as it was taken from publicly available sources. The education material is meant for licensed professionals with a solid body of knowledge, experience and understanding of complex medical scenarios. The material presented here does not replace sound scientific and up-to-date guidelines from professional sources. Because of the dynamic nature of medical and scientific advancements, these training materials should not be used as the sole basis for medical practice. Individual practitioner should exercise their critical thinking and clinical reasoning skills in dealing with complex medical scenarios. APRNWORLD® does not bear any responsibility for the claims that the information presented through its platforms caused injury or unwanted outcomes in any clinical situations.

Depression :
Is it a curse or worth fighting ?

ANCC Accredited NCPD Hours: 2.5hrs

Target Audience: RN/APRN

Need Assessment

In light of the different aspects related to depression, the present article has the following aims:

(1) To analyse the construct of depression offered by the two main mental disorder classifications (DSM-5 and ICD-10);

(2) To provide an overview of the main explanatory theories of depression;

(3) To outline the child and adolescent depression evaluation instruments most commonly used in scientific literature;

(4) To provide a brief overview of child, adolescent and old-age depression prevention programs in the school environment; and

(5) To describe the most scientifically rigorous and effective clinical treatments for this mental disorder.

Objectives

- Describe the various types of depression
- Discuss the biological factors contributing to depression
- Identify the triggers for depression
- Describe the clinical treatments for depression
- Discuss the benefits of combination treatment for depression

Goal

The goal of this article is to discuss various types of depression, diagnosis of depression, management strategies of depression and recent guidelines related to the topic

Introduction

Major depression disorder (MDD) is an important public health issue, predicted to be the second leading cause of disability behind only ischemic heart disease. ***MDD is the most commonly diagnosed psychiatric disorder in adults over 60 years of age. The Diagnostic and Statistical Manual of Mental Disorders (DSM-V) describes that for the diagnosis of MDD, five or more symptoms have to be present during a 2-week period and represent a change from previous functioning.*** At least one of the symptoms (As shown in fig.1) should be either: (i) depressive mood or (ii) loss of interest or pleasure for the major part of the day. The other symptoms that may be present are significant weight loss or weight gain, insomnia or hypersomnia, fatigue or loss of energy, diminished ability to concentrate or indecisiveness, recurrent thoughts of death and suicidal ideation or attempt. [1, Rank 5]

Not only the high incidence of MDD and the disability associated with the disease, but also the high rate of inadequate treatment of the disorder remains a serious concern. It is estimated that 30–50% of the patients do not respond to treatment with antidepressants due to either lack of efficacy or intolerable side effects. Another possible reason for the ineffectual treatment

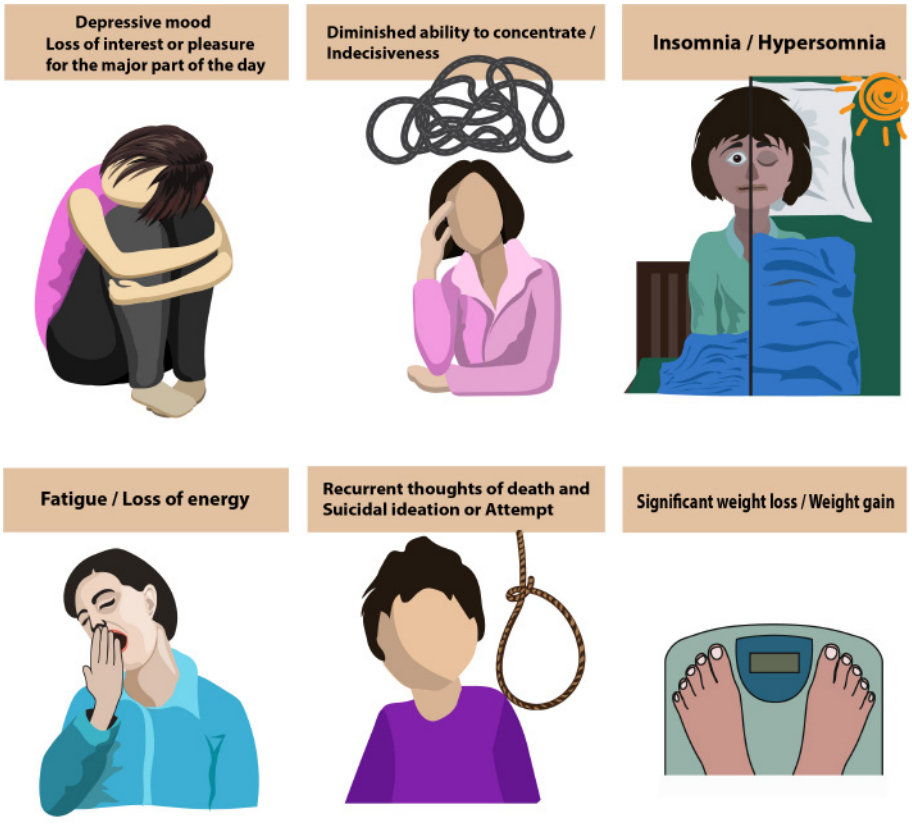

Figure 1 : Symptoms of major depressive disorder

of MDD has been the incomplete understanding of the nature of depression. ***The high rate of treatment resistance, together with the high suicide risk in unresponsive patients and the overwhelming economic costs to society constitute the basis of the search for new therapeutic agents.*** Remission, that is, (virtual) absence of symptoms should be the objective of MDD treatment, since it is related to better functioning and a better prognosis than a response without remission. [2, Rank 3]

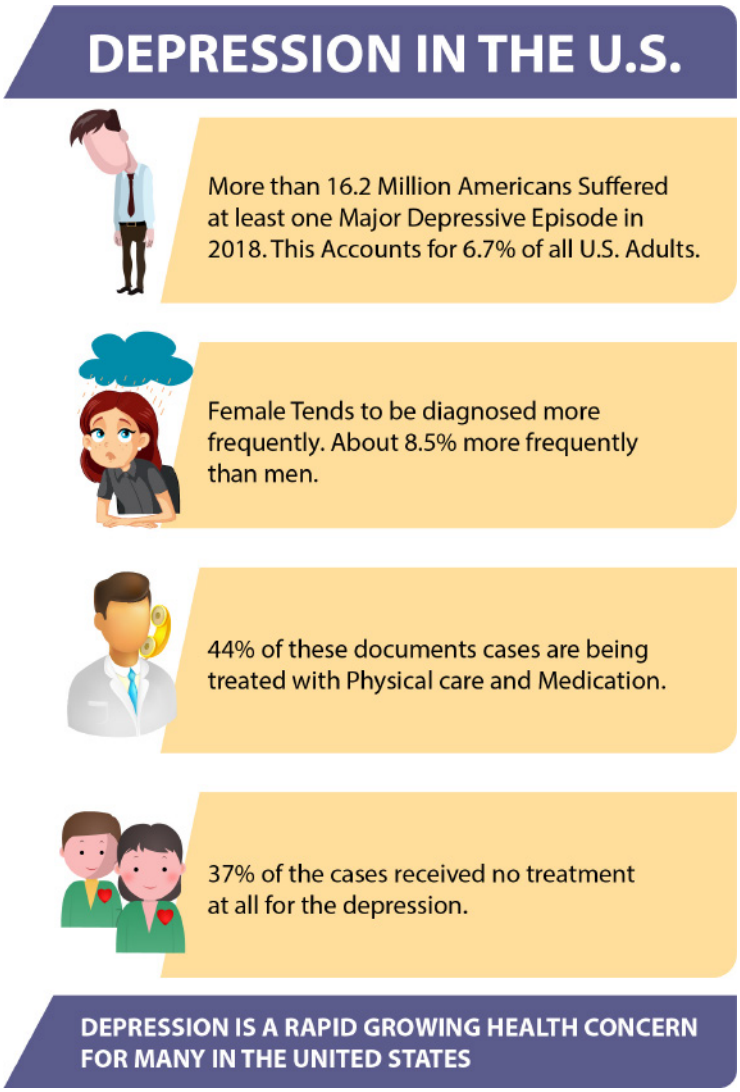

Figure 2 : Depression in US

Types of Depression

According to the DSM-5, depressive disorders all have one common feature, namely the presence of sad, empty or irritable mood, accompanied by somatic and cognitive changes that significantly affect the individual's capacity to function (DSM-5). They may become a serious health problem if allowed to persist for long periods of time and occur with a moderate-to-severe degree of intensity. One important consequence of depression is the risk of suicide, which is, according the World Health Organization (WHO), the second most common cause of death among young people aged between 15 and 29.

"According to the DSM-5, depressive disorders all have one common feature, namely the presence of sad, empty or irritable mood, accompanied by somatic and cognitive changes that significantly affect the individual's capacity to function (DSM-5). They may become a serious health problem if allowed to persist for long periods of time and occur with a moderate-to-severe degree of intensity"

The main novelty offered by the DSM-5 in its section on depressive disorders is the introduction to ***Disruptive mood dysregulation disorder*** (which should not be diagnosed before the age of 6 or after the age of 18). This disorder is characterized by severe recurrent temper outbursts manifested verbally (e.g., verbal rages) and/or behaviourally (e.g., physical aggression toward people or property). These outbursts often occur as the result of frustration and in order to be considered a diagnostic criterion must be inconsistent with the individual's developmental level, occur three or more times per week for at least a year in a number of different settings (at home, at school, etc.) and be severe in at least one of these. This disorder was added to the DSM-5 due to doubts arising in relation to how to classify and treat children presenting with chronic persistent irritability as opposed to other related disorders, specifically pediatric bipolar disorder. The prevalence of this disorder has been estimated at between 2 and 5%, with male children and teenage boys being more likely to suffer from it than their female counterparts. [5, Rank 5]

Figure 3 : Types of depression

Major Depressive Disorder

Major depressive disorder is characterized by a depressed mood most of the day, nearly every day, although in children and adolescents this mood may be irritable rather than depressed. The disorder causes a markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day, significant weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness, or excessive or inappropriate guilt, diminished ability to think or concentrate, recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide. These symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. In the United States, the 12-month prevalence is ~7%, although it is three times higher among those aged between 18 and 29 than among those aged 60 or over. Moreover, the prevalence rates for women are ~1.5–3 times higher than for men. [2, Rank 4]

Persistent Depressive Disorder

Persistent depressive disorder (dysthymia) is a consolidation of DSM-5-defined ***chronic major depressive disorder and dysthymic disorder, and is characterized by a depressed mood for most of the day, for more days than not, for at least 2 years. In children and adolescents, mood can be irritable and duration must be at least 1 year.*** The DSM-5 specifies that patients presenting symptoms that comply with the diagnostic criteria for major depressive disorder for 2 years should also be diagnosed with persistent depressive disorder. When the individual in question is experiencing a ***depressive mood episode,*** they must also present at least two of the following ***symptoms: poor appetite or overeating, insomnia or hypersomnia, low energy or fatigue, low self-esteem, poor concentration, or difficulty making decisions and feelings of hopelessness.*** The prevalence of this disorder in the United States is 0.5%.

Premenstrual Dysphoric Disorder

The diagnostic criterion for premenstrual dysphoric disorder states that, in the majority of menstrual cycles, ***at least five symptoms must be present during the last week before the start of menstruation, and individuals should start to feel better a few days later, with all symptoms disappearing completely or almost completely during the week after menstruation.*** The most important characteristics (As shown in fig.4) of this disorder are affective lability,

intense irritability or anger, or increased interpersonal conflicts, markedly depressed mood and/or over-excitation, and symptoms of anxiety which may be accompanied by behavioral and somatic symptoms. Symptoms must be present during most menstrual cycles during the past year and must negatively affect occupational and social functioning. The most rigorous estimations of the prevalence of this disorder claim that 1.8% of women comply with the criterion but have no functional impairment, while 1.3% comply with the criterion and suffer functional impairment and other concomitant symptoms of another mental disorder. [8, Rank 4]

Depressive Disorder Due to Another Medical Condition

Depressive disorder due to another medical condition is characterized by the appearance of a depressed mood and a mark-

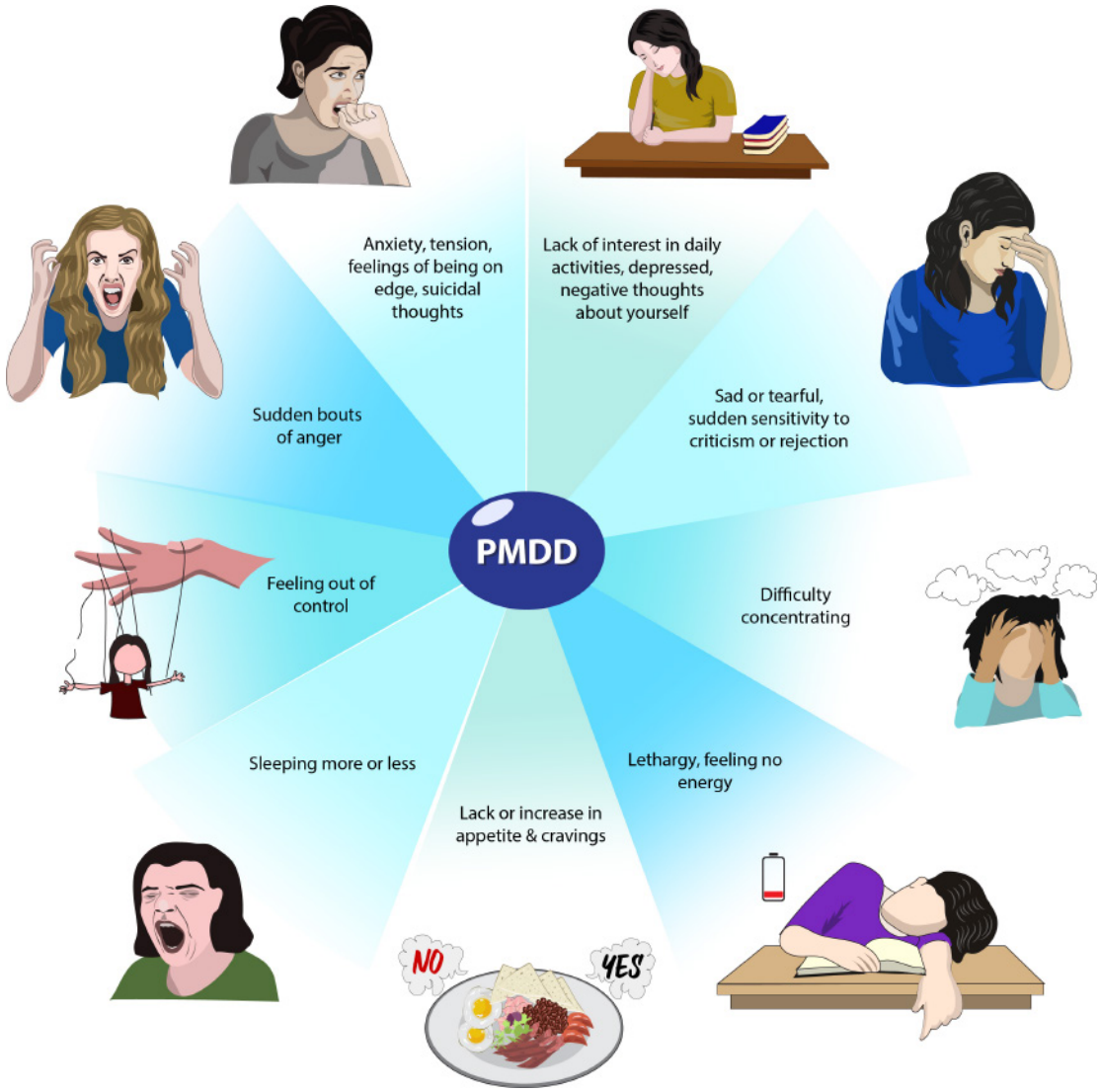

Figure 4 : Characteristics of Premenstrual Dysphoric Disorder

edly diminished interest or pleasure in all activities within the context of another medical condition. The DSM-5 offers no information about the prevalence of this disorder.

The category **Other specified depressive disorder** is used when the symptoms characteristic of a depressive disorder appear and cause significant distress or impairment in social, occupational or other areas of functioning but do not comply with all the criteria of any depressive disorder, and the clinician opts to communicate the specific reason for this. In the **Other unspecified depressive disorder category,** on the other hand, the difference is that the clinician prefers not to specify the reason why the presentation fails to comply with all the criteria of a specific disorder and includes presentations about which there is insufficient information for giving a more specific diagnosis. [7, Rank 3]

Single Depressive Episode

The classification Single depressive episode distinguishes between depressive episodes of varying severity: ***mild, moderate, and severe without psychotic symptoms.*** Characteristics (As shown in fig.5)common to all of them include lowering of mood, reduction of energy, and decrease in daily activity. There is a loss of interest in formerly pleasurable pursuits, a decrease in the capacity for concentration, and an increase in tiredness, even during activities requiring minimum effort. Changes occur in appetite, sleep is disturbed, self-esteem and self-confidence drop, ideas of guilt or worthlessness are present and the symptoms vary little from day to day. In its mildest form, two or three of the symptoms described above may be present, and the patient is able to continue with most of their daily activities.

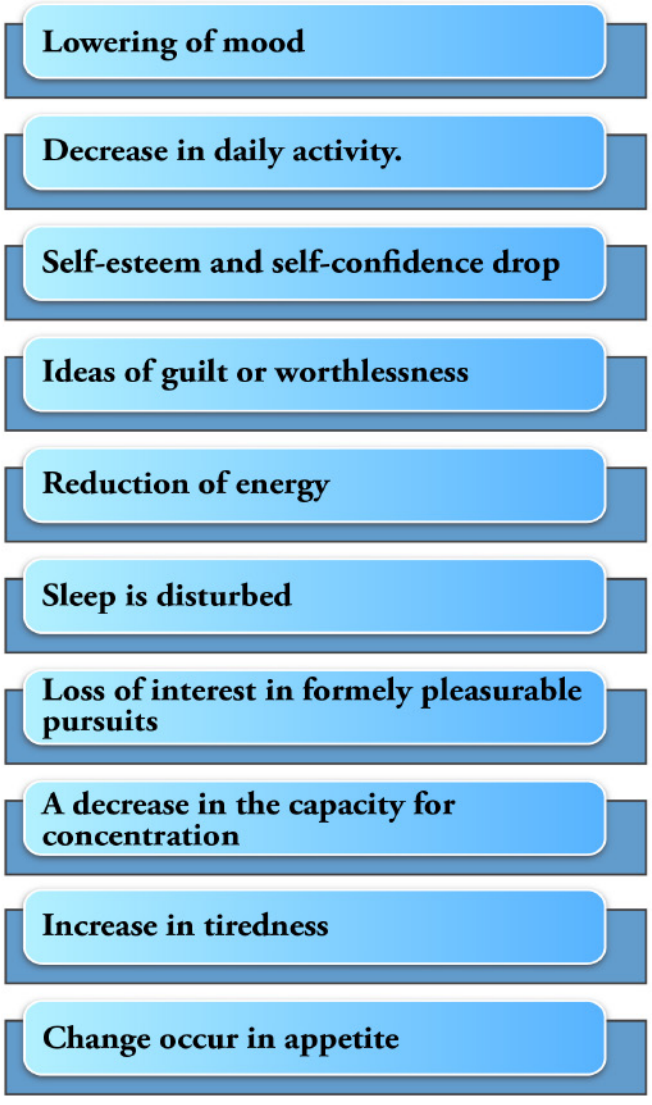

Figure 5 : Characteristics of Single Depressive Episode

When the episode is moderate, four or more of the symptoms are usually present and the patient is likely to have difficulty continuing with ordinary activities. In its most severe form, several of the symptoms are marked and distressing, typically loss of self-esteem and ideas of worthlessness or guilt. Suicidal thoughts and acts are common and a number of somatic symptoms are usually present. If the depressive episode is ***with psychotic symptoms, it is characterized by the presence of hallucinations, delusions, psychomotor retardation, or stupor so severe that ordinary social activities are impossible; there may be danger to life from suicide, dehydration, or starvation.*** [8, Rank 3]

Recurrent Depressive Disorder

Recurrent depressive disorder is characterized by repeated episodes of depression similar to those described above for single depressive episodes without mania. There may be brief episodes of mild mood elevation and over activity (hypomania) immediately after a depressive episode, sometimes precipitated by antidepressant treatment. ***The more severe forms of this disorder are very similar to manic-depressive depression, melancholia, vital depression, and endogenous depression.*** The first episode may occur at any age, from childhood to old age. The onset may be either acute or insidious and can last from a few weeks to many months. Recurrent depressive disorder can be mild or moderate, but in neither of these is there any history of mania. This section also includes recurrent depressive disorder currently in remission, in which the patient may have had two or more depressive episodes in the past, but has been free from depressive symptoms for several months. [15, Rank 2]

Persistent Mood [Affective] Disorders

Persistent mood disorders are persistent and usually fluctuating disorders in which the majority of episodes are not sufficiently severe to warrant being diagnosed as hypomanic or mild depressive episodes. Since they last for many years and affect the patient's normal life, they involve considerable distress and disability. This section also includes cyclothymia and dysthymia. Cyclothymia is a persistent instability of mood involving numerous periods of depression and mild elation, none of which are sufficiently prolonged to justify a diagnosis of bipolar affective disorder or recurrent depressive disorder. This disorder is frequently found among the relatives of patients with bipolar affective disorder and some patients with cyclothymia eventually develop bipolar affective disorder. For its

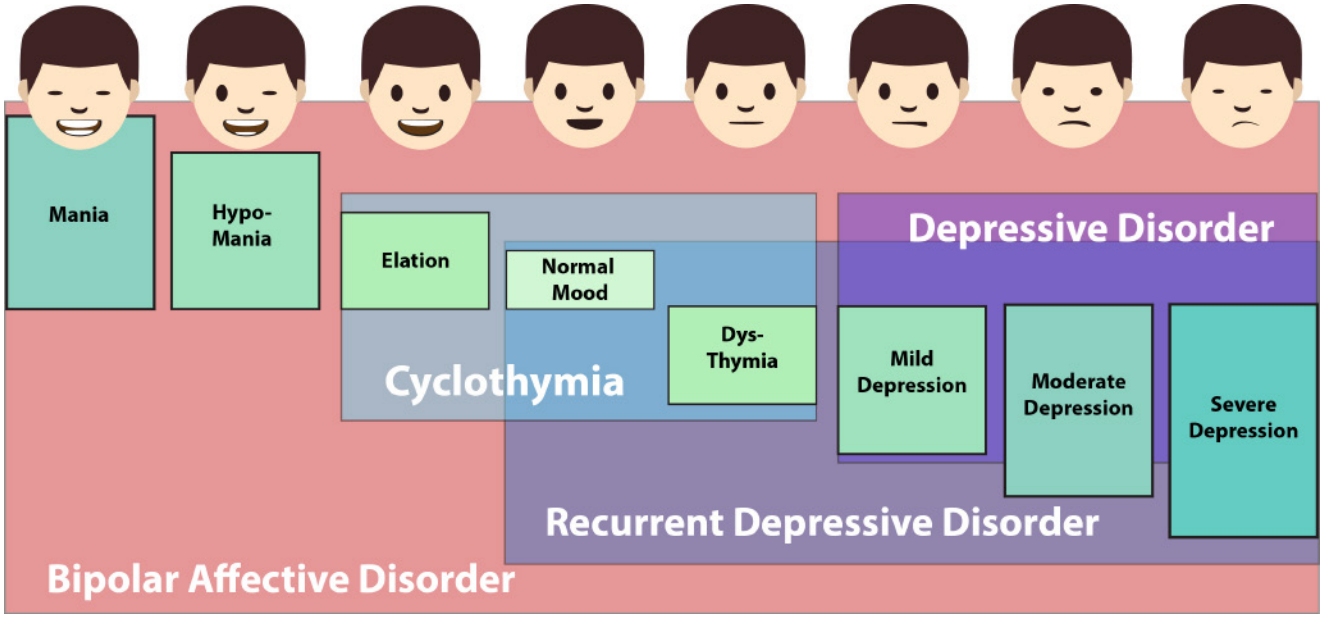

Figure 6 : Bipolar affective disorder and depressive disorder

part, dysthymia is a chronic depression of mood, lasting at least several years, which is not sufficiently severe, or in which individual episodes are not sufficiently prolonged, to justify a diagnosis of mild, moderate, or severe recurrent depressive disorder. [18, Rank 3]

Other Mood (Affective) Disorders

Finally, other mood (affective) disorders include any mood disorders that do not fall into the categories described above because they are not of sufficient severity or duration. They may be single, recurrent (brief), or specified episodes.

The manifestations and symptoms of depression vary in accordance with age and level of development. However, it is clear that the DSM-5 and the ICD-10 do not distinguish between adult and child depression, although by including disruptive mood dysregulation disorder, the DSM-5 does take into account the fact that children and young people aged between 7 and 18 may express their distress in other ways, through chronic, severe, and recurrent irritability manifested verbally and/or behaviorally. Similarly, major depressive disorder specifies that in children the mood may be irritable rather than depressed. However, no distinctions of this kind are found in the ICD-10, an absence which may lead to the faulty inference that the characteristics of child and adolescent depression are similar to those of adult depression. [22, Rank 5]

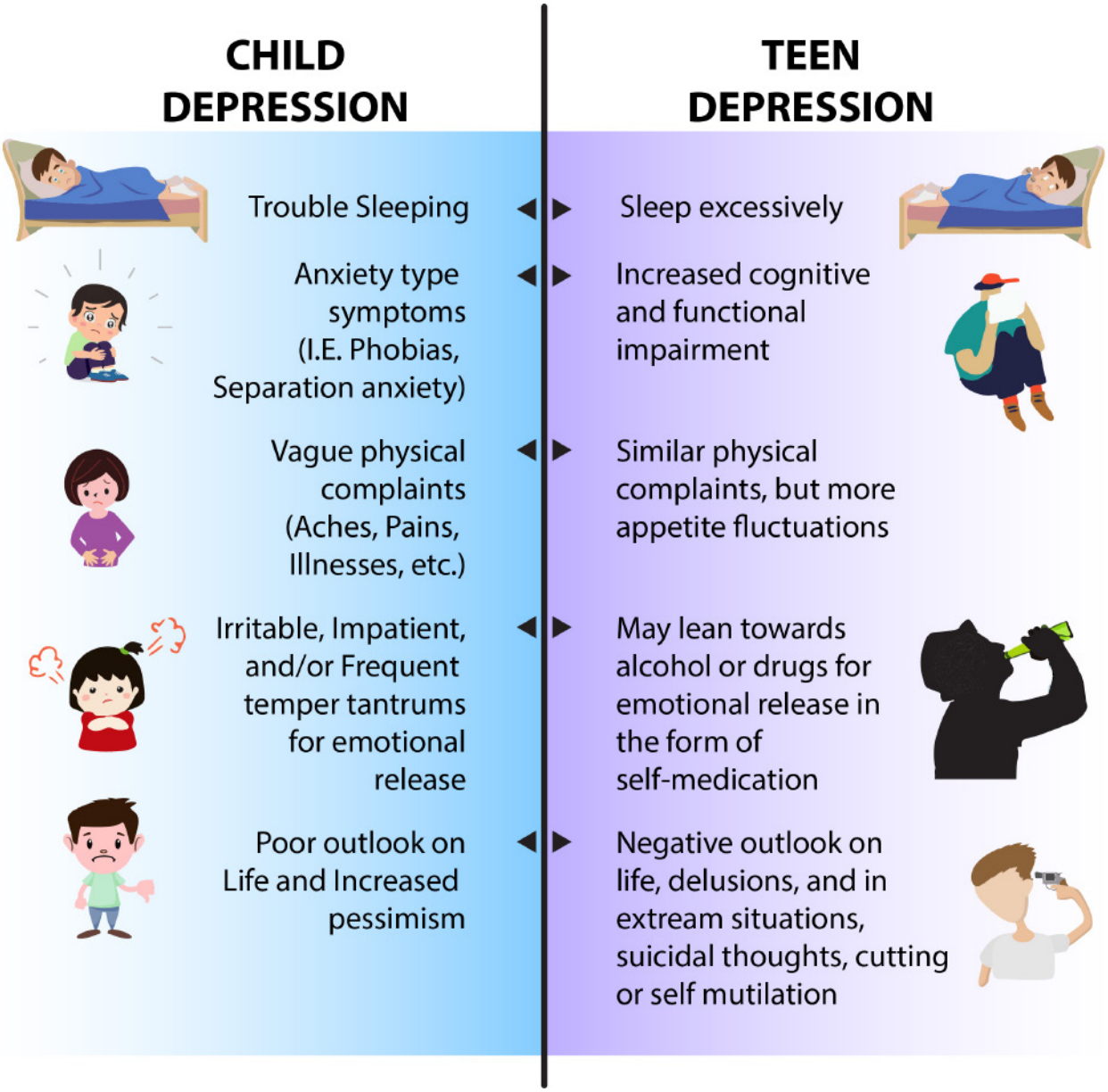

Figure 7 : Comparison between child depression and teen depression

The Biological Factors Contributing to Depression

Depressive disorders cannot be explained by any single theory, since many different variables are involved in their onset and persistence. The principal biological and psychological theories were therefore taken as the main references for this section. With the constant key words being depression, child depression and adolescent depression, the search for information cross-referenced a series of other key words also in accordance with the specific theory in question. Due to the importance of some seminal works in relation to the development of psychological theories of depression, certain authors have remained key references for decades. The following is a

summary of the various explanations for the onset of depression, according to the different theoretical frameworks. [15, Rank 5]

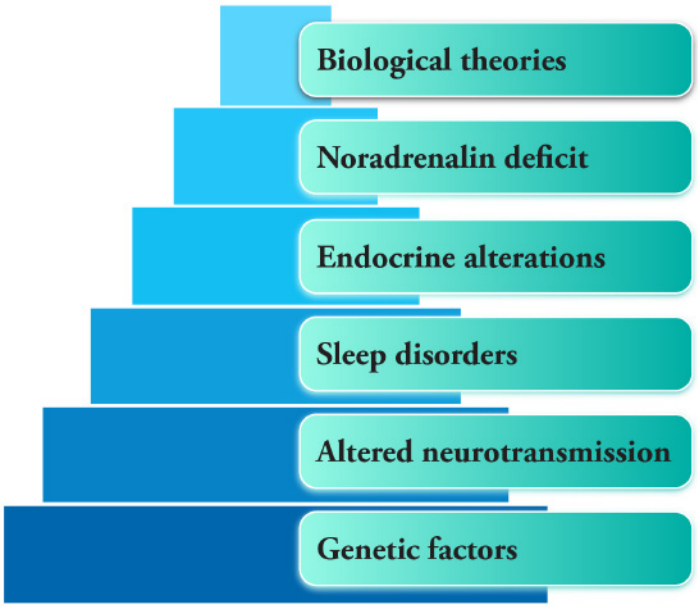

Figure 8 : Biological Factors Contributing to Depression

Biological Theories

If a mood disorder ***cannot be explained by family history or stressful life events, then it*** may be that the child or adolescent in question is suffering from a neurological disease. In such a case, depressive symptoms may ***manifest early in children and adolescents as epileptic syndromes, sleep disorders, chronic recurrent cephalalgias, several neurometabolic diseases, and intracranial tumors.***

Noradrenalin Deficit

Serotonin is a monoamine linked to adrenaline, norepinephrine, and dopamine which plays a key role in important life regulation functions (appetite, sleep, memory, learning, temperature regulation, and social behaviors etc.) and many psychiatric pathologies. Serotonin modulates neuroplasticity, particularly during the early years of life, and dysfunctions in both systems contribute to the physiopathology of depression. MRI tests in animals have revealed that a reduction in neuron density and size, as well as a reduction in hippocampal volume among depressive patients may be due to serotonergic neuroplasticity changes.

Researchers argue that improving serotonin levels may increase the likelihood of both developing and recovering from the psychopathology, and underscores the role played by the social environment in this process. In this sense, they point out that the quality of the social environment may influence the development and activity of neural systems, which in turn have an impact on behavioral, physiological, and emotional responses. [29, Rank 3]

Endocrine Alterations

Age-related changes and the presence of biological risk factors, including endocrine, inflammatory or immune, cardiovascular and neuroanatomical factors, make people more vulnerable to depression. Indeed, some studies suggest that depression may be linked to endocrine alterations: nocturnal cortisol secretions, nocturnal growth hormone secretion, thyroid stimulating hormone secretion, melatonin and prolactin secretions, high cortisol levels, or decreased growth hormone production. Puberty and the accompanying hormonal and physical changes require special attention as they could be associated with an increased incidence of depression. [32, Rank 4]

Sleep Disorders

Sleep problems are often associated with situations of social deprivation, unemployment, or stressful life events (divorce, bad life habits, or poor working conditions). It also seems, however, that sleep disorders are linked to the development of depression. This relationship occurs as a result of how insufficient sleep affects the hippocampus, heightening neural sensitivity to excitotoxic insult and vulnerability to neurotoxic challenges, resulting in a net decrease in gray matter in the hippocampus in the left orbitofrontal cortex.

Researchers state that bidirectional associations between sleep disturbances (particularly insomnia) and depression make it more difficult to distinguish cause-effect relations between them. It is therefore unclear whether depression causes sleep disturbances or whether chronic sleep disturbances lead to the appearance of depression. What does seem clear, however, is that treating sleep disturbances (both insomnia and hypersomnia) may help reduce the severity of depression and accelerate recovery. [11, Rank 3]

Longitudinal studies have identified insomnia as a risk factor for the onset or recurrence of depression in young people and adults. In comparison with the non-clinical population, depressed children and adolescents report both trouble sleeping and longer sleep duration.

Studies observed that, among preadolescent girls, early and later sleep problems directly or indirectly predicted a wide variety of social and emotional adjustment disorders (depressive symptoms, low school competence, poor emotion regulation, and risk-taking behaviors). [12, Rank 2]

Altered Neurotransmission

Studies conducted over the past 20 years have shown that ***increased inflammation and hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis may explain major depression.*** Some of the pathophysiological mechanisms of depression include altered neurotransmission, HPA axis abnormalities involved in chronic stress, inflammation, reduced neuroplasticity, and network dysfunction. Other studies report alterations in the brain structure: smaller hippocampus, amygdala, and frontal lobe. Nevertheless, the underlying molecular and clinical mechanisms have yet to be discovered.

Major depressive disorder in children and adolescents has been associated with increased intracortical facilitation, a direct neurophysiological result of excessive glutamatergic neurotransmission. However, contrary to the findings in adults with depression, no deficits in cortical inhibition were found in children and adolescents with major depressive disorder. [14, Rank 5]

Genetic Factors

Other studies have highlighted the importance of genetics in the onset of depression (40%). ***It is important to recognize that a genetic predisposition to an excessive amygdala response to stress, or a hyperactive HPA axis (moderate hyperphenylalaninemia) due to stress during early childhood may trigger an excessive effect or alter an otherwise healthy psychological system.*** Researchers also support a potential role for genes related to the homeobox 2 gene of Orthodenticle (OTX2) and to the OTX2-related gene in the physiopathology of stress-related depressive disorders in children. Furthermore, genetic anomalies in serotonergic transmission have been linked to depression. The serotonin-linked polymorphic region (5-HTTLPR) is a degenerate repeat in the gene which codes for the serotonin transporter (SLC6A4). The s/s genotype of this region is associated with a reduction serotonin expression, in turn linked to greater vulnerability to depression.

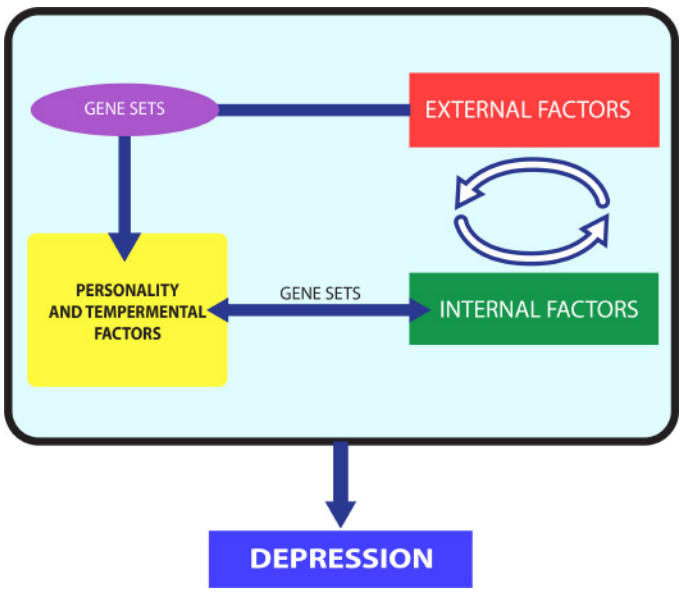

Figure 9 : Genetic factors and depression

Researchers claim that psychological disturbances may trigger changes in physiological parameters, such as DNA transcription, or may result in epigenetic modifications which alter the sensitivity of the neurotransmitter receptor. [30, Rank 5]

Psychological Reasons Leading to Depression

Several studies outline the different psychological theories which have attempted to explain the phenomenon of depression. Depression is a highly complex disorder influenced by multiple factors, and it is clear that no single theory can fully explain its etiology and persistence. It is likely that a more eclectic outlook must be adopted if we are to make any progress in determining the origin, development, and maintenance of this pathology.

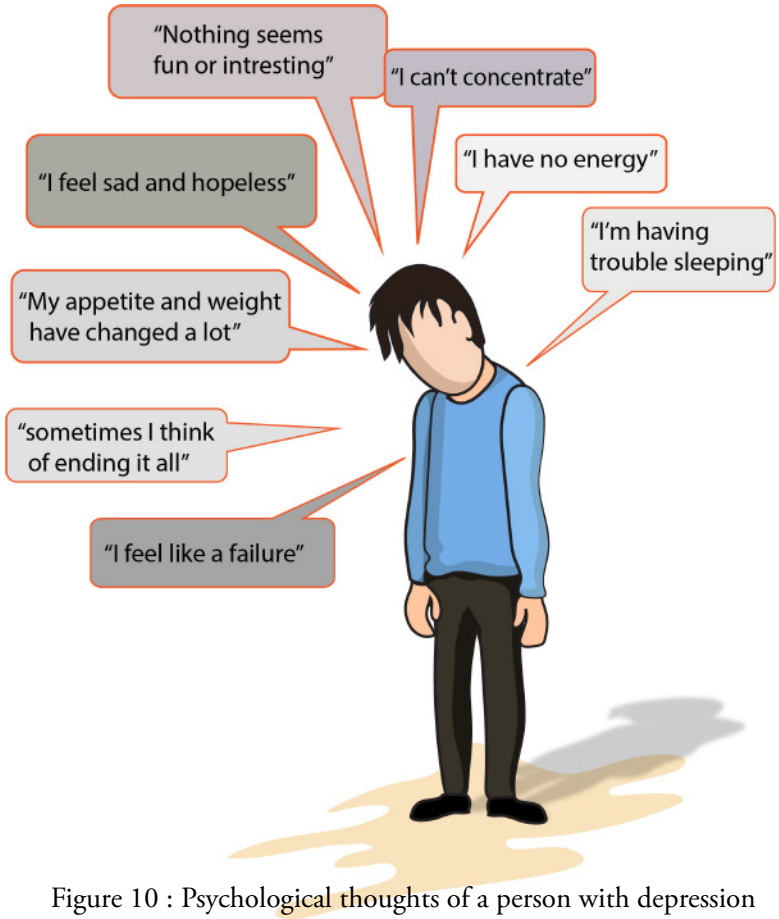

Figure 10 : Psychological thoughts of a person with depression

Attachment-Informed Theories

Attachment theory was the term used to refer to a specific conceptualization of human beings' propensity to establish strong and long-lasting affective ties with other people. One study proposes that consistency, nurturance, protectiveness, and responsiveness in early interactions with caregivers contribute to the development of schemas or mental representations about the relationships of oneself with others, and that these schemas serve as models for later relationships. Its ethological model of attachment postulates that vulnerability to depression stems from early experiences which failed to satisfy the child's need for security, care and comfort, as well as from the current state of their intimate relations. [33, Rank 3]

Adverse early experiences can contribute to disturbances in early attachments, which may be associated with vulnerability for depression. Associations between insecure attachment among children and negative self-concept, sensitivity to loss, and an

increased risk of depression in childhood and adolescence have been reported. Relationships between secure attachment and depression seem also to be mediated by the development of maladaptive beliefs or schemas. Thus, attachment theory has become a useful construct for conceptualizing many different disorders and provides valuable information for the treatment of depression. Researchers described three attachment styles, in accordance with the child's response to the presence, absence, and return of the mother (or main caregiver): secure, anxious-avoidant, and anxious-resistant. The least secure attachment styles may give rise to traumatic experiences during childhood, which in turn may result in the appearance of depressive symptoms. [42, Rank 2]

Figure 11 : symptoms of child depression

Similarly, it was proposed that the central mechanism regulating infant emotional survival was proximity to attachment figures, i.e., those figures who help the child cope with frightening situations. ***Using Ainsworth's strange situation procedure,*** studies found that abused children engaged in more disorganized, disruptive, aggressive, and dissociative behaviors during both childhood and adolescence. It was also found that many people with clinical disorders have insecure attachment and that psychological-disoriented and disorganized children are more vulnerable.

Several studies explored the nature of depression and the life experiences which contribute to its appearance in more depth, ***identifying two types of depression which, despite a common set of symptoms, nevertheless have very different roots: (1) anaclitic depression, which arises from feelings of loneliness and abandonment; and (2) introjective depression, which stems from feelings of failure and worthlessness.*** This distinction is consistent with psychoanalytical formulations, since it considers

defencelessness/dependency and desperation/negative feelings about oneself to be two key issues in depression. [45, Rank 3]

Researchers also found that at age 3 weeks, babies demonstrate a series of interactive behaviors during face-to-face mother-infant interactions. These behaviors were not found to be present in more disturbed interactions, which may trigger infant anxiety.

In a longitudinal study focusing on the relationship between risk of maternal depression and infant attachment behavior, the study analyzed babies at age 6 weeks, 4 and 12 months. The study found that mothers at risk of depression soon after the birth of their child may have difficulty responding appropriately to their infant's attachment needs. This will lead to disorganized attachment, with all the psychological consequences that this may involve. Similarly, it was found that among infants aged between 2 and 18 months, greater maternal social support was linked to decreasing levels of maternal depressive symptoms over time, and that boys were more vulnerable than girls to early caregiving risks such as maternal depression, with negative consequences for mother-child attachment security during toddlerhood. [31, Rank 2]

Researchers have attempted to find solutions to the problems arising in relation to the DSM diagnostic categories, developing the Shedler Westen Assessment Procedure (SWAP-200) to capture the wealth and complexity of clinical personality descriptions and to identify possible diagnostic criteria which may better define personality disorders. [27, Rank 1]

> **"It is estimated that 30–50% of the patients do not respond to treatment with antidepressants due to either lack of efficacy or intolerable side effects. Another possible reason for the ineffectual treatment of MDD has been the incomplete understanding of the nature of depression"**

Clinical Treatments for Depression

Although the World Health Organization (WHO) claims that prevention programs reduce the risk of suffering from depression, it has yet to be ascertained what type of programs and what contents are the most effective. ***The WHO also states that there are effective treatments for moderate and severe depression, such as psychological treatments (behavioral activation, cognitive behavioral therapy, and interper-***

sonal psychotherapy) and antidepressant drugs (although it also warns of adverse effects), as well as psychosocial treatments for cases of mild depression. Moreover, a study conducted with adolescents found that the combination of cognitive-behavioral therapy and fluoxetine (antidepressant drug) was more effective than drug therapy alone. [20, Rank 4]

The efficacy of treatment with antidepressants has been called into question for some years now. ***Tricyclic antidepressants (imipramine, clomipramine, amitriptyline) are not recommended in childhood and adolescence since no benefits other than the placebo effect have been proven and furthermore, they generate major side effects due to their cardiotoxicity.*** They are therefore particularly dangerous in cases of attempted suicide. These same authors also advise against the use of monoamine oxidase inhibitors (MAOIs) due to dietary restrictions, interactions with other medication and the lack of clinical trials with sufficiently large groups which guarantee their efficacy. SSRIs or serotonergic antidepressants are the ones that have been most extensively studied in this population. The most effective is fluoxetine, the use of which is recommended in association with cognitive psychotherapy for cases of moderate and severe child depression.

On another hand, a study analyzed the efficacy of pharmacological treatment in children and adolescents and stated that, at best, antidepressant therapy for depressed youth was moderately effective. There is a great debate about the safety of selective serotonin reuptake inhibitors (SSRIs) in childhood. SSRIs, except for fluoxetine in the United States, have never been authorized by any agency for use in children or adolescents, mainly because of the risk of suicide to which they are associated. The Food and Drugs Administration (FDA) claimed that there was insufficient evidence to confirm a causal association between SSRIs and suicide. Several researchers conducted a systematic review of the topic and found more than 30 controlled clinical trials in adolescents and a few studies with children. Most studies found no differences between studies that administered drugs and those that used placebo, but they did find fluoxetine to be effective. They noted that antidepressants increased the risk of suicide (suicidal ideation and behaviors) compared to studies that had used placebos. The authors recommend using antidepressants with caution in young people and limiting them to patients with moderate to severe depression, especially when psychosocial interventions are not effective or are not feasible. [34, Rank 4]

As regards the effectiveness of psychodynamic treatments, studies advocate the inclusion of psychoanalytic therapy in the treatment of child, adolescent and adult depression. After conducting a review of both the theoretical assumptions of psychodynamic treatments of depression and the evidence supporting the efficacy of these interventions, these authors concluded that brief psychoanalytic therapy (BPT) is as effective in treating depression as other active psychotherapeutic treatments or pharmacotherapy, and its effects tend to be maintained in the longer term. They also observed that the combination of BPT and medication obtained better results than medication alone. Longer-term psychoanalytic treatment (LTPT) was found to be effective for patients suffering from chronic depression and co-morbid personality problems. Together, the authors argue, these findings justify the inclusion of psychoanalytic therapy as a first-line treatment in adult, child, and adolescent depression. [33, Rank 3]

In a qualitative study carried out on parents' expectations regarding the recovery of their depressed children, a direct relationship was observed between said expectations and type of attachment. Parents who remained more passive and expected expert helpers to fix their child experienced reduced hope months after finishing the program. However, when parents changed their interactions with their child and adopted more positive expectations regarding their cure, they felt a more sustained sense of hope. Moreover, when parents themselves participated in therapy sessions, as part of their child's treatment, they felt greater hope and effectiveness in contributing to their child's recovery. [19, Rank 4]

The American Psychological Association's Society of Clinical Psychology has published a list of psychological treatments that have been tested with the most scientific rigor and have been found to be most effective in treating depression. These treatments are as follows:

Self-Management/ Self-Control Therapy:

Depression is due to selective attention to negative events and immediate consequences of events, inaccurate attributions of responsibility for events, insufficient self-reinforcement, and excessive self-punishment. During therapy, the patient is provided with information about depression and taught skills they can use in their everyday life. This 10-session program can be delivered either in group or individual formats, at any age.

Cognitive Therapy:

Individuals suffering from depression are taught cognitive and behavioral skills to help them develop more positive beliefs about themselves, others, and the world. Researchers argue that therapists working with depressed children should pursue three changes: (1) Learn to value their own feelings; (2) Replace behaviors which generate negative feelings with more appropriate behaviors; and (3) Modify distorted thoughts and inaccurate reasoning. The number of sessions varies between 8 and 16 in patients with mild symptoms. Those with more severe symptoms show improvement after 16sessions. [37, Rank 4]

Interpersonal Therapy:

Studies identified four typical focal points for tension in depression, related to loss (complicated mourning), conflicts (interpersonal disputes), change (life transitions), and deficits in relations with others (interpersonal deficits), which generate and maintain a depressive state. It uses certain behavioral strategies such as problem solving and social skills training and lasts between 12 and 16 sessions in the most severe cases, and between 3 and 8 sessions in milder cases.

Cognitive Behavioral Analysis System of Psychotherapy:

This therapy combines components of cognitive, behavioral, interpersonal, and psychodynamic therapies. According to researchers, it is the only therapy developed specifically to treat chronic depression. Patients undergoing this therapy generate more empathic behaviors and identify, change and heal interpersonal patterns related to depression. Patients are recommended to combine the therapy with a regime of antidepressant medication.

Behavior Therapy/ Behavioral Activation (BA):

Depression prompts sufferers to disengage from their routines and become increasingly isolated. Over time, this isolation exacerbates their depressive symptoms. Depressed individuals lose opportunities to be positively reinforced through pleasant experiences or social activities. The therapy aims to increase patients' chances of being positively reinforced by increasing their activity levels and improving their social relations. The therapy usually lasts between 20 and 24 sessions, with the brief version consisting of between 8 and 15 sessions. [44, Rank 5]

Problem-Solving Therapy:

The aim is to enhance patients' personal adjustment to their problems and stress using affective, cognitive, and behavioral strategies. The therapy usually comprises around 12 sessions, although substantial changes are generally observed from the fourth session onwards. This therapy is widely used in primary care. It is an adaptation that is easy to apply in general medicine by personnel working in those contexts, and can be completed in around 6 weeks.

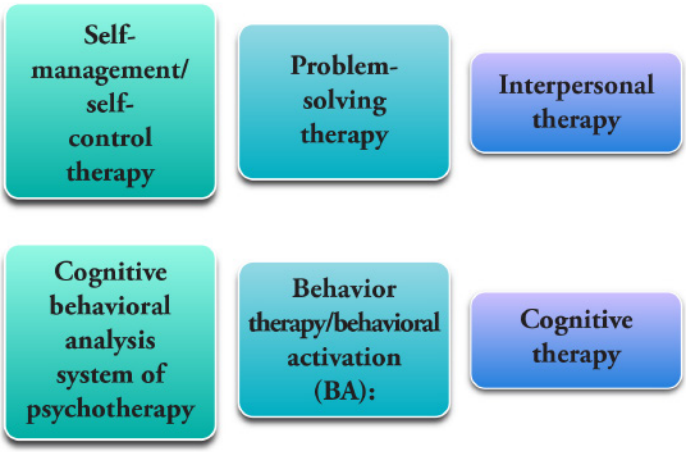

Figure 12 : The psychological treatments has published by American Psychological Association's Society of Clinical Psychology

The treatments that, according to the American Psychological Association, Society of Clinical Psychology, have modest research support and could be used with children are as follows:

Rational Emotive Behavioral Therapy:

This short-term, present-focused therapy works on changing the thinking which contributes to emotional and behavioral problems using an active-directive, philosophical and empirical intervention model. Using the A-B-C model (A: events observed by the individual; B: Individual's interpretation of the observed event; C: Emotional consequences of the interpretations made), the aim is to bring about the cognitive restructuring of erroneous thoughts, so as to replace them with more rational ones. The most commonly used techniques are cognitive, behavioral, and emotional. [21, Rank 3]

Self-System Therapy:

Depression occurs as the result of the individual's chronic failure to achieve their established goals. During therapy, patients review their situation, analyze their beliefs and, on the basis of the results, alter their regulation style and move toward a new vision of themselves. Therapy generally consists of between 20 and 25 sessions.

Short-Term Psychodynamic Therapy:

The aim of this therapy is to help patients understand that past experiences influence current functioning, and to analyze

affect and the expression of emotion. The therapy focuses on the therapeutic relationship, the facilitation of insight, the avoidance of uncomfortable topics and the identification of core conflictual relationship themes. It is usually combined with pharmacological treatment to alleviate depressive episodes. [33, Rank 3]

Emotion-Focused Therapy (emotion regulation therapy or Greenberg's experiential therapy):

This therapy combines elements of client-based practices, Gestalt therapy, the theory of emotions and a dialectic-constructivist meta-theory. The aim is to create a safe environment in which the individual's anxiety is reduced, thereby enabling them to confront difficult emotions, raising their awareness of said emotions, exploring their emotional experiences in more depth and identifying maladaptive emotional responses. The therapy is delivered in 8–20 sessions.

Acceptance and Commitment Therapy:

This theory has become increasingly popular over recent years and is the contextual or third-generation therapy that is supported by the largest body of empirical evidence. It is based on a realization of the importance of human language in experience and behavior and aims to change the relationship individuals have with depression and their own thoughts, feelings, memories, and physical sensations that are feared or avoided. Strategies are used to teach patients to decrease avoidance and negative cognitions, and to increase focus on the present. The aim is not to modify the content of the patient's thoughts, but rather to teach them how to change the way they analyze them, since any attempt to correct thoughts may, paradoxically, only serve to intensify them. [39, Rank 4]

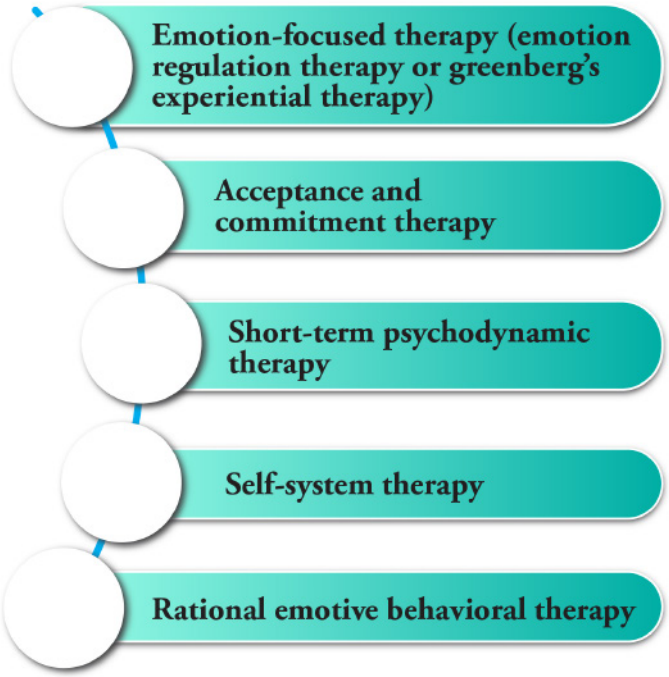

Figure 13 : The treatments according to the American Psychological Association, Society of Clinical Psychology, for children

Researchers, in a theoretical review of the treatment of depression in children and adolescents, concluded that the cognitive-behavioral-therapy-based specific programs of the Penn Prevention program meet

the criteria to conduct effective interventions in children with depression. In adolescent depression, the cognitive-behavioral therapy and the Interpersonal Therapy–Adolescent seem to have a well-established efficacy. Another study, in this same line, state that, although the efficacy of treatments in children is rather weak, cognitive-behavioral therapy is probably the most effective therapy. They also confirm that, in depressed adolescents, cognitive behavioral therapy, and interpersonal psychotherapy are appropriate interventions.

There are other studies also which focus on treatments for depression in childhood. For example, a meta-analysis of the effects of Cognitive Behavioral Therapy (CBT) on children suffering from anxiety and depression, concluded that CBT can be considered an effective treatment for child depression. According to these researchers, the majority of protocols for children have been adapted from protocols for adults, and the most common techniques are psychoeducation, self-monitoring, identification of emotions, problem solving, coping skills, and reward plans. Similarly, cognitive strategies include the identification of cognitive errors, also known as cognitive restructuring. In another meta-analysis conducted to analyze the efficacy and acceptability of CBT in cases of child depression, Several studies observed that, in comparison with the control groups that did not receive treatment, the experimental groups showed significant improvement, although they also pointed out that the relevance of this finding was limited due to the small size of the trial groups. [47, Rank 4]

Another study carried out concluded that student counseling in schools may help combat and directly reduce anxiety and depression levels among Saudi children and adolescents.

Family-based treatment may also be effective in treating the interpersonal problems and symptoms observed among depressed children. The data indicate that the characteristics of the family environment predict recovery from persistent depression among depressed children. In this sense, the study compared the effects of a family-focused treatment for child depression (TCF-DI) with those of individual supportive psychotherapy among children aged 7–14 with depressive disorders. The results revealed that incorporating the family into the therapy resulted in a significant improvement in depressive symptoms, global response, functioning, and social adjustment.

Potential Moderators of Depression Prevention Programme

Depression is one of the most prevalent psychiatric disorders experienced by adolescents and often recurs during adulthood. Adolescent depression is associated with suicidal behavior, substance abuse, interpersonal problems, academic failure, and comorbid psychopathology. Despite the significance of depressive disorders, less than 50% of depressed adolescents receive treatment, suggesting the need for effective depression prevention programs that could be widely implemented.

Various cognitive-behavioral (CB) depression prevention programs have reduced depressive symptoms and future depressive disorder onset in adolescents, but the average magnitudes of effect have been small to moderate, with smaller average effects for universal versus selective or indicated programs. However, the effectiveness of such programs can vary considerably depending on individual, environmental, and demographic factors, highlighting the need to investigate potential moderators of depression prevention program effects, a central concept in personalized medicine. Moderational analyses are important for several reasons. First, knowledge about moderators provides information regarding the conditions under which optimal prevention effects occur. Second, neglecting potential moderators of prevention effects can lead to misinterpretation of results. Third, determining which individuals are most or

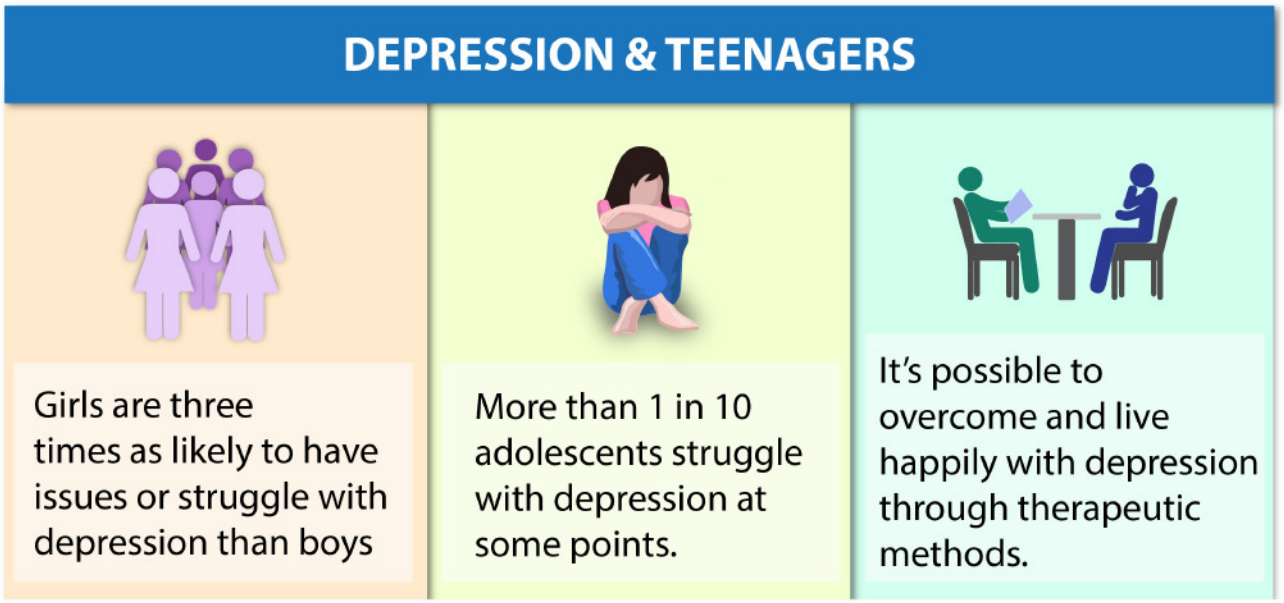

Figure 14 : Depression and teenagers

least likely to benefit from an intervention can inform optimum inclusion and exclusion criteria. For instance, through moderation analyses youth that are unlikely to benefit from a specific prevention program or even experience iatrogenic effects can be identified, and this may provide direction regarding alternative intervention for those individuals. Fourth, moderation analyses may also lead to program refinement because important aspects that contribute to the effectiveness of a program for a specific population can be discovered.

Conversely, documenting that there are few moderators for an intervention in an adequately powered evaluation would suggest that the intervention is effective for a broad range of individuals and could be widely implemented. Information about all of these aspects helps to maximize economical and cost-effective program dissemination. Thus, moderators can serve to provide specific, novel, and valuable information which guides future modification of intervention decision making and program development. [46, Rank 5]

> **"One important consequence of depression is the risk of suicide"**

Depressive Symptom Profiles that Indicate the Presence of Depressive Disorder

In medical populations, the continuum of depression can range from nonpathological sadness and grief to depressive disorders specified in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5). The depressive disorders specified in the DSM-5 include major depressive disorder (MDD), dysthymia, premenstrual dysphoric disorder, depressive disorder due to another medical condition, and other specified depressive disorders.

Geriatric patients with depression predominantly present with atypical clinical features and this often hamper the detection of depression. The age-specific manifestations of geriatric depression are regarded as the important clinical concerns; and its manifestations are characterized by hypochondriasis and somatic preoccupation associated anxiety and insomnia rather than typical features including melancholia/persistent sadness. A theoretical speculation is that geriatric depression is continuous with minor cognitive impairment and major depressive disorder and can be regarded as a prodromal state of major cognitive disorder. A systemic review and meta-analysis demonstrated that disability, bereavement,

sleep disturbance, female gender and others are identified as important risk factors for depressive disorder in elderly community subjects. Another review showed that biological factors are regarded as more important predictors for development of geriatric depression. Thus, chronic physical diseases are regarded as possible risk factors for depressive disorder.

The relationship between depressive disorder and physical diseases can be bidirectional and complex. There is a positive relationship trend between the number of chronic physical diseases and risk of depressive disorder. In addition, co-incidence of depressive disorder and chronic physical diseases can contribute to poor prognosis and increased mortality. Moreover, since medically ill patients often show fatigue, anorexia, weight loss, retardation, reduced concentration, loss of interest, and desire to die independent of co-morbid depression, evaluating the presence or absence of depression might be complicated. Hence, detection and management of depressive disorder in the elderly patients with chronic physical diseases can be an important clinical issue in the realm of consultation-liason psychiatry or psychosomatic medicine. In addition, depressive symptom profiles indicating the presence of depressive disorder need to be identified to efficiently detect depressive disorder in elderly patients with chronic physical diseases. [48, Rank 5]

Identifying the Triggers for Depression

Even though information concerning the epidemiology, symptoms and complications of mood disorders are well documented, the etiology and pathophysiology of depression are not completely elucidated. The monoamine depletion hypothesis has historically dominated the view on the pathophysiology of depression. It suggests that an imbalance, mainly in serotonergic and noradrenergic neurotransmission is the core of the pathophysiology of depression.

However, the lack of responsiveness to conventional treatment with antidepressants and high rates of treatment resistance suggests that additional mechanisms might play a role in depression. Over the last 20 years, psychiatric research has provided support for the hypothesis that inflammatory processes and brain–immune interactions are involved in the pathogenesis of MDD and may contribute to the serotonergic and noradrenergic dysfunction. Stimuli like inflammation, ***chronic stress and infection can trigger the activation of microglia, the brain's immune cells, to release pro-inflammatory cytokines that can act on two***

pathways that may lead to MDD and neurodegeneration, such as: (1) activation of the hypothalamic–pituitary adrenal axis, generating an imbalance in the serotonergic and noradrenergic circuits; (2) increased activity of the enzyme indoleamine-2,3-deoxygenase (IDO), resulting mainly in depletion of serotonin. Considering that MDD is a very complex and heterogeneous disorder, it is possible that immune deregulation is not present in all depressed patients, but only in specific sub-populations. Evidence also shows that lack of therapeutic benefit of antidepressants might be associated with persistent immunological impairment. [43, Rank 3]

Association between pro-inflammatory cytokines and depression: the role of microglia

The hypothesis of a causal relationship between pro-inflammatory cytokines and depression was first described by Smith et al. in 1991, in the macrophage theory of depression. The theory was based on observations that cytokines produced by macrophages, when given to healthy volunteers, induced symptoms of depression and had brain effects that included the activation of the HPA axis. Afterwards, researchers cor-

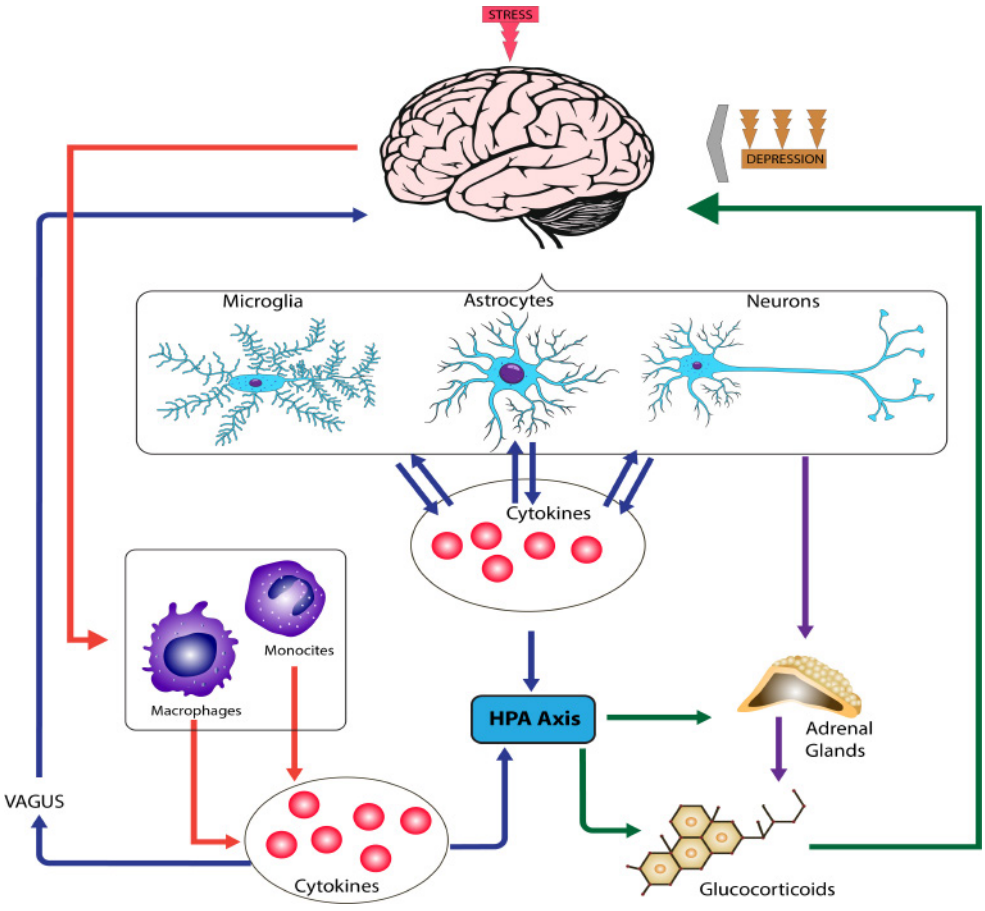

Figure 15 : Microglia and proinflammatory actions in brain in depressive disorders

roborated the theory by collecting biochemical evidence for the immunological activation in depressed patients.

In response to infection or inflammatory conditions, peripherally produced cytokines can act on the brain and cause behavioral symptoms, such as malaise, prostration, fatigue, numbness and anorexia. ***The main elucidated pathways to which pro-inflammatory cytokines can reach the brain include:*** (1) cytokine passage through leaky regions in the blood–brain barrier (BBB); (2) active transport via saturable transport molecules; (3) activation of endothelial cells and other cell types (including perivascular macrophages) lining the cerebral vasculature (which in turn produce cytokines and other inflammatory mediators); (4) binding to cytokine receptors associated with peripheral afferent nerve fibers (e.g. vagus nerve), delivering cytokine signals to relevant brain regions including the nucleus of the solitary tract and hypothalamus. The nuclear factor NF-κB has been identified as an essential mediator at the blood–brain interface that communicates peripheral inflammatory signals to the central nervous system (CNS). Production of inflammatory cytokines can also be induced directly within the brain, via stress or other processes (e.g. vascular insults in late life depression). [46, Rank 3]

In the CNS, microglia cells are the main cellular regulators of the innate immune response to both physiological and pathological conditions. They transform from an immunesurveillant into an activated state in response to pathogens and to synaptic and neuronal injury in several neurological disorders. During their activation, microglia change from a ramified to a hyper-ramified phenotype and subsequently adopt an amoeboid morphology, a mechanism which has been suggested to help microglia to invade lesions.

This activation can be acute or chronic, depending on the type of stimulus (inflammation, stress, infection, neuronal injury) and its duration. Thus, activation of microglia in stress might be different from microglial activation during inflammation or infection. When chronically activated, microglia can produce a wide variety of neurotoxins such as pro-inflammatory cytokines, free radicals, nitric oxide, chemokines, proteinases and eicosanoids that may cause neuronal dysfunction and aggravate underlying pathologies. As such, activated microglia can be a triggering factor for mood disorders. Activated microglia have already been found in the brain of stress-induced animal models of depression,

however the data that would confirm the presence of activated microglia in humans are still limited. Evidence for neuroinflammation in MDD could be obtained non-invasively by positron emission tomography (PET) using radioligands that bind to the translocator protein (TSPO), a receptor that is upregulated in the mitochondria of activated microglia cells. [12, Rank 2]

Recently, the presence of neuroinflammation in depressed patients during a major depressive episode was demonstrated using PET with the TSPO radioligand. The study was conducted on 20 patients in a major depressive episode secondary to MDD that were medication free for at least 6 weeks, and 20 healthy controls. A significant increase in the uptake of the tracer was found in the prefrontal cortex, anterior cingulated cortex and insula, indicating the presence of activated microglia in these brain regions. Moreover, PET tracer uptake (microglia activation) was correlated with the Hamilton Depression Rating Scale (HDRS) score in the anterior cingulated cortex.

Researchers also conducted a study to evaluate the presence of neuroinflammation in patients with mild-to-moderate depression using another TSPO ligand. No difference between patients and controls was found in this study. This could be due to the small sample size and the fact that patients with signs of peripheral immune activation (as defined by elevated high-sensitive C-reactive protein, hsCRP) were excluded. Further studies with PET imaging should be conducted in order to corroborate or not the presence of activated microglia in MDD in a non-invasive manner. Thus, an increased density of activated microglia was observed post mortem in the anterior midcingulate cortex, dorsolateral prefrontal cortex and mediodorsal thalamus of suicidal patients with affective disorders. [27, Rank 1]

More recently, an increased gut permeability or 'leaky gut' theory was described as a possible contributor to the peripheral and central production of pro-inflammatory cytokines by microglia in a subgroup of depressed patients. The investigated subjects were diagnosed with MDD and presented specific symptoms which have been correlated to increased levels of IgM and IgA to lipopolysaccharide (LPS) of enterobacteria in chronic fatigue syndrome. The observed symptoms were pain, muscular tension, fatigue, concentration difficulties, failing memory, irritability, stress and irritable bowel, among others. [34, Rank 4]

Association Between Depression and Inflammatory Biomarkers

Numerous studies have indicated that MDD is accompanied by elevated levels of inflammatory biomarkers, such as the pro-inflammatory cytokines interleukin (IL)-1β, IL-6, IL-18, tumor necrosis factor alpha (TNF-α), interferon-gamma (INF-γ) and the acute phase proteins such as C-reactive protein (CRP) even suggested that, besides, for example, stress hormones and psychopathological measures, cytokines may serve as biomarkers for individualized treatment of depression. Thus, animal studies have shown that systemic exposure to inflammatory challenges, such as LPS, not only causes a systemic inflammation but also induces a central inflammatory response in the brain, which is reflected by activation of microglia. [19, Rank 4]

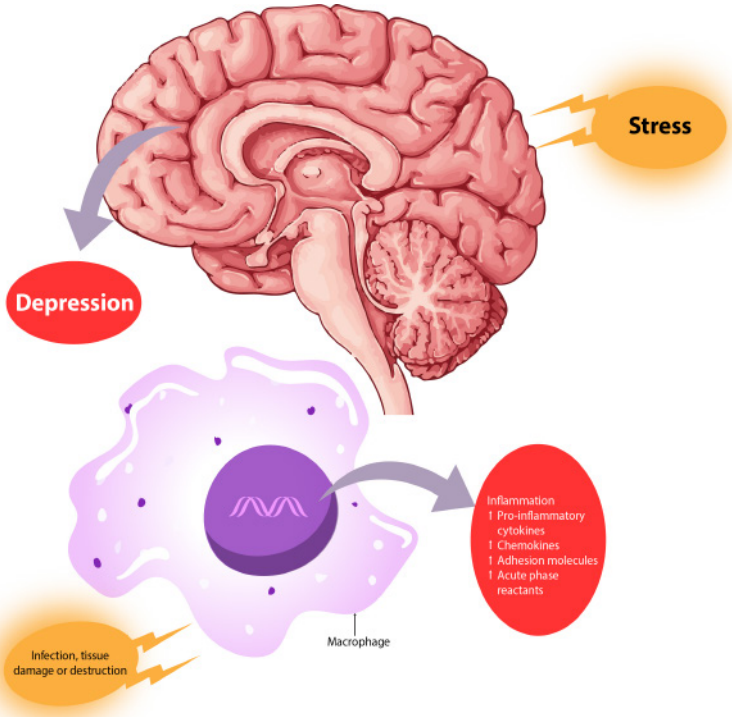

Figure 16 : Depression and inflammatory biomarkers

The pro-inflammatory cytokines produced during activation of microglia might have an effect on central serotonin levels and affect the HPA axis. The immune and neuroendocrine systems act together in order to restore and maintain physiological homeostasis during inflammation and other harmful stimuli that might induce systemic cytokine production. Therefore, it has been suggested that abnormalities in the HPA axis might play a key role in the development and recurrence of depression. Increased cytokine production may contribute to the development of depression directly via activation of the HPA axis or indirectly through cytokine-induced glucocorticoid receptor resistance.

The release of TNF-α and IL-6 increases the production of corticotrophin-releasing hormone, adrenocorticotropic hormone and cortisol by acting directly on hypothalamic and pituitary cells. Cytokines might also increase glucocorticoid receptor resistance through several signaling pathways, including activation of the p38 mitogen-activated protein kinase (MAPK) and by stimulating changes in the expression

of glucocorticoid receptors. The high levels of circulating stress hormones in the CNS might affect the neurotransmitter homeostasis, the neuronal growth factor synthesis and ultimately, disturb the functioning of neuronal circuits of the limbic system. HPA hyperactivity has been associated with the pathophysiology of suicidal behavior, excessive activity of the noradrenergic system and dysfunction of the serotonergic system. [48, Rank 5]

Structure of Major Depressive Disorder Treatment

Treatment of major depressive disorder is typically structured into three phases, with three different goals. Acute phase treatment, typically six to 12 weeks, is focused on reducing symptoms, improving functioning, and achieving remission from the major depressive episode. Continuation phase treatment occurs after acute response (preferably remission) has been achieved, and it lasts four to nine months to prevent relapse back into the major depressive episode. Maintenance phase treatment begins at the end of the combination phase and involves ongoing provision of care or active monitoring of symptoms to prevent recurrence of a new major depressive episode. In studies where the acute treatment is not followed by a period of continuation treatment, patients who experience subsequent major depressive episodes may be classified under the single outcome of relapse-recurrence. Combination treatment with psychotherapy and antidepressant medication can be initiated or continued at any of these three phases of treatment.

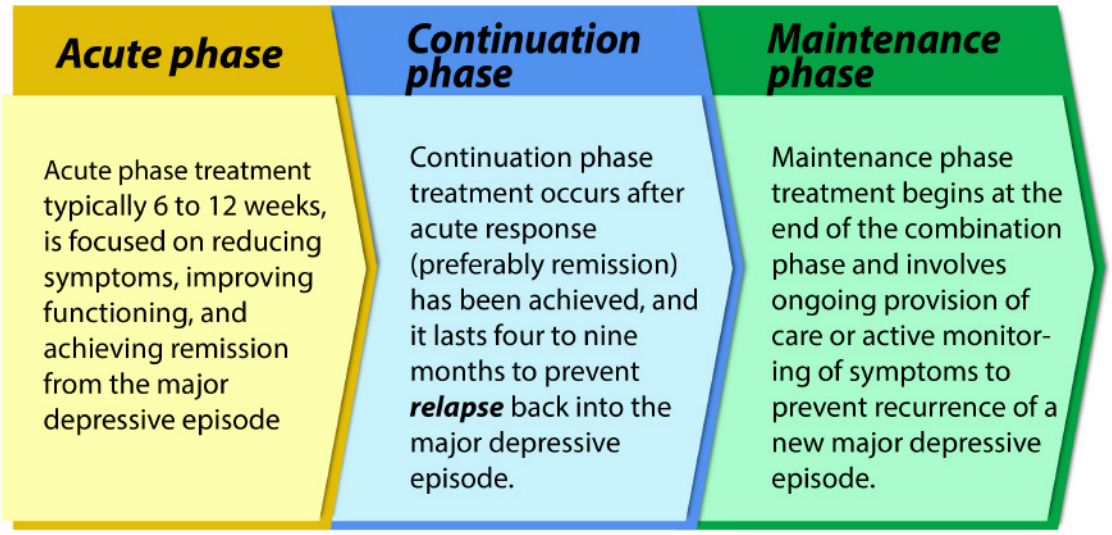

Figure 17 : Treatment of major depressive disorder in 3 phases

Benefits of Combination Treatment in Depression

Combination treatment during acute and continuation phases may increase the likelihood of achieving remission, shorten the time required to achieve remission, and enhance adherence to treatment. Potential maintenance phase benefits of combination treatment include reduced risk for depressive recurrence and improvements in role function and quality of life.

Meta-analyses have concluded that the combination of pharmacotherapy with psychotherapy produces small effect sizes for improvement over either modality alone. Meta-analyses of studies evaluating a broad array of patient samples have found similar small effect sizes in favor of combination treatment over pharmacotherapy alone. However, the summary conclusions provided by meta-analyses obscure the variability of effects across studies, which emerge from differences in design features, sample characteristics, and the type of psychotherapy or pharmacotherapy used. [44, Rank 4]

Challenges of Combination Treatment

Beyond the obvious issues of time and cost, perhaps the greatest challenge in providing combination treatment is communication between the psychotherapist and pharmacotherapist. Today, receiving both components of combination treatment by the same clinician occurs only in expensive private practice settings. More commonly the treatment components are split between two clinicians. The ideal of coordinated care between pharmacotherapist and psychotherapist is undermined by crowded schedules and lack of insurance reimbursement for the time required to coordinate treatment. Nevertheless, understanding of the patient's difficulties, appropriate goal-setting, treatment adherence, prevention of defensive splitting, and identification of comorbid psychiatric conditions and medication side effects are enhanced when treating clinicians communicate. Clinicians engaging in split treatment should prioritize communication with each other early in the acute treatment phase and periodically thereafter to maximize the benefits of combination treatment. [31, rank 3]

An important ongoing uncertainty about combination treatment is identifying

the optimal timing of delivery of the treatment components. In general practice, it is probably most often the case that patients receive a single modality of treatment initially, moving on to combination treatment only if they fail to achieve adequate benefit from the initial treatment. The main drawback of this sequential combination strategy is the delay in time to remission compared with combination provided at the beginning of treatment. Both treatment strategies, combination from initiation and combination sequentially, suffer from the uncertainty of knowing whether the patient's improvement is simply due to the effect of a single modality or whether the combination truly provides synergistic effects. This concern is most pronounced during the maintenance phase, when the question of treatment discontinuation arises. [9, Rank 5]

Treatments Used in Combination

Pharmacotherapy treatments used in studies of combination treatment may be a single antidepressant or a medication algorithm that allows switching or combining medications over the acute treatment phase. Antidepressant medication is typically provided via clinical management (CM) visits, typically 20- to 30-minute sessions involving education, support, encouragement of adherence, and monitoring for adverse events. Only a few combination trials have used placebo controls in the acute treatment phase. When the control arm of a combination study is treatment as usual, patients may not be required to take medication, the duration and class of pharmacotherapy are not limited, and the structure and frequency of visits with the prescribing clinician are not specified.

Psychotherapy treatments studied in combination trials have most often used a manual-based version of the evidence-based psychotherapies: cognitive-behavioral therapy (CBT), or its variants, or interpersonal therapy. Acute phase psychotherapy may be followed by less frequent continuation sessions of interpersonal therapy or CBT (continuation cognitive therapy) to solidify treatment gains and to reach recovery. Several trials have used versions of psychodynamic psychotherapy, which is currently not considered an evidence-based treatment for major depressive disorder. Few combination trials have used a comparator form of psychotherapy; when included, it has most often been a form of supportive therapy or education. Therapist experience and adherence to the treatment manual, as well as the number of sessions of therapy delivered, are major variables of concern across trials. [22, rank 5]

Figure 18 : Common depression treatments

Combination Treatment from Initiation of Care

Several large trials have compared the combination of antidepressant medication and psychotherapy from the beginning of treatment versus one or both of the components provided as a single-modality treatment. The greatest emphasis has been on assessing combination treatment among patients with chronic forms of depression because chronicity is often associated with poorer clinical outcomes. Results of these trials have been mixed, and conclusions about the value of combination treatment can only be tentative because of variations in design features across the trials.

Combination treatment may be superior to each component alone through either additive or synergistic effects. Additive effects simply reflect the possibility that certain patients can specifically respond to only one form of treatment (antidepressant medication or psychotherapy). In the synergistic model, benefits that can be obtained only when both treatments are present drive the greater benefit of combination treatment. For example, the relatively rapid antidepressant effects of medication may allow for greater patient engagement with the work of psychotherapy; alternatively, provision of psychotherapy may prevent dropout and may increase medication adherence compared with medication provided without psychotherapy. Furthermore, patients who experience only partial remission (i.e., obtain improvement but have residual symptoms) with one treatment may need the mechanisms activated by the alternative treatment to achieve full remission. [50, Rank 3]

Cognitive behavioural therapy (CBT) With Antidepressant Medication

The first study evaluating cognitive therapy combined with an antidepressant versus an antidepressant alone from the beginning of treatment found a large effect in favor of combination treatment among treatment completers, although the very poor response to the tricyclic antidepressants used and inconsistent effects across study sites presaged the challenges that would face

future studies of combination treatments. Also foreshadowing findings from subsequent studies, the two-year naturalistic follow-up of these patients found greater relapse-recurrence rates among patients treated with medication alone versus cognitive therapy. Subsequent small-to-moderate-sized studies generally found similar, although more modest, benefits for combination. [40, Rank 3]

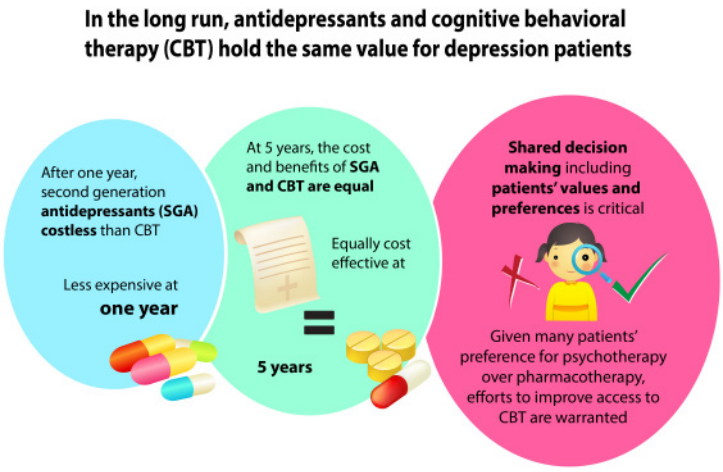

Figure 19 : Depression and combination therapy

Benefits of Acute-Phase Combination Treatment

Speed of response

A theorized benefit of combination treatment is that patients will recover more quickly than with a single treatment intervention, which may be particularly important for patients with strong suicidal ideation or severe role dysfunction. An early mega-analysis of studies that compared combining interpersonal therapy with medication versus psychotherapy alone (either interpersonal therapy or CBT) concluded that for patients with mild depression, time to sustained remission recovery did not differ; however, among patients with more severe depression, psychotherapy alone was significantly slower to generate a response compared with combination treatment Presumably, this paradoxical result arose from patient-level factors (e.g., severity, functioning, locus of control, comorbid conditions) that informed their treatment choices. [31, Rank 2]

Sequential Combination Treatments in the Acute Phase

Sequencing treatments requires initially selecting a single-modality treatment. Given that acute treatment with CBT or antidepressant medication is equally likely to be effective for most patients, the choice of treatment may be driven by patient preference and other practical factors. The specific form of any added second treatment will depend on the patient status at the end of monotherapy. Specifically, the second treatment can be designed to address a lack of response to the initial treatment (i.e., patient still in a full major depressive episode), residual symptoms after

improvement with initial treatment, or prevention of relapse and recurrence.

Despite the large number of studies examining sequential treatment of depression, the variety of designs used limits clear interpretation of the results. Some trials have compared an active second intervention, typically psychotherapy, with treatment as usual, in which patients may or may not adjust their mental health treatments on the basis of their preferences and clinician's recommendations. Treatment-as-usual designs are relatively easy to implement, but treatment as usual is a weak comparator arm for sequential treatment combination studies because a significant percentage of patients may not be receiving an active treatment of any kind. Moreover, treatment-as-usual comparisons carry a significant bias in favor of finding efficacy of the added treatment because of placebo responses. Specifically, because blinding of patients in such designs is not possible, patients randomly assigned to treatment as usual may experience demoralization effects of not getting the desired treatment, whereas those in the active condition have greater interaction with mental health professionals, with consequent mobilization of known placebo effects. [38, rank 5]

Sequential Combination to Address Residual Symptoms After Monotherapy

The importance of residual symptoms after acute treatment as a potent predictor of eventual return of full-syndrome major depressive episode is one of the most robust findings in depression research. Patients who improve after acute treatment but who have persisting subthreshold symptoms of major depressive disorder carry a significant risk of relapse and recurrence, whether the initial treatment was medication or CBT.

Combination Treatments to Prevent Relapse and Recurrence

Maintenance antidepressant medication has well-established superiority over placebo for preventing future depressive episodes among patients with recurrent major depressive disorder who have responded to acute and continuation phase medication, with reduction in absolute risk of recurrence by about 20% over 12–24 months Patients in remission who complete acute phase CBT alone demonstrate greater protection against recurrence than patients in remission who took acute phase antidepressant

medication if the medication discontinued during follow-up. In contrast, acute phase CBT is not significantly better in preventing recurrence if the acute phase antidepressant is continued during recovery. Despite the enduring effect of psychotherapy, relapse-recurrence rates of 40%–50% within two years of achieving remission occur among responders to acute CBT or medication if maintenance treatments are not instituted. Thus, continuation and maintenance treatments are indicated for patients with major depressive disorder at risk of recurrence, regardless of the form of beneficial acute treatment. [36, Rank 3]

Sequential addition of psychotherapy to prevent depressive relapse-recurrence after response to antidepressant medication has been the focus of many studies, all of which have evaluated CBT or its related variants. [20, Rank 2]

Future Directions

A potentially more affordable means of providing combination treatment is provision of psychotherapy via telephone or Internet. A large trial comparing telephone-administered CBT versus in-person CBT among primary care patients with major depressive disorder (only one third of whom were taking an antidepressant) found similar levels of short-term efficacy, but inferior benefits at six months posttreatment, among the patients who were treated with telephone-administered CBT. In contrast, a 12-week trial of patients with major depressive disorder started on open-label escitalopram (10–20 mg/day) who were randomly assigned from the beginning of treatment to receive either eight telephone-delivered CBT sessions or eight medication adherence reminder calls found no symptomatic benefit of the added CBT. Similarly, patients starting treatment with agomelatine who were randomly assigned to receive eight weeks of telephone delivery of either CM or social rhythm therapy showed no difference in outcomes between treatment arms. Thus, combination treatment of antidepressant medication with telephone-administered psychotherapy has yet to demonstrate efficacy over medication treatment alone.

Beyond Symptomatic Improvement

Beyond improvements in depressive symptoms and prevention of relapse-recurrence, combined treatments may have effects on quality of life and functioning that are of great value to patients. Although functioning and quality of life typically improve along with reduction in symptom burdens, treatments may have independent effects on these measures. Quality of life at end of treatment is modestly higher among

patients with chronic depression receiving combination treatment than patients receiving medication only, despite a relatively small effect size on depressive symptoms. Combining interpersonal therapy with antidepressant medication for five weeks during inpatient hospitalization produced higher levels of social adjustment one year after hospital discharge compared with medication treatment alone.

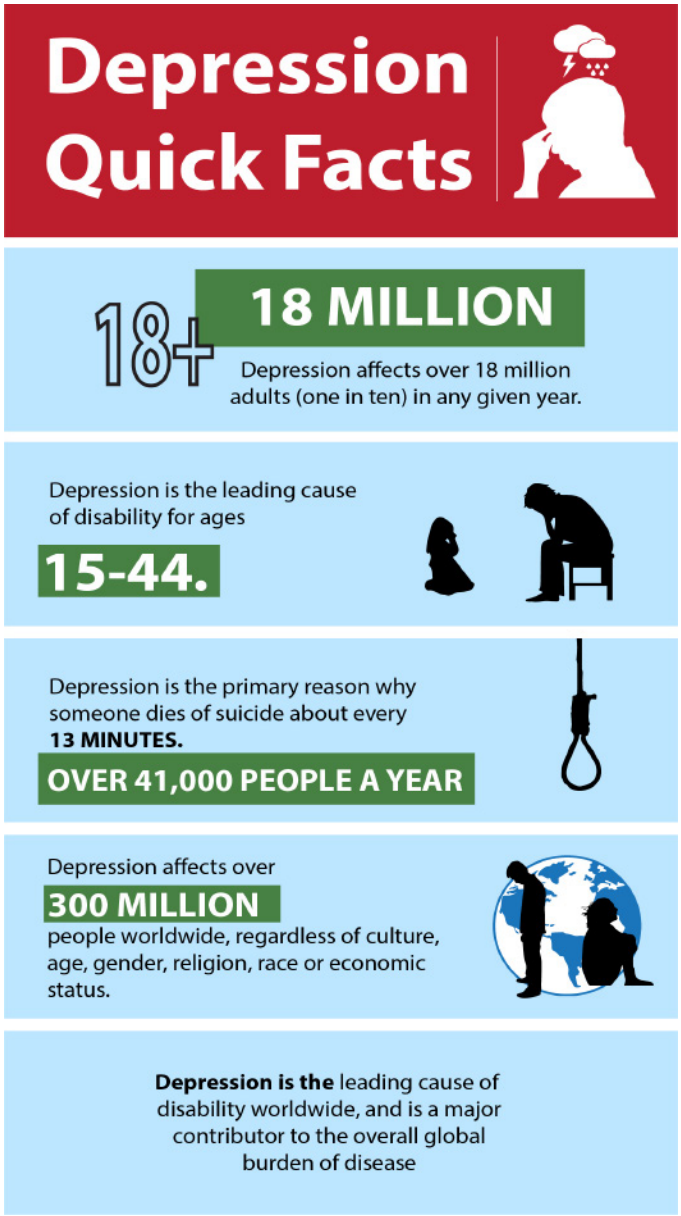

Figure 20 : Depression and facts

Conclusion

The current depression prevention programs reveal that the vast majority coincide in adopting a cognitive-behavioral approach, with contents including social skills and problem solving training, emotional education, cognitive restructuring, and strategies for coping with anxiety. These contents are probably included because they are important elements in the treatment of depression. But if their inclusion is important and effective in the treatment of depression, it is still a question as why they do not seem to be so effective in preventing this pathology. There are probably many factors linked to prevention programs which, in one way or another, influence their efficacy: who implements the program and what prior training they receive; the characteristics of the target group; group dynamics; how sessions are run; how the program is evaluated; and if the proposed goals are really attained (e.g., training in social skills may be key, but perhaps we are not training students correctly). Moreover, in universal prevention programs, the intervention focuses on students themselves rather than adopting a more holistic approach. It is commonly accepted that depression is multifactorial and that risk and protection factors may be found also in the family and social contexts' hence prevention is also multifactorial. [16, Rank 5]

***Important information for post-test are highlighted in red letters, boxes and diagrams.**

References

1. Diagnostic and Statistical Manual of Mental Disorders DSM-5, Fifth Edition. Arlington, Va: American Psychiatric Publishing; 2018

2. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), 4th Edition. Arlington, Va: American Psychiatric Association; 2017

3. Dredze M. How social media will change public health. IEEE Intell Syst. 2015

4. Eysenbach G. Infodemiology and infoveillance: framework for an emerging set of public health informatics methods to analyze search, communication and publication behavior on the Internet. J Med Internet Res. 2019

5. Chew C, Eysenbach G. Pandemics in the age of Twitter: content analysis of Tweets during the 2009 H1N1 outbreak. PLoS One. 2016

6. Paul MJ, Dredze M, Broniatowski D. PLoS Curr. 2017

7. Myslín M, Zhu S, Chapman W, Conway M. Using twitter to examine smoking behavior and perceptions of emerging tobacco products. J Med Internet Res. 2015

8. Hanson CL, Cannon B, Burton S, Giraud-Carrier C. An exploration of social circles and prescription drug abuse through Twitter. J Med Internet Res. 2015

9. Chen AT, Zhu S, Conway M. What online communities can tell us about electronic cigarettes and hookah use: a study using text mining and visualization techniques. J Med Internet Res. 2017

10. Conway M, O'Connor D. Social media, big data, and mental health: current advances and ethical implications. Curr Opin Psychol. 2016

11. Ritter A, Clark S, Mausam. Etzioni O. Named entity recognition in tweets: an experi-

mental study. Proceedings of the Conference on Empirical Methods on Natural Language Processing; July 27-31, 2017

12. Mikal J, Hurst S, Conway M. Ethical issues in using Twitter for population-level depression monitoring: a qualitative study. BMC Med Ethics. 2016

13. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. 2016

14. CDC. [2016-12-19]. Behavioral risk factor surveillance system survey data; 2008, 2009, 2012

15. Bloom D, Cafiero E, Jae-Llopis E, Abrahams-Gessel S, Bloom L, Fathima S, Feigl A, Gaziano T, Mowafi M, Pandya A, Prettner K, Rosenberg L, Seligman B, Stein A, Weinstein C. Hsph.harvard. 2016

16. Sanderson CL, Feng S, Cañar J, McGlinchey FM, Tercyak KP. Social and behavioral correlates of cigarette smoking among mid-Atlantic Latino primary care patients. Cancer Epidemiol Biomarkers Prev. 2015

17. Witkiewitz K, Villarroel NA. Dynamic association between negative affect and alcohol lapses following alcohol treatment. J Consult Clin Psychol. 2015

18. Ten Hacken NH. Physical inactivity and obesity: relation to asthma and chronic obstructive pulmonary disease? Proc Am Thorac Soc. 2019

19. Coulombe JA, Reid GJ, Boyle MH, Racine Y. Sleep problems, tiredness, and psychological symptoms among healthy adolescents. J Pediatr Psychol. 2015

20. De Choudhury M, Counts S, Horvitz E. Social media as a measurement tool of depression in populations. Proceedings of the 5th Annual ACM Web Science Conference; May 2-4, 2015

21. De Choudhury M, Gamon M, Counts S, Horvitz E. Predicting depression via social media. Proceedings of the 7th International Association for the Advancement of Artificial Intelligence Conference on Weblogs and Social Media; June 8-10, 2016

22. Schwartz HA, Eichstaedt J, Kern ML, Park G, Sap M, Stillwell D, Kosinski M, Ungar L. Towards assessing changes in degree of depression through Facebook. Proceedings of the Workshop on Computational Linguistics and Clinical Psychology: From Linguistic Signal to Clinical Reality; June 27, 2015

23. Tausczik Y, Pennebaker JW. The psychological meaning of words: LIWC and computerized text analysis methods. J Lang Soc Psychol. 2017

24. Coppersmith G, Dredze M, Harman C. Quantifying mental health signals in Twitter. Proceedings of the Workshop on Computational Linguistics and Clinical Psychology: From Linguistic Signal to Clinical Reality; June 27, 2015

25. Coppersmith G, Dredze M, Harman C, Hollingshead K. From ADHD to SAD: analyzing the language of mental health on Twitter through self-reported diagnoses. Proceeding of 2nd Workshop on Computational Linguistics and Clinical Psychology: From Linguistic Signal to Clinical Reality; June 5, 2016

26. Preotiuc-Pietro D, Eichstaedt J, Park G, Sap M, Smith L, Tobolsky V, Schwartz A, Ungar L. The role of personality, age, and gender in tweeting about mental illness. Proceeding of 2nd Workshop on Computational Linguistics and Clinical Psychology: From Linguistic Signal to Clinical Reality; June 5, 2015

27. Baer L, Jacobs D, Meszler-Reizes J, Blais M, Fava M, Kessler R, Magruder K, Murphy J, Kopans B, Cukor P, Leahy L, O'Laghlen J. Development of a brief screening instrument: the HANDS. Psychother Psychosom. 2016

28. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2018

29. Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, Markowitz JC, Ninan PT, Kornstein S, Manber R, Thase ME, Kocsis JH, Keller MB. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol Psychiatry. 2017

30. Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, Currier GW, Melvin GA, Greenhill L, Shen S, Mann JJ. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2017

31. Mowery D, Bryan C, Conway M. Toward developing an annotation scheme for depressive disorder symptoms: a preliminary study using Twitter data. Proceeding of 2nd Workshop on Computational Linguistics and Clinical Psychology; From Linguistic Signal to Clinical Reality. Association for Computational Linguistics; June 5, 2015; Denver, Colorado. 2015

32. Coppersmith G, Dredze M, Harman C, Hollingshead K, Mitchell M. CLPsych 2015 shared task: depression and PTSD on Twitter. Proceedings of the 2nd Workshop on Computational Linguistics and Clinical Psychology; From Linguistic Signal to Clinical Reality; June 5, 2015

33. Hripcsak G, Rothschild AS. Agreement, the f-measure, and reliability in information retrieval. J Am Med Inform Assoc. 2015

34. Witten I, Frank E, Hall M. Data Mining: Practical Machine Learning Tools and Techniques. 3rd ed. Boston, Masschusetts: Morgan Kaufmann Publishers; 2018

35. Conway M. Mining a corpus of biographical texts using keywords. Literary and Linguistic Computing. 2016

36. Yang Y, Pedersen J. A comparative study on feature selection in text categorization. Proceedings of the Fourteenth Annual Conference on Machine Learning; 2017

37. Cohen J. A power primer. Psychol Bull. 2018

38. Landis J, Koch G. The measurement of observer agreement for categorical data. Biometrics. 2017

39. Mowery D, Smith H, Cheney T, Bryan C, Conway M. Identifying depression-related tweets from Twitter public health monitoring. Open J Public Health Inform. 2016

40. Cavazos-Rehg PA, Krauss MJ, Sowles S, Connolly S, Rosas C, Bharadwaj M, Bierut LJ. A content analysis of depression-related Tweets. Comput Human Behav. 2016

41. Mowery D, Park A, Bryan C, Conway M. Towards automatically classifying depressive symptoms from Twitter data for population health. Proceedings of the Workshop on Computational Modeling of People's Opinions, Personality, and Emotions in Social Media; December 12, 2016

42. Mowery D, Bryan C, Conway M. Feature studies to inform the classification of depressive symptoms from Twitter data for population health. Proceedings of the WSDM 2017 Workshop on Mining Online Health Reports; February 10, 2017

43. Fields C, Drye L, Vaidya V, et al. Celecoxib or naproxen treatment does not benefit depressive symptoms in persons aged 70 and over: findings from a randomized controlled trial. Am J Geriatr Psychiatry 2018

44. Frick LR, Williams K, Pittenger C. (2013) Microglial dysregulation in psychiatric disease. Clin Dev Immunol 2016

45. Friedman A. Jump-starting natural resilience reverses stress susceptibility. Science 346: 2017

46. Funk C, FitzGerald G. COX-2 inhibitors and cardiovascular risk. J Cardiovasc Pharm 2019

47. Gałecki P, Gałecka E, Maes M, et al. The expression of genes encoding for COX-2, MPO, iNOS, and sPLA2-IIA in patients with recurrent depressive disorder. J Affect Disorders 2017

48. Guillemin GJ. Quinolinic acid, the inescapable neurotoxin. FEBS J 279: 2018

49. Guloksuz S, Rutten BPF, Arts B, et al. The immune system and electroconvulsive therapy for depression. 2017

50. Guo J-Y, Li C-Y, Ruan Y-P, et al. Chronic treatment with celecoxib reverses chronic unpredictable stress-induced depressive-like behavior via reducing cyclooxygenase-2 expression in rat brain. Eur J Pharmacol 2019