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Review Article

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Major Depression Research: A Narrative Review

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Abstract

Major depression is one of the most common mental disorders. This narrative review summarizes research on major depression that was published this year (2024). This current research has focused on negative effects of major depression, predictors/risk factors, potential underlying biological mechanisms and interventions. The negative effects have included anxious distress, pain, sleep disorders, touch aversion, hoarding and global functioning problems even after remission. The predictors/risk factors have included female gender, early onset age and hospitalization, accelerated aging, sleep disorders, anhedonia and lipid dysregulation. Psychological interventions have been exclusively focused on cognitive behavioral therapy. Physical interventions have included electroconvulsive therapy, vagal nerve stimulation, acupressure, exercise, and dietary interventions. Pharmacological interventions have included escitalopram, duloxetine, and ketamine. Potential underlying biological mechanisms have included tryptophan metabolism dysfunction, inflammation, cytokines, polygenic risk, orbito- frontal cortex involvement, connectivity dysfunction, and reductions in cortical thickness, white matter and gray matter. Although this research has been informative, most of the current publications are systematic reviews and meta-analyses rather than empirical studies. In addition, the Patient Health Questionnaire-9 rather than a DSM-5 diagnosis following a structured clinical interview has frequently been used to identify those with major depression.

1. Introduction

Major depression (also called major depressive disorder) is the most commonly diagnosed mental disorder in clinical practice, affecting more than 350 million globally [1]. Thirty million is the estimated prevalence in Europe, and 20% of people in the U.S. have reported lifetime symptoms [2]. Major depression has been defined as a mental health disorder characterized by persistently depressed mood or loss of interest in activities causing significant impairment in daily life including a range of behavioral and physical symptoms. These may include changes in sleep, appetite, energy level, concentration, daily behavior, self-esteem and suicidal thoughts.

The various aspects of major depression have been identified in three diverse longitudinal datasets on patients with major depression (N= 1483) [3]. The Patient Health Questionnaire – 9 was the standard screening tool for measuring and tracking the symptoms of depression. The scale was factor-analyzed and yielded four factors based on the 9 items of the scale including: 1) Affective (anhedonia and depressed mood); 2) Somatic (Sleep, fatigue and appetite); 3) Internalizing (Worth/Guilt and suicidality); and 4) Sensorimotor (Concentration and psychomotor). Evidence-based therapies have included cognitive behavioral therapy and medications including serotonin reuptake inhibitors.

2. Methodology

This narrative review includes summaries of 42 papers on major depression in adults that were derived from a search on PubMed and PsycINFO entering the terms major depression and the year 2024. Exclusion criteria for this review included papers on proposed protocols, case studies, and non-English language papers. The publications can be categorized as negative effects of major depression, predictors/risk factors, potential underlying biological mechanisms and interventions for major depression. This review is accordingly divided into sections that correspond to those categories. Although some papers can be grouped in more than one category, 7 papers are focused on the negative effects of major depression, 7 on predictors/risk factors, 13 on potential underlying biological mechanisms for major depression and 18 on interventions. These sections are followed by a discussion on methodological limitations of this literature.

3. Negative Effects of Major Depression

Several negative effects have been noted for major depression in this current literature. They include anxious distress, pain, sleep disturbance, touch aversion, hoarding and disturbed global functioning even after full or partial remission.

3.1 Anxious Distress

In a study entitled "Anxious distress in people with major depressive

episodes", two-thirds of the sample with major depression (N= 200) had anxious distress [4]. These findings were not surprising given that anxiety Is frequently comorbid with depression. The authors may have used the term anxious distress to distinguish anxious behavior from a diagnosis of generalized anxiety disorder. It is surprising that anxiety disorder did not appear in this current literature given the frequent comorbidity of depression and anxiety disorders.

3.2 Pain

Pain has been the focus of at least two studies in this current literature on major depression. In research entitled "Changes in pain during a depressive episode", three fourths of the sample (N = 50 patients with major depression) experienced pain, and pain and depression were significantly correlated.

Pain has also been the focus of a systematic review and meta-analysis that included 20 studies [5]. In six of the 20 studies greater baseline pain was reported by those who were nonresponsive to treatment. In six other studies pain was significantly associated with poor treatment response. In five studies greater pain interference levels were reported by non-responders. In four studies greater baseline pain was reported by non-remitters and in eight studies pain was associated with treatment – non-remission.

The directionality of pain and depression is not clear in these cross-sectional studies. Pain and depression may be reciprocal problems. Pain might be expected to cause depression and depression exacerbate pain.

3.3 Sleep Disturbances

Sleep disturbances have been viewed as both negative effects and risk factors of major depression in this current literature, again highlighting the reciprocal nature of these conditions. Major depression may contribute to sleep disturbances just as sleep disturbances may contribute to major depression. In a systematic review and meta-analysis entitled "Actigraphic monitoring of sleep and circadian rest – activity rhythms", 53 studies were included (N=11,115 participants) [6]. Longer sleep latency and longer awake time after sleep onset were consistently noted. In addition, lower sleep efficiency and more night wakings were reported. These sleep disturbances may derive from the participants engaging in less daytime activity just as sleep disturbances may contribute to less daytime activity.

3.4 Touch Aversion

In a paper entitled "Altered reward network responses to social touch in major depression", fMRIs were conducted during social touch (N= 53 depressed participants and 41 healthy controls) [7]. Only 43% of the depressed individuals were responders to treatment, suggesting severe depression in this sample. More aversion to interpersonal touch and more discomfort with the fMRIs were noted in the depressed participants. Aversion to social touch has been noted in individuals with mental health problems including depression and post-traumatic stress disorder, but, surprisingly, massage therapy has reduced symptoms of depression and PTSD [8].

3.5 Hoarding Disorder

In a study that was focused on major depression and hoarding disorder (N =73 adults with late life depression and 580 with major depression disorder/lifetime), hoarding disorder was present in 12–33% of those with major depression disorder (Nutley et al, 2024). This was considered a comorbid disorder by the authors, although causality or directionality could not be determined in this cross-sectional study.

3.6 Global Functioning Problems After Remission

In a systematic review and meta-analysis on 42 databases (N=17,999 with major depression and 35,550 healthy control participants), global functioning problems were noted in those with major depressive disorder versus the healthy control participants [9]. These were reported by individuals even after they had experienced partial or total remission. Interventions may need to be focused on reducing global functioning problems as well as depressive symptoms, as disturbances in global functioning would enhance depression.

4. Predictors/Risk Factors for Major Depression

Several predictors/risk factors have been the focus of studies in this current literature on major depression. They include female gender, early age of onset and hospitalization for depression, accelerated aging, few circadian activities, sleep disturbances, and lipid dysregulation.

4.1 Female Gender

Female gender was implicated in the inflammation – depression link in a systematic review and meta-analysis on 23 studies [10]. In this meta-analysis, females with major depression had higher C-reactive protein (CRP) and higher IL-6 levels (both pro-inflammatory cytokines). No gender differences were noted on TNF-alpha (another pro-inflammatory cytokine), although TNF-alpha is usually elevated along with CRP and IL-6 as a trio of pro-inflammatory cytokines. The inflammation/depression link has been noted in several studies. Whether depression results in inflammation or inflammation is an underlying mechanism for depression is not clear as most of the literature is comprised of cross-sectional, not longitudinal data.

4.2 Age of Depression Onset

Age of depression onset and hospitalization were notable risk factors for major depression in a six- year retrospective cohort study (N= 6113) [11]. Higher risk for severe depression was noted in an adolescent onset group who had a longer hospital stay. These risk factors were associated with a greater risk of two or more relapse hospitalizations within one year. Depression in adolescents, and even in children, has become more prevalent reputedly related to social media and upward comparisons as well as cyberbullying [12]. At the same time, it may be more widely reported.

4.3 Accelerated Aging

In a study entitled "Mediating role of accelerated aging in the association between depression and mortality risk: findings from NHANES", a sample from the National Health and Nutrition

Examination Survey was assessed (N= 12,761, mean age = 47 years) [13]. Seven percent of this sample were experiencing depression based on a score of greater than 10 on the PHQ-9 scale. Age acceleration was based on phenotypic age (a measure of a person's biological age based on their physical characteristics and blood markers). Over an 11-year follow-up period, major depression was associated with an increase in all-cause mortality and cardiovascular mortality that was mediated by accelerated aging. Phenotypic age may not be related to chronological age, as older age adults reputedly experience less depression than middle-age adults (those sampled in this study) [14]. And, these results may be related to the sample averaging 47 at close to the age of a significant increase in depression (40 years), possibly related to the noted "midlife crisis".

4.4 Less Circadian Activity

In a three – day actigraphy study, major depression was associated with less circadian activity (mental, behavioral and physical changes) (N = 83) [15]. Fewer activities were also associated with greater suicidal ideation. These data are not surprising given that physical inactivity has been associated with depression and lower serotonin levels (antidepressant neurotransmitter) and physical activity /exercise has been noted to boost serotonin levels [16].

4.5 Sleep Disturbances

In a polysomnographic study on patients with major depression and insomnia (N= 30), two nights of sleep were recorded [17]. Sleep duration and depth of sleep were positively correlated with cognitive function which was not surprising as sleep is critical for alertness and attention and, in turn, for effective cognitive functioning.

4.6 Anhedonia

In a paper entitled "Effects of anhedonia on health-related quality of life and functional outcomes in major depression disorder: a systematic review and meta- analysis", 20 studies were included in the meta-analysis [18]. Not surprisingly, those individuals who had major depression disorder plus anhedonia had worse prognoses. That grouping of major depression disorder plus anhedonia was surprising given that anhedonia is a primary symptom for the diagnosis of major depression.

4.7 Lipid Dysregulation

In another subsample from the NHANES longitudinal study (N= 526), depression and cognition were associated with lipid dysregulation [19]. The protective effect of HDL (high density lipoprotein) on cognition was absent in those individuals with major depression. This relationship was not surprising as several other significant relationships were reported for the NHANES study, for example accelerated aging and depression.

5. Potential Underlying Biological Mechanisms for Major Depression

Several different but interrelated potential underlying biological mechanisms have been suggested for major depression. They include impairments in tryptophan metabolism, inflammation/ increased cytokines, polygenic risk, connectivity problems in the orbito-frontal cortex, reduction in cortical thickness as well as reduced white matter and gray matter.

5.1 Impaired Tryptophan Metabolism

Impairments have been noted in tryptophan metabolism in individuals with major depression (the major pathway for the synthesis of serotonin, the mood regulating neurotransmitter) [20]. In this model, the impaired tryptophan metabolism leads to oxidative stress, neuroinflammation and neurotoxicity. The authors suggested that protection against depression could be provided by protein, tryptophan (in foods like nuts and fish and in supplements), antioxidants, and flavonoids (foods that have antioxidant and anti-inflammatory properties).

5.2 Inflammatory Disease

In another model depression is viewed as an inflammatory disease [21]. Treatment resistant depression is often associated with elevated levels of pro-inflammatory cytokines. According to these authors this occurs in 25% of patients with depression. They suggested that "educated immune cells reach the border regions of the central nervous system, which modulates the immune response via efferent parts of the vagus nerve". They concluded that depression is reduced by therapeutic stimulation of the vagus nerve. This view is consistent with the data reported earlier on positive effects of vagus nerve stimulation modulating inflammation in patients with treatment resistant depression [22].

5.3 Pro-inflammatory Cytokines

The specific pro-inflammatory cytokines that have been implicated in depression are C-reactive protein, IL – 6 and TNF – alpha. As already noted in a systematic review and meta-analysis of 23 studies, females versus males with depression had two times the levels of C-reactive protein and IL – 6, although no gender differences were noted on TNF – alpha [10]. In at least one other study, TNF-alpha has been elevated in major depression [23]. In their analysis, TNF-alpha was negatively correlated with processing speed in those individuals with major depression. Processing speed is notably slow in those individuals with depression, but several other cognitive functioning variables are also related to depression. As in many of these studies, researchers have seemingly selected variables of interest and focused on them as opposed to conducting regression or structural equations analyses to determine the relative significance of more than one variable.

5.4 Less Reward Sensitivity in the Medial Orbitofrontal Cortex

In still another model on depression, the roles of the medial and lateral orbito-frontal cortex in major depression have been discussed [24]. In this model, the reward – related medial orbitofrontal cortex has less reward sensitivity that has been associated with anhedonia symptoms in major depression. The authors suggested that ketamine might target this area of the brain. In contrast, non-reward related lateral orbito-frontal cortex has more sensitivity to aversive stimuli and is associated with negative bias symptoms. They suggest that antidepressants might target this area of the brain. The relative contributions of reward insensitivity

and responsivity to non-reward stimuli in the different areas of the orbito-frontal cortex have not been assessed.

5.5 Reduced Functional Connectivity

In a study on functional connectivity between different parts of the brain, a sample of depressed inpatients (N= 30) were compared to healthy control individuals (N.=30) [25]. Decreased functional connectivity was noted between the insula cortex and frontal and occipital cortical brain regions in those with major depression. In contrast, in the same group of individuals, increased functional connectivity was noted between the medial prefrontal cortex and the insula cortex. These opposite directions in functional connectivity in related regions of the brain are complex and difficult to interpret.

5.6 Reduced Cortical Thickness

Less cortical thickness has been noted in individuals with depression. For example, in a comparison between depressed individuals (N= 110) and healthy control individuals (N=88) reduced cortical thickness was noted in the frontal parietal and the default networks (Gheng et al, 2024). The lower cortical thickness probably resulted from less functional connectivity although the developmental trajectory of these effects of depression have not been assessed in the same study given the cross-sectional rather than the longitudinal sampling of the data.

5.7 White Matter Tract Abnormalities

White matter tract integrity has been reduced in depression and in individuals with genetic liability to depression [26]. This was noted in the UK Bio Bank Imaging Cohort (N= 19,183) on depressed individuals and those with liability for depression quantified by polygenic scores.

5.8 Gray Matter Reduction

In another sample of MRIs scanned for the UK Bio Bank (N= 2682 participants), contributions of polygenic risk and disease status were noted for gray matter abnormalities in major depression [27]. In this sample, females with current depression had gray matter reductions in ventral and medial prefrontal, insular and medial temporal regions. Elevated polygenic risk for depression in women, but not men, was associated with reduced cerebellar gray matter volume. This, in turn, was associated with poor performance on tests of attention and executive function. The association with gray matter volume for women but not for men was likely related to the greater depression symptoms noted for women. Again, it's not clear if the depression resulted in the gray matter volume reduction or the reverse. Directionality cannot be determined form these cross-sectional data.

6. Interventions for Major Depression

Several intervention studies have appeared in this current literature on major depression. They include psychological, physical and pharmacological interventions.

6.1 Psychological Interventions

Cognitive Behavioral Therapy: Most of the psychological intervention studies as well as the systematic reviews and meta-analyses have involved CBT (cognitive behavioral therapy). That therapy has been studied in its traditional in-person form, in a form that was developed for comorbid depression and insomnia (CBT-I) and in an internet-delivered form. A study has also appeared in this literature that compared CBT with psychodynamic therapy (PDT). CBT has continued to be considered one of the most effective psychological therapies for major depression.

In a randomized controlled trial comparing CBT and CBT plus CBT-I for depression, insomnia and comorbid depression and insomnia, these therapies were offered for 3-months, and a 6-month follow-up assessment was conducted (N=126) [28]. CBT plus CBT-I was more effective for insomnia, but not for depression. The authors concluded that CBT–I alone should be offered for individuals with comorbid depression and insomnia. The results of this randomized controlled trial were supported by the findings of a systematic review and meta-analysis (Furukawa et al, 2024). In this meta-analysis on 19 trials (N=4808 participants) CBT – I was an effective treatment for comorbid depression and insomnia. Cognitive behavioral therapy for insomnia has also been offered over the Internet. In a study entitled "Digital CBT for patients with insomnia and depression", a systematic review and meta-analysis were conducted on seven articles (N= 1864 participants) [29]. The internet therapy reduced the severity of depression and insomnia. The post-intervention effects were said to be related to the duration of treatment and the severity of insomnia prior to the treatment.

CBT has also been compared to other forms of psychotherapy, including psychodynamic therapy (PDT). In research that compared CBT and PDT, both treatments reduced self-criticism and sociotropy (a personality trait characterized by excessive investment in interpersonal relationships) [30]. The reduction in self-criticism and sociotropy were associated with better outcomes for the CBT group. In addition, depression scores were decreased in the CBT group.

6.2 Physical Interventions

Several physical interventions have appeared in this literature on major depression. These include electroconvulsive therapy, vagal nerve stimulation, acupressure, exercise and nutritional therapy.

Electroconvulsive Therapy: In a study entitled "Changed brain entropy and functional connectivity ", individuals with major depression disorder and healthy control participants were compared (N= 84) [31]. Greater resting state functional connectivity occurred following electroconvulsive therapy (ECT) and greater brain entropy (complexity) was noted in the right precuneus and the right angular gyrus of the brain. Greater complexity likely also occurred in other related regions, although researchers often focus on their areas of interest.

In another ECT study entitled "Characterization of gray matter volume changes from one week to six months after termination of ECT", increased gray matter was noted one week after the treatment [32]. However, a decrease in gray matter volume was noted six months after the treatment and no differences were noted

between the baseline and the follow-up values at six months. These data suggested that the ECT had a transient neurological effect which was not surprising given that the treatment was short-lived. However, it was surprising that the neurological effect was not related to a reduction in depression scores.

Still another research group found a similar increase in gray matter volume following ECT with a decrease occurring two years later, suggesting again a transient neurological effect [33]. A greater decrease in gray matter volume was associated with poorer long-term outcome in those with major depression.

Vagal Nerve Stimulation: In another type of physical intervention for major depression, vagal nerve stimulation was given to six patients with refractory depression (a form of major depressive disorder that is not responsive to at least two antidepressants) [22]. A response rate of 87% was noted and depression severity was decreased by 60%. Anxiety levels also decreased as well as inflammation biomarkers, suggesting that vagal nerve stimulation may enhance immune function. Elevated vagal activity is accompanied by a decrease in cortisol which may underly the decrease in inflammation biomarkers and enhanced immune function [34].

Acupressure: In a systematic review and analysis of 19 randomized control trials on acupressure for depression (N=86 participants), the decrease in severity of depression was consistently noted to have a moderate effect size [35]. These data were derived from the Hamilton Depression Scale, the Self-Rating Depression Scale, and the Geriatric Depression Scale. The mechanism for these effects may be similar to that of massage therapy. The stimulation of pressure receptors under the skin leads to an increase in serotonin (the antidepressant neurotransmitter) [36].

Exercise: Exercise has also been an effective therapy in at least three studies in this literature. Like acupressure and massage therapy, exercise involves stimulation of pressure receptors under the skin which would lead to increased serotonin levels and lower depression [36].

In one of the studies entitled "Feasibility and preliminary efficacy of a theory – informed resistance exercise training", 10 individuals with DSM-five diagnosed major depression were given resistance training exercises to be practiced twice per day for 16 weeks [37]. Assessments occurred at baseline, eight, 16 and 26 weeks. The rates were reported at 98% for adherence, 93% for compliance and 90% for retention. Remission occurred in eight of the nine participants at 16 and 20 weeks. Large decreases in clinician-rated and self-reported symptoms occurred at each assessment. In addition, a small to moderate increase occurred in middle cerebral artery velocity and conductance.

In another exercise study, 40 individuals with major depression were randomly assigned to an aerobic exercise or an “aerobic exercise with motor complexity” group [38]. The training occurred for 60 minutes two times per week for 24 weeks. Both groups experienced reduced hopelessness and increased affective responses. In addition, the aerobic exercise group showed increased volumes in the amygdala, thalamus and left nucleus accumbens. Changes in the right amygdala explained 72% of the changes in affective responses.

In a study entitled "The relationship between BDNF (brain derived neurotrophic factor) and physical activity on depression", 13 studies were included in a systematic review and meta-analysis [39]. Depression scores decreased, and physical activity was related to BDNF (a protein in the brain that helps nerve cells survive, grow and mature). However, the authors suggested that there was a need for more homogeneous and standardized criteria for the studies that were included in their analysis.

Nutritional Therapy: At least one study on nutritional therapy has demonstrated that a low carbohydrate diet was a good intervention for depression [40]. These authors elaborated on BDNF (brain derived neurotrophic factor) being a target of sugar restriction diets in terms of neuroplasticity.

6.3 Pharmacological Interventions

Surprisingly, only a few papers appeared in this literature on pharmacological interventions. Those included studies on escitalopram, duloxetine and ketamine.

Escitalopram and Duloxetine: In a paper on rumination in patients with major depression disorder (N=92), duloxetine (a serotonin-norepinephrine inhibitor) was given if there was no response to escitalopram (a serotonin release inhibitor) [41]. Rumination decreased at four, eight and 12 weeks after the antidepressant treatment. However, these results are inconclusive as the study lacked a placebo control group.

Ketamine: In research that tested the cognitive safety of ketamine, no difference was noted between ketamine and midazolam on cognitive outcomes [42]. Cognitive safety has been defined as the ability to perceive, process, understand and store information, make decisions and respond appropriately. Although the authors concluded that ketamine was cognitively safe, the results were confounded by the two groups having received different doses of the medications.

In a systematic review and meta-analysis of six randomized controlled trials that were conducted with depressed adults (N=655 inpatients), ketamine was compared with ECT (electroconvulsive therapy) [43]. ECT Led to lower depression scores while ketamine led to higher cognitive scores and less muscle pain. ECT also led to a greater change in depression scores as well as remission.

7. Methodological Limitations of this Literature

This recent literature on major depression has methodological limitations that include the variety of sampling methods, the different measures of depression and the data analysis methods used by the different researchers. The samples have varied by being either diagnosed with major depression disorder or having self-reported symptoms of depression and having been in-patients

or survey samples. Those groups have not been compared, and individuals within those groups have not been compared by severity level. Chronicity of the disorder would also be expected to have different effects, but chronicity was not typically assessed. Further, the developmental course of major depression was rarely explored in longitudinal studies, as most of the research in this current literature is cross-sectional.

Demographic factors like age and gender were rarely reported. Age differences might be expected on the severity of depression, and early onset of depression was a risk factor in one study. Gender differences were noted in a few studies with females having more severe depression or more frequently experiencing depression. This was often attributed to females experiencing comorbid anxiety. Surprisingly, the comorbidity of depression and anxiety was rarely mentioned.

Surprisingly, only seven studies focused on negative effects of major depression and only seven studies focused on risk factors. At least one of the negative effects, namely sleep disturbance, was also treated as a risk factor, raising the question of directionality. Most of the studies have been cross-sectional rather than longitudinal, suggesting that the directionality of the risk factors and negative effects could not be determined.

The research on potential underlying biological mechanisms highlights many neurological problems including neuroinflammation, connectivity problems and reductions in cortical thickness, gray and white matter. These were typically interpreted as causal factors or at least contributory to major depression. These problems could have also resulted from major depression. Again, directionality cannot be determined from the typically cross-sectional studies. Gene studies were not found, although they have been, for example, in the recent literature on the related post-traumatic stress disorder [44].

Many of the intervention studies were systematic reviews and meta-analyses of the most frequently used and most effective therapies for major depression. These included meta-analyses of cognitive behavioral therapy studies, and pharmacology studies. The studies on cognitive behavioral therapy would have been more informative if they had compared the specific CBT techniques. Surprisingly, only a few pharmacology studies appeared in this literature, two of which focused on ketamine but without a placebo group. Both the psychological and pharmacological studies measured the change in symptoms of major depression, but not the remission of major depression which would be the ultimate measure of a treatment's effectiveness [45-48].

8. Conclusion

Despite these methodological limitations, this literature has highlighted the severity of major depression. The relative absence of recent research on the negative effects and risk factors for major depression highlights the need for longitudinal studies on individuals experiencing major depression. Further research on predictors/risk factors would seemingly help identify those who may need therapy. Future research is also needed to specify the relative significance of the predictors/risk factor variables for identifying those who need intervention and the specific intervention techniques that are effective in reducing major depression. Nonetheless, these data are informative and will help advance the field of clinical research on major depression.

Negative Effects	First Authors
Anxious distress	Bartoli
Pain	Liu
Sleep disturbances	Ho, Mielacher
Hoarding disorder	Nutley
Global functioning problems	Schwarz

Table 1: Negative Effects of Major Depression (and First Authors)

Predictor/Risk Factors	First Authors
Female gender	Jarkas,
Young age of depression onset	Yao
Accelerated aging	Xu
Less circadian activity	Salvatore
Sleep disturbances	Olivera- Lopez
Anhedonia	Wong
Lipid dysregulation	Mehdi

Table 2: Negative Effects of Major Depression (and First Authors)

Mechanisms	First Authors
Impaired tryptophan metabolism	Pearson
Inflammatory disease	Steffen
Pro-inflammatory cytokines (C-reactive protein and IL-6)	Jarkas
TNF-alpha	Finkenflugel
Less reward sensitivity	Zhang
Reduced functional connectivity	Blickle
Reduced cortical thickness	Gheng
White matter tract abnormalities	Nothdurfter
Gray matter reduction	Kampe

Table 3: Potential Underlying Biological Mechanisms for Major Depression (and First Authors)

Psychological Interventions	First Authors
Cognitive behavioral intervention for depression and insomnia (CBT-I)	Blom, Furukawa
CBT-I on internet	Bai
CBT vs. Psychodynamic therapy (PDT)	Norman
Physical Interventions	
Electroconvulsive therapy (ECT)	Fan, Laroy, Bergers
Vagal nerve stimulation	Lesperance
Acupressure	Li
Exercise	Aloreia-Neto, Zarza-Rebollo, Meyer
Nutritional therapy	Walaszek
Pharmacological Interventions	
Escitalopram or duloxetine	Segerberg
Ketamine	Martin, Petrucci

Table 4: Psychological, Physical and Pharmacological Interventions for Major Depression (and First Authors)

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