Recovery-Oriented Treatments in Major Depressive Disorder

14

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14.1 Toward a Recovery-Oriented Model of Major Depression

Major depressive disorder (MDD) is a common, often chronic, and recurring severe mental disorder affecting more than 264 million people worldwide [1, 2]. By the year 2030, MDD is expected to be the leading cause of diseases burden around the world, accounting now for 2.5% of global disability-adjusted life years lost (DALYs). It is estimated that about 30 million of people suffer from MDD in Europe, and that one in five US adults reports symptoms of depression in the lifetime [3]. MDD is associated with a very high mortality risk, mainly due to suicide and physical diseases such as cardiovascular diseases (CVD).

Historically, major depression has been considered an affective syndrome only, and until 1980s no attention was paid to other symptom clusters. At that time, clinicians had to distinguish between endogenous vs. exogenous depression, with the former being basically considered a biological disorder (and therefore being responsive to pharmacological treatment) and the latter being due to external causes (and therefore being sensible to psychotherapies). The reality is much different, and several biological, clinical, and social studies have found that MDD should be conceptualized as a systemic syndrome characterized by different affective, physical, and cognitive symptom domains, and that immune, neuroendocrine, and inflammatory systems are involved in the pathogenesis of the disorder [4, 5]. This theory has led to the discovery of a third generation of antidepressant agents that act at different levels, and to the conceptualization of full functional recovery as

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the final aim of treatment of MDD patients. In fact, while in the past the aim of therapy was response (i.e., reduction of symptoms' severity by, e.g., ≥50% assessed by Montgomery–Åsberg Depression Rating Scale - MADRS or Hamilton Rating Scale for Depression - HAM-D scale) or remission (i.e., defined as MADRS score of ≤10 or HAM-D17 score ≤7), more recently it became clear that this goal was not satisfying anymore, and that the patients' perspective should be taken into account [6, 7]. All this has led to the recovery-oriented movement, according to which MDD treatment should be personalized, individualized, and shared with the patient [8]. This new paradigm of care for major depression is described and discussed in the next paragraphs.

14.2 Toward Full Functional Recovery: How to Improve Patients' Outcome with Personalized and Precision Interventions

Full functional recovery can be defined as a condition in which the patient starts to enjoy again his/her usual activities, returns to work, and is able to take care of him/herself [9, 10]. This is a continuing and evolving clinical process, and several patient, illness, and contextual factors can influence it. The response rate for an initial antidepressant treatment is between 50 and 75% [8]. This will lead to treatment failure, multiple trials, poor treatment response, and patient frustration. Therefore, when choosing a treatment for MDD, clinicians should do it according to a series of factors, including patient's age, pre-morbid level of functioning, educational level, working condition, social network, cognitive schemas, presence of comorbidities, severity and type of symptoms, duration of illness, clinical staging, previous treatments, time to remission, patient's social network, family ties, and environmental exposures (Table 14.1). This process is now known as personalized medicine, which can help to identify a priori which patients will best respond to the different therapeutic approaches.

In fact, the current symptoms of MDD are not predictive of response to any antidepressant or psychotherapy or psychosocial intervention. We still choose the

Table 14.1 Factors predicting recovery in patients with MDD

Patient-related factors	Illness-related factors	Contextual-related factors
Age	Symptoms	Access to care
Personal history	Neurocognition	Neighborhoods
Family history	Severity	Social network
Antecedent environmental factors	Clinical staging	Therapeutic relationship
Recent environmental factors	Physical comorbidities	
Personality traits and coping strategies	Duration of illness and duration of untreated illness	
Cognitive schemas	Number of episodes	
Social functioning		

"best" treatment on the basis of a clinical diagnosis, and not taking into account the different clinical and personal characteristics of the patient. We still rely on clinical algorithms and guidelines, while in many cases they have proved to be far away from clinical practice [11]. What we really need now is an individualized approach aiming to treat the "person" with depression and not the "depressive illness" [2].

All the abovementioned factors should be taken into account by clinicians when selecting the appropriate treatment in order to fulfill the goal of full functional recovery.

In fact, a systematic review on 21 antidepressants showed that these drugs have a similar efficacy and tolerability [12], and the same happens with psychotherapies and psychosocial interventions [13]. Therefore, what is most important in the selection of the "right" treatment is the assessment of patients' individual characteristics, needs, and desires. For example, a young patient affected by MDD will most probably benefit from an antidepressant which is different from the one effective in a person with a late-life depression. Unfortunately, the basic general assumption is that the illness "depression" can be treated with the same "antidepressant" and that all antidepressants are equally effective. This has led to an increased use of antidepressants of 5% in the last decade [14], with about 25% of individuals taking antidepressants for more than 10 years.

However, clinicians are unable to predict what drug works more or less in a given patient for the treatment of MDD symptoms. In the absence of validated biomarkers and genetic data, the personalized approach of major depression will include patients' personal account and the shared decision-making approach [15–17]. In some patients, the adoption of the shared clinical decision-making approach is hampered by anhedonia, lethargy, amotivation, physical and cognitive symptoms, as well as by patient's feelings of vulnerability and self-stigma [18, 19], thus making more difficult a personalized approach.

14.3 Recovery-Oriented Pharmacological Treatments

When antidepressant agents had been developed in the late 1950s, the only aim of clinicians was symptoms' remission. And in fact, the discovery of antidepressants along the years has followed three different lines. The first antidepressants were discovered by "serendipity" searching for the treatment of tuberculosis. These drugs include the tricyclic and I-MAO antidepressants [20], which have been used as first-line treatment for patients with major depression, regardless of their side effect profile [21].

Following the introduction of the Selective Serotonin Reuptake Inhibitors (SSRIs) in 1974, with the fluoxetine being the first antidepressant of that class, the paradigm of care started to change. Clinicians began to consider the profile of side effects when choosing the "appropriate" medication, and the "refinement" era started [22, 23]. In the last 20 years, with the introduction of several other antidepressants with very different pharmacological profiles, clinicians can finally "tailor" their treatment approach. Although the new antidepressants have less side effects compared to I-MAOs and tricyclics, the tolerability of these compounds remains an unsolved

issue, with many patients still reporting side effects such as headache, gastrointestinal problems, obesity, insomnia, nausea, and sexual dysfunctions. Therefore, many patients have a low treatment adherence and remission rates are still not satisfying, being approximately ≤50% for any given drug in clinical trials [24], and even lower in everyday clinical practice. This may be due to the fact that the choice of antidepressants in clinical practice is largely based on clinicians' preferences, drugs' availability, and costs. In fact, antidepressants are frequently chosen through "trial-and-error" steps, paying little or no attention to the individual characteristics of the patient and to his/her clinical history [2]. This may be one of the reasons why the majority of patients with a diagnosis of major depression do not achieve a full remission after the first treatment, and at least 30% of them do not respond to two consecutive evidence-based treatments and are classified as treatment-resistant.

Therefore, since the profile of efficacy of antidepressant drugs varies significantly, a personalized approach in drug selection can help in identifying a priori which group of patients will respond better to the different medications [25].

Moreover, in order to have a better response, the treatment should be initiated as soon as possible, since inadequate or delayed interventions are correlated with brain damage and altered morphometry, in terms of hippocampal loss of volume, probably due to chronic neuronal losses, suppressed neurogenesis and disruption of neural connections in mood-related circuits [26, 27].

Finally, even those patients who have responded well to antidepressants may present persistent residual symptoms, such as lack of energy, sleep disturbances, and cognitive deficits. Recently, new drugs targeting the altered domains in MDD have been developed. In particular, since cognitive deficits represent the missing link between symptomatic remission and functional recovery, drugs addressing cognitive symptoms are welcome.

These novel targets for pharmacological drugs have a focus on the glutamatergic, GABAergic, opioidergic, and inflammatory systems, which are implicated in the pathophysiology of MDD. In particular, among the new drugs, ketamine, esketamine, and rapastinel are effective on the glutamatergic system; brexanolone and SAGE-217 act through the GABAergic system; minocycline influences the inflammatory system; the combinatory agent buprenorphine + samidorphan works through the opioidergic system.

The glutamate represents the main excitatory neurotransmitter in the central nervous system; it binds the presynaptic and postsynaptic receptors, and those on astrocytes. Ketamine, a non-competitive N-methyl-D-aspartate (NMDA) antagonist (channel blocker), gives rapid and prolonged antidepressant effects [28]. Ketamine is a dissociative anesthetic drug with hallucinogenic features, approved by the U.S. Food and Drug Administration (FDA) in 1970 as short-acting anesthetic. During mid-1990s, it became a drug of recreational abuse, also known as "Special K". At subanesthetic or emergency use from anesthetic doses, ketamine may produce altered perceptions, depersonalization and derealization lasting from 30 to 60 min. The use of ketamine as antidepressant has been tested in several preclinical and clinical studies, supporting the idea of a complex and multistep cascade of events on different targets: antagonism of NMDA receptors, reduction of nitric-oxide production, increase of glutamate release, increased activation of

α-Ammino-3-idrossi-5-Metil-4-isossazol-Propionic Acid (AMPA) receptors, activation of mTOR, and increased signaling of neurotrophic factors [29]. Due to the potential risk of addiction, ketamine has not been approved for use in clinical practice as antidepressant, but in 2019, the U.S. FDA approved esketamine, the s-enantiomer of ketamine, for the treatment of adults with treatment-resistant depression, i.e., patients who have not responded adequately to at least two different trials with antidepressants at adequate dose and duration [30]. This innovative drug provides a rapid response, with reduction of depressive symptoms within 24 h, as opposed to weeks noted with conventional antidepressants.

14.4 Psychotherapies and the Role of Combination Therapies

The individual response to treatments depends on biological, clinical, psychological, and environmental factors. Therefore, interventions addressing the different factors implicated in the etiopathogenesis of MDD should be used and coordinated. For the most severe cases of depression, psychotherapy is recommended as add-on treatment in combination with pharmacotherapy, while for the less severe cases it may be provided alone [31]. Cognitive behavioral therapy (CBT), interpersonal therapy (IPT), psychodynamic therapy, and Internet-based therapy are among the most effective psychotherapeutic approaches in MDD (Table 14.2).

However, other psychotherapeutic approaches are being studied and look promising, such as mindfulness and problem-solving therapy.

Patients receiving psychotherapies consistently show brain activation changes with a decreased activation in specific brain areas, with peak coordinates in the left anterior cingulate cortex, inferior frontal gyrus (bilaterally), and in left insula [32–34]. These changes seem to be independent from the type of psychotherapy and outline the importance of nonspecific factors in psychiatric treatments. Combination therapy is more effective than psychotherapy or pharmacotherapy alone in achieving full recovery [13]. Moreover, acceptability is significantly better in patients treated with a combined therapy compared with those receiving pharmacotherapy alone.

Psychotherapeutic approaches have been recently adapted to be provided through tele-medicine. Most of Internet-delivered treatments are based on the cognitive behavior therapy (CBT). iCBT is now considered a valid option for the treatment of patients with major depression at a distance [35–38].

Table 14.2 Psychotherapies in patients with major depressive disorder

Type of intervention	Acronym	Description
Cognitive behavioral therapy	CBT	It is focused on cognitive distortions and behaviors, aims to improve emotional regulation, and to develop personal coping strategies
Internet-based CBT	i-CBT	CBT delivered through Internet
Interpersonal therapy	IPT	A brief, attachment-focused psychotherapy focusing on solving interpersonal problems and symptomatic recovery
Psychodynamic therapy	PT	It focuses on the interpretation of individual's mental and emotional processes rather than on behavior

14.5 Psychosocial Interventions

In the last 20 years, several studies have highlighted the role of psychosocial interventions in the treatment of patients with MDD (Table 14.3).

Individual, group, or family psychoeducation aims to: (a) increase the levels of knowledge of patients and families about the illness; (b) improve the recognition of early warning signs of relapses and the identification of patient's dysfunctional cognitive schemas; and (c) improve communication skills and problem-solving strategies [39, 40].

The cognitive remediation techniques are effective in the treatment of cognitive impairments in verbal fluence, visual-spatial ability, verbal learning, and executive functioning in patients with MDD [41–43].

Stress, fatigue, unbalanced diet, heavy tobacco smoking, disturbed sleep hygiene, and low physical activity are among the altered lifestyle behaviors in patients with MDD. Recently, psychosocial interventions aimed to improve patients' lifestyle have been developed and found to be effective [44]. Most international guidelines suggest including these interventions in the recovery-oriented management plan of MDD patients [45–47]. Physical activity and healthy diet have in fact a protective factor by increasing the neurogenesis in the hippocampus. Exercise interventions are the ones with the most robust evidence from clinical trials.

Some psychosocial interventions can be provided through the Internet [35–38]. These approaches have demonstrated their efficacy as an initial intervention for mild depression in the stepped managed care of mood disorders in primary care [46]. Many models of online delivery have been explored, from simple information to self-help strategies and supported time-limited structured therapies. Another opportunity to improve the recovery process of patients with depression is the use of smartphone apps. Other psychosocial interventions successfully used in MDD include art therapies and behavioral activation (Table 14.3).

Table 14.3 Psychosocial interventions for patients with major depressive disorder

Type of intervention	Main features
Psychoeducation	A structured intervention to be delivered in an individual, group or family format; trained professionals provide participants with information on the illness, possible causes and risk factors, possible treatments
Lifestyle intervention	A structured intervention aiming to provide information on healthy lifestyle behaviors, physical activity and treatment adherence
Cognitive remediation	A computerized or paper-and-pencil intervention aiming to improve patient's cognitive functioning (verbal fluence, visual-spatial ability, verbal learning, and executive functioning)
Internet-based/ smartphone-based intervention	A variety of interventions provided through Internet or using dedicated applications for smartphones aiming to provide practical strategies on how to deal with (mild) depressive symptoms

14.6 Conclusions

Depression is a heterogeneous, complex, and multidimensional syndrome, representing the leading cause of disability worldwide. The final aim of the management plan of MDD patients has shifted from symptom remission to full recovery. The need for personalized recovery-oriented interventions is confirmed. The treatment plan for MDD patients should be tailored on patients' preferences according to the shared decision-making approach. An active involvement of patients in their therapeutic plan is associated with an improvement in long-term outcome [48–50].

The recovery-oriented management of patients with MDD starts with the clinical characterization of the individual patient, even considering that there is "no one size that fits for all," and that the concept of interchangeability of treatments is very far from clinical reality. The comparisons between antidepressant medications and psychotherapies, and between different psychotherapeutic techniques, have suffered from this limitation, supporting the idea that all treatments for depression are "equivalent" and interchangeable. Of course, this paradigm has proven to be false, and it has had detrimental effects on education, research, and clinical practice. We do believe that all patients with major depression are treatable, but the treatment will have to be differentiated on the basis of several clinical, personal, and contextual factors.

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