New concept of depression and its management

Ahmed Okasha

WHO Collaborating Center for Research and Training in Mental Health, Okasha Institute of Psychiatry, Ain Shams University, Cairo, Egypt

Correspondence to Ahmed Okasha MD, PhD, FRCP, FRC, Psych, FACP (Hon) Director of WHO Collaborating Center for Research and Training in Mental Health Okasha Institute of Psychiatry, Ain Shams University President Egyptian Psychiatric Association Hon. President Arab Federation of Psychiatrists President of WPA (2002-2005) Chairperson of WPA Ethics and Review Committee 3, Shawarby Street, Kasr El Nil Cairo- Egypt
Tel: +(202) 29200900,1,2,3,4,5,6
fax: +(202) 29200907,8
e-mail: aokasha@internetegypt.com; aokasha35@gmail.com

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Introduction

The prevalence of psychiatric disorders in the community is high; out of every 100 citizens, 30% suffer from a mental problem that needs attention, 20% will seek traditional healers or general practitioners' help, 10% will be identified by the general practitioner as psychiatric cases, only 2.3% will be referred to a psychiatrist, and 0.5% will need inpatient treatment (Goldberg and Huxley, 1980). The global burden of depression as measured by disability-adjusted life years, that is, how many years are lost because of illness and premature mortality was projected to be the third in 2004 (Murray and Lopez, 1996). According to information from WHO, depressive disorders are of high socioeconomic and health-economic importance as these psychiatric disorders most frequently cause psychosocial disability. Despite intensive biologically oriented psychiatric research over the last few decades, the etiology of depressive disorders is not yet fully understood, but a multifactorial genesis is assumed and has been elucidated in increasing detail. Besides psychological and social factors, biological variables apparently play a major role, which lead as a whole to a disturbed central nervous homeostasis (Baghai *et al.*, 2011).

Global disparity

Depression currently affects ~121 million people worldwide. By 2020, depression is projected to become the second highest contributor to the global burden of disease in terms of disability-adjusted life years, whereas by 2030, it will be the first highest contributor. Studies suggest large geographical variations in the burden of depression. Depression is a low priority in most low-income to middle-income countries and there is apparently a higher incidence of depression in rural than in urban areas (Sartorius *et al.*, 1993; Prince *et al.*, 2007).

The prevalence of depressive disorders in various patient populations is estimated as follows: in the general population 5.8%, chronically ill patients 9.4%, hospitalized patients 33.0%, geriatric inpatients 36.0%, cancer outpatients 33.0%, cancer inpatients 42.0%, stroke patients 47.0%, myocardial infarction (MI) patients 45.0%, and Parkinson's disease patients 39.0% (The World Psychiatric Association, 2008).

Changing conceptualizations of major depressive disorder (MDD) are shown by the differences between the past clusters of situational versus endogenous depression and the recent concept of interplay between biology and environment. Previously, high treatment response rates and full recovery were considered as the rule, nowadays, depression is viewed as a progressive disorder with worse outcomes over time. There was no known cell pathology and a possible 'chemical imbalance,' but recently, evidence of cellular pathology has been emerging. In treatment, there was a wait-and-see attitude, with a habit-based prescribing; however, now, aggressive, individualized treatment is followed (Aston-Jones *et al.*, 2000).

When does depression become a mental disorder?

The *Diagnostic and Statistical Manual of Mental Disorders* definition of MDD fails to exclude intense sadness arising from the way human beings naturally respond to major losses. 'Normal' sadness may therefore be treated as a depressive disorder, which may undermine normal recovery by disrupting normal coping processes and use of informal support networks. Depression, in contrast to normal sadness, is unrelated to a preceding event in the intensity, duration, and degree of functional impairment it produces (Maj, 2011). The experimental induction of depressed mood has led to a significant increase in reports of recent stressful events. The presence itself of a depressive state may expose a person to adverse life events. Among patients with a diagnosis of MDD, those with a score of less than 20 on the Hamilton Scale for Depression (who made up more than 60% of the sample) did not recover more frequently with imipramine than with placebo plus clinical management (Maj, 2011). The psychosocial impairment associated with the presence of two to four depressive symptoms has been repeatedly reported to be comparable with that associated with the presence of five or more symptoms. The threshold for a depressive state deserving clinical attention may be lower than that fixed by the *Diagnostic and Statistical*

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Manual of Mental Disorders, fourth edition, but the threshold for a depressive state requiring pharmacological treatment is likely to be higher. These thresholds may need to be based on the overall severity of depressive symptoms, rather than, or in addition to, their number (Maj, 2011).

In medicine, the term depression has at least three different meanings: (a) a mood, a feeling, an emotion, an affective state; (b) a symptom of a depressive disorder; and (c) the depressive disorder itself. This text presentation focuses primarily on depressive disorders.

Essential features of depressive disorders

There are numerous types and variations of depressive disorders, and differentiation is important for effective management. Depressive disorders share a number of clinical manifestations: (a) mood and affect (diurnal rhythm): sadness, anxiety, decreased reactivity, tension, decreased motivation, irritability, emptiness, anger, apathy, and a sense of frustration (The World Psychiatric Association, 2008), (b) thought-cognition: decreased concentration, helplessness, indecisiveness, hopelessness, loss of confidence, pessimism, decreased self-esteem, death wishes, inappropriate guilt, and suicidal ideas, (c) psychomotor activity: (i) retardation: decreased body movements, stupor, decreased facial expression, and decreased inhibited interpersonal communication, (ii) agitation: restlessness, fidgeting, and purposeless uncontrollable hyperactivity (The World Psychiatric Association, 2008), (d) somatic manifestations (masked depression) 50–70% of depressed patients: (i) basic functions: insomnia (Early Morning Wakening EMW) (Aka terminal insomnia), hypersomnia, appetite and body weight, sexual drive, (ii) vitality: tiredness, fatigability, energy, and vigor, (iii) bodily sensations: pains and aches, pressure, coldness, heavy limbs, any other vague undifferentiated sensations, (iv) *v*isceral symptoms: gastrointestinal (GI) complaints, Cardio-Vascular (CV) complaints, and vague complaints about a bodily function (The World Psychiatric Association, 2008).

Clinically, the main presentations of depression are fatigue, lack of concentration, and painful bodily symptoms rather than depressive symptoms.

There are two questions for provisional diagnosis. (a) In the past month, have you felt 'down,' depressed, or hopeless? (b) In the past month, have you had little pleasure or interest in doing things?

The test can identify 96% of patients with depression. However, its specificity is only 57%; the clinician should obtain additional information to substantiate the diagnosis (Whooley and Simon, 2000).

Epidemiological studies

(a) Lifetime prevalence: 16.6 US, 12.8 Europe, 16.0 New Zealand, 7.2 Mexico, 3.3 Nigeria, (b) 12-month prevalence: 6.2 US, 3.9 Europe, 5.7 New Zealand, 3.7 Mexico, 1.0 Nigeria (Kessler *et al.*, 2008).

Gene–environment interactions may play a role in the etiology of mood disorders

Genetic epistasis means complex interactions between the 'vulnerability' genes, whereby they potentiate or cancel out each other's effects. Epigenetic modulation explains that life events may influence gene expression. Diathesis toward mood disorders is most likely a product of a complex interaction of a large number of genes, with minor individual effects and environmental factors as shown in Fig. 1 (Maletic and Raison, 2009).

The interaction between genetic vulnerability affected by stress or injury and influenced by epigenetic modulation can reinforce or extinguish the gene expression.

Multiple roles of brain-derived neurotrophic factor and neurotrophic factors in mood disorders

Brain-derived neurotrophic factor (BDNF) and neurotrophic factors play a role in neurogenesis, neuroplasticity, and neural resilience. It plays a central role in translating functional into structural change and an important role in neuroendocrine regulation. BDNF and other neurotrophic factors may be altered in depression, anxiety, pain, and mania. Successful treatment of mood disorders may restore appropriate BDNF function (Dunn *et al.*, 2005; Chen *et al.*, 2006; Cunha *et al.*, 2006; Duman and Monteggia, 2006; Schule *et al.*, 2006; Castren *et al.*, 2007; Post, 2007).

Stress and 5-HTT polymorphism interaction may precipitate depression

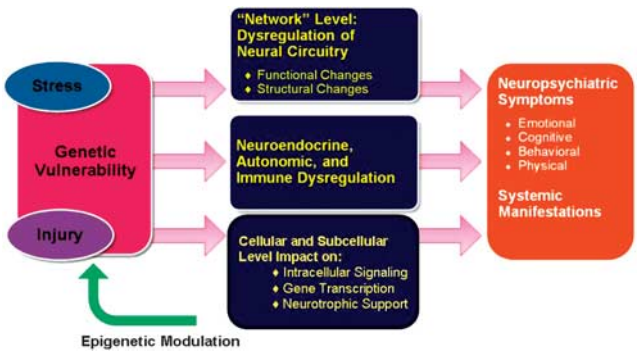
This study characterized the risk for major depression and generalized anxiety syndrome as a function of serotonin transporter (5-HTT) genotype, sex, and the occurrence of all stressful life events. Individuals with two short (S) alleles at the 5-HTT locus were more sensitive to the depressogenic effects of all stressful life events than those with one or two long (L) alleles (Kendler *et al.*, 2005).

Cumulative effect of risk factors on depression

The following factors were investigated for contribution to risk: serotonin transporter (5-HTTLPR) (locus SLC6A4), BDNF (variant val66met), history of maltreatment, and social support.

There was a three-way interaction between the BDNF genotype, 5-HTTLPR, and a history of maltreatment in predicting depression. The vulnerability associated with these two genetic factors was only evident in maltreated children (Kaufman *et al.*, 2006).

Figure 1



Neurobiology of major depressive disorder (Maletic and Raison, 2009).

Impact of comorbid anxiety-depression

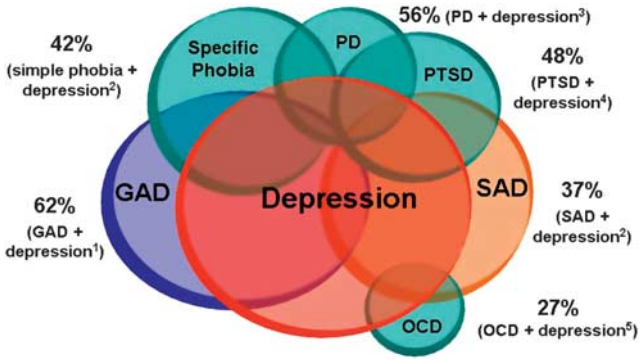
Greater symptom severity, more illness chronicity, increased risk of suicide, greater function impairment, disability, poorer response to treatment, poorer prognosis, excessive medical utilization, and poor quality of life.

Goldberg suggested for International Classification of Diseases-11 (ICD-11) that the emotional disorders (internalizing) may all be similar and should be one cluster instead of splitting them into many disorders, namely: mood disorders: depression (nonpsychotic), dysthymic disorders, neurotic, and stress-related disorders: specific phobias, social phobias, generalized anxiety, panic disorder, obsessional states, posttraumatic stress, somatoform disorders, neurasthenia, anxious, personality disorder, mixed disorder of conduct and emotions, and phobic anxiety disorder of childhood. He proceeds by explaining that, among emotional disorders, the following are especially important and similar: temperamental antecedents, rates of comorbidity, genetic risk factors, symptom similarity, course, treatment response, familiarity, environmental risk factors, the neural substrate, cognitive, emotional processes, and biomarkers (Goldberg *et al.*, 2009) (Fig. 2).

The severity of symptoms, diagnostic subtypes, and the presence of specific symptoms, as well as age and comorbidity, play a role in the course of illness and choice of treatment. The treatment that provides the highest likelihood of response and the best tolerability should be preferred in treatment plans and algorithms.

Treatment of depressive disorders mostly consists of a combination therapy, determined by the current clinical features, the main constituents of a multimodal antidepressant therapy being pharmacotherapy, psychotherapy, psychoeducation, and social support. Whereas pharmacotherapy is not always mandatory for less severe forms of depression, moderate and severe depression usually requires pharmacotherapy or electroconvulsive therapy (ECT) in treatment-resistant illness (Baghai *et al.*, 2011).

Figure 2



Depression/anxiety disorders comorbidity. [Lifetime prevalence of major depressive disorder among individuals with lifetime diagnoses of each anxiety disorder (Weissman *et al.*, 1994; Wittchen *et al.*, 1994; Kessler *et al.*, 1995; Magee *et al.*, 1996; Roy-Byrne *et al.*, 2000). GAD, generalized anxiety disorder; OCD, obsessive compulsive disorder; PD, personality disorder; PTSD, post traumatic stress disorder; SAD, seasonal affective disorder.

A further problem in the pharmacotherapy of depression is the latency of up to several weeks before the symptoms begin to alleviate (Baghai *et al.*, 2006), although a faster onset of response has been reported for newer dual-acting compounds such as mirtazapine (Leinonen *et al.*, 1999; Benkert *et al.*, 2000) and venlafaxine (Benkert *et al.*, 1996; Montgomery, 1999). The fact that total or partial sleep deprivation can produce a rapidly occurring antidepressant effect in up to two-thirds of patients (Wu *et al.*, 1990) shows that it is indeed possible to achieve antidepressant effects within a very short period. However, these effects may not be strong enough and are usually not sustained; thus, it is a clinical standard to strengthen them using maintenance strategies such as multiple repetitions of the sleep deprivation or subsequent phase advance procedures (Wirz-Justice *et al.*, 1999). Intravenous administration of the N-methyl-D-aspartate (NMDA) antagonist ketamine has been shown to cause a rapid improvement in mood in depressed patients (Zarate *et al.*, 2006; Paul *et al.*, 2009; Price *et al.*, 2009; Diazgranados *et al.*, 2010a, 2010b; Larkin and Beautrais, 2011), but again, in most cases, this effect is not persistent and may only be used as an acceleration strategy. The only therapeutic intervention that is more potent than sleep deprivation and leads to a more rapid improvement than pharmacotherapy is ECT (Gangadhar *et al.*, 1982; ECT Review Group, 2003). Unfortunately, transcranial magnetic stimulation and other ways of stimulating the brain seem to be less effective than ECT (Hasey, 2001; Eitan and Lerer, 2006; Slotema *et al.*, 2010).

In this text, we use the term efficacy to describe the ability of an antidepressant to produce antidepressant effects; by contrast, clinical effectiveness is the capability and success of the treatment in achieving sufficient amelioration of depressive symptoms in wider practice. The definition of efficiency includes effectiveness together with safety and tolerability as an important part of the benefit/risk analysis of a treatment. In psychiatry, the distinction between efficacy (outcome under ideal use of a treatment) and clinical effectiveness (outcome under typical use of a treatment) is often drawn. Whereas efficacy may be shown in randomized double-blind clinical trials, clinical effectiveness has to be demonstrated in the so-called effectiveness studies in wider clinical practice (Baghai *et al.*, 2011).

A further problem in the treatment of depression is the nonresponse rate of approximately 30% (Charney *et al.*, 2002): the recent US STAR*D study found lower response and remission rates even after multiple treatment trials (Fava *et al.*, 2006; Rush *et al.*, 2009). High dropout rates occur due to tolerability problems, which limit adherence, complicate the successful treatment of depression, and contribute to the high rate of nonresponse. Adequate treatment comprises the use of a treatment with proven efficacy over at least 4–6 weeks in a sufficient therapeutic dose with reliable patient adherence (Sackeim, 2001; Fava, 2003; Kupfer and Charney, 2003), but following this situation, approximately half of the patients do not respond to a second antidepressant treatment trial. If several

antidepressant treatment trials have been unhelpful, even lower response rates after switching to other approaches may be expected (Fava *et al.*, 2006). Others consider that it should include combined treatment, for example, using two antidepressants with divergent pharmacodynamic modes of action or the use of two dually acting antidepressants that may provide superior efficacy over antidepressant monotherapy (Bauer *et al.*, 2009). Others argue that augmentation approaches such as lithium augmentation or supplementation with cognitive behavioral therapy (CBT) and interpersonal psychotherapy are needed in addition, before concluding that the condition is therapy resistant (Thase *et al.*, 1997). Other factors such as measuring treatment adherence using therapeutic drug monitoring, determining plasma concentrations of the prescribed antidepressants, and deciding on the adequate dosage may also be included in the definition of treatment-resistant illness.

The traditional definition of response to antidepressant therapy is a 50% improvement in symptom severity, whereas remission is defined as the virtual absence of depressive symptoms and a full return to premorbid levels of functioning (Thase, 2003). Besides clearly comprehensible biological factors underlying therapy resistance, such as occult medical conditions, substance abuse interfering with antidepressant treatments, or an abnormal metabolism (Rush *et al.*, 2003), it is also hypothesized that psychiatric comorbidities (Souery *et al.*, 2007) and psychosocial factors may be responsible for many failed treatment trials (Grote and Frank, 2003).

Currently available antidepressants are classified according to their chemical structure and their mode of action. Currently, tricyclic antidepressant (TCA) and tetracyclic antidepressant, selective and nonselective inhibitors of monoamine oxidase, selective serotonin reuptake inhibitors (SSRI), selective noradrenaline reuptake inhibitors, and antidepressants with a dual mode of action such as selective serotonin and noradrenalin reuptake inhibitors (SNRI), noradrenergic and specific serotonergic antidepressants, bupropion (Sartorius *et al.*, 2007), and a melatonergic MT1/MT2 receptor agonist with 5-HT2C receptor antagonistic properties are available for use (Kasper and Hamon, 2009). Current investigational compounds include dopaminergic, serotonergic, and noradrenergic triple reuptake inhibitors (SNDRI) that have reached phase II clinical trials and glutamatergic mechanisms (Kulkarni and Dhir, 2009) (Fig. 3).

The evolution of antidepressants is shown in the following diagram (Andrews and Nemeroff, 1994; Slattery *et al.*, 2004)

The following figure 4 shows the treatment gap worldwide in psychiatric disorders, with almost 50% of depressed patients untreated.

Unipolar versus bipolar

Hantouche *et al.* (1998) found that 28% of a population of depressed patients had bipolar disorders. Benazzi (1997) found that 49% of the outpatients presenting with depression had a bipolar spectrum disorder. Depression represents about three quarters of the time spent with mood symptoms in bipolar I disorder and over 90% of the time spent with mood symptoms in bipolar II disorder (Jamison, 2000; Judd *et al.*, 2002, 2003).

The risks and consequences of misdiagnosis

Hirschfeld *et al.*, 2003 noted that 69% of respondents reported that they had initially been misdiagnosed as having Unipolar Disorder (UD). Among the respondents to this survey, 35% reported that they had waited 10 years or longer to receive a correct diagnosis. The issue of misdiagnosis is particularly serious because antidepressants used alone can lead to induction of mania or acceleration of cycling frequency over time, phenomena that have been reported to occur in approximately 25–40% of patients with bipolar disorder (Goldberg and Truman, 2003; Hirschfeld *et al.*, 2003).

Obstacles to recognition of depression

(a) Stigma: one out of three patients with a depressive disorder ever seeks medical help. (b) Masked depression: many depressed patients present to physicians with mainly somatic symptoms. In primary care settings, more than half of the patients ultimately found to have a depressive disorder originally presented with somatic complaints: headache, backache, or vague, undifferentiated pain. (c) Comorbid medical illness: fatigue and loss of appetite are common in both. (d) Tacit collusion: physicians' attitudes can also present obstacles to the recognition of depression. (e) Time constraints. (f) Inadequate medical education: many physicians currently in practice receive only limited psychiatric education during medical school or postgraduate training (Goldberg and Lecrubier, 1995; Regier *et al.*, 1998).

The natural course of untreated depression shows that after one year, 40% will recover, 20% will show partial recovery (dysthymia), and 40% will remain depressed. With antidepressants, we expect about 70% response and 30% nonresponse (Kupfer *et al.*, 1992; Stahl, 2008).

Aim of treatment

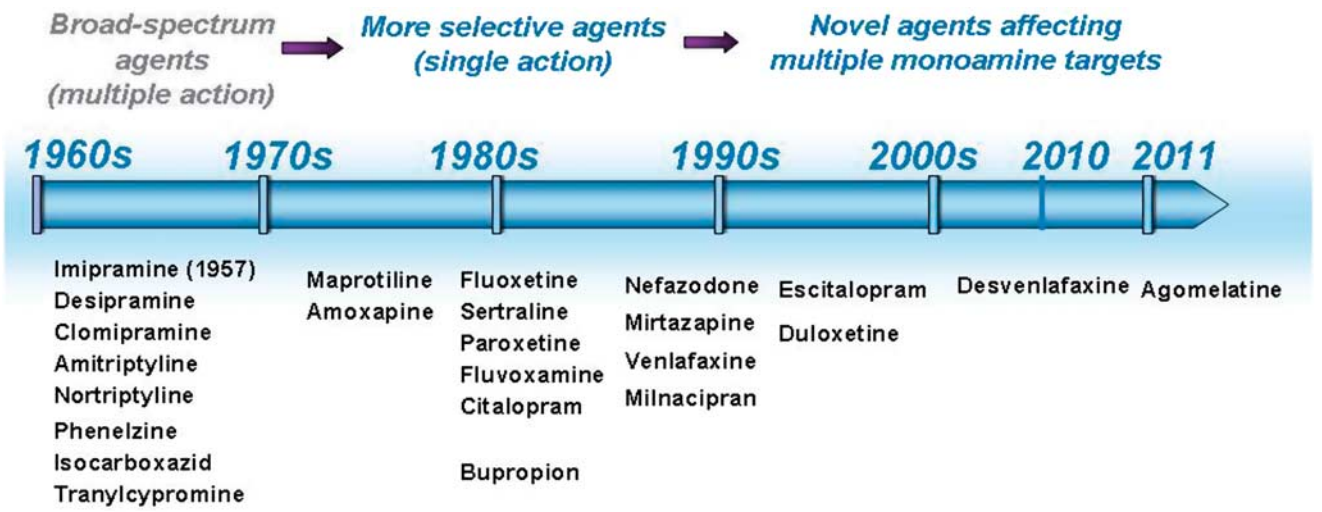
Response is not sufficient: remission is the goal of treatment. If residual symptoms are present (32%), there is a need for vigorous and aggressive treatment. The functional impact of residual symptoms should be taken into account in the treatment plan. Pharmacotherapies that increase Norepinephrine (NE) and/or Dopamine (DA) neurotransmission may improve residual symptoms.

Therapeutic simple clinical approach:

(1) *Psychotic depression:* SGA + AD (SNRI or TCA) + ECT (BST),
(2) *Melancholic depression:* AD (SNRI or TCA + ECT (BST).
(3) *Nonmelancholic depression:* SSRI + CBT
(4) *Painful depression:* TCA or SNRI + CBT (ECT or BST) (Parker and Hyett, 2009).

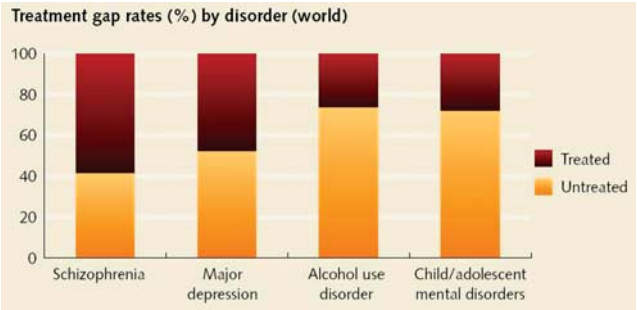
AD indicates antidepressants; BST, brain synchronization therapy; SGA, second-generation antipsychotics.

Figure 3



Antidepressant started with Imipramine in 1957 and went through many stages, the last was Agomelatine and more are in the pipeline.

Figure 4



Treatment gap rates (%) by disorder (Kohn *et al.*, 2004).

Myocardial infarction

After an episode of major depression, the risk of MI increases to fivefold. Subsyndromal forms of depression have a twofold increased risk of MI. Six months after MI, the mortality rate is about 17% in patients with depression, whereas it is only 3% in patients without depression. Twelve months after bypass show those with depression had a higher incidence of subsequent cardiac events, angina, heart failure, MI, repeat surgery. MD is a significant risk factor for the development of coronary artery disease and stroke (Frasure-Smit *et al.*, 1993).

Criteria for choosing an antidepressant

The selection of antidepressants from more than 42 AD depends on: (a) patient preference, (b) nature of prior response to medication and family history, (c) relative efficacy and effectiveness, (d) safety, (e) tolerability and anticipated side effects, (f) adverse effects (sexual dysfunction – suicidal thoughts – weight, sedation, or anxiety – GI symptoms), (g) potential drug interactions, (h) co-occurring psychiatric or general medical conditions, (i) cognitive functions, (j) type of depression, for example, painful, melancholic, psychotic etc…, (k) half-life, and (l) cost.

There are three treatment phases, namely, acute (6–12 weeks), continuation (4–9 months), and maintenance (1 or more years).

Treatment with antidepressants in the acute phase

The adequate treatment should be used long enough to establish whether it is effective. Once treatment with antidepressant medication is initiated, the patient is seen every 1 to 2 weeks, and more often if the patient has severe depression or requires titration of a TCA. Response to therapy (clearly better, not better) is assessed at 6 weeks, although a patient may respond earlier (The World Psychiatric Association, 2008).

All antidepressants are efficacious

There is 70–80% efficacy with any marketed antidepressants. SRIs or SNRI or Bupropion are excellent first-line choices. TCAs may be superior for some 'severe' depressions. Monoamine Oxidase Inhibitors (MAOIs) may be preferred for some atypical depressions.
See Tables 1–4 for types of antidepressants.

Potential for drug interactions

Many medications are metabolized through the cytochrome P-450 enzyme pathway: co-administration can lead to drug–drug interactions and can lead to clinically significant effects, increased side effects, and decreased effectiveness, Use Antidepressants (AD) with the least drug–drug interaction, for example, Sertraline, Ecitalopram, Mianserin, that is, no induction or inhibition of liver enzymes (Preskorn *et al.*, 2008) (Table 5).

Interaction with cardiac medications

SSRIs may increase blood levels of β blockers, and anticoagulants, for example, warfarin, and other cardiac medications through cytochrome P-450 isoenzyme inhibition. Least escitalopram, Mirtazepine, venlafaxine,

Table 1 Mixed serotonin norepinephrine tricyclic antidepressants: (The World Psychiatric Association, 2008)

Drugs	Starting dose (mg/day)*	Dose range (mg/day)*
Amitryptiline	25–75	150–300
Amitriptylinoxide	30–60	180–300
Dibenzepine	120–180	240–720
Dosulepine/ dothiepin	75	75–150
Doxepin	25–75	150–300
Imipramine	25–75	150–300
Melitracen	20	20–30
Protriptyline	10	20–60
Clomipramine	25–50	100–250

*Dosages recommended by the producer.

Table 2 Monoamine oxidase inhibitors and reversible inhibitors of monoamine oxidase (The World Psychiatric Association, 2008)

Drugs	Starting dose (mg/day)*	Dose range (mg/day)*
Phenelzine	15	30–40
Isocarboxacid	20	20–60
Tranylcypromine	10	20–40
Moclobemide1	150–300	300–600

*Dosages recommended by the producer.

Table 3 Serotonin–norepinephrine reuptake inhibitor (The World Psychiatric Association, 2008)

Drugs	Starting dose (mg/day)*	Dose range (mg/day)*
Venlafaxine	75	75–375
Duloxetine	40/602	60–120
Milnacipram	50	100–200
Noradrenalin reuptake inhibitor		
Reboxetine	4	8–12

*Dosages recommended by the producer.

Table 4 Modulating antidepressants (The World Psychiatric Association, 2008)

Drugs	Starting dose (mg/day)*	Dose range (mg/day)*
Modulating antidepressants		
Trazodone	50–100	200–600
Nefazodone3	100	300–600
Dopamine and noradrenalin reuptake inhibitors		
Bupropion	100	200–300
Noradrenergic and specific serotonergic antidepressants		
Mianserin	30	60–120
Mirtazapine	15	30–45
Melatonergic antidepressants		
Agomelatine	25	25–50

*Dosages recommended by the producer.

duloxetine. Agomelatin and SSRIs may also reduce platelet aggregation. Patients who receive concomitant aspirin or warfarin may bruise or bleed easily and may require dosage reductions or medication changes.

'Common' serotonin reuptake inhibitor adverse effects

Common adverse effects of SRI include GI disturbances, headache changes, sleep disturbances, appetite changes, sexual function changes, anxiety level changes, allergic reactions, and rarely bleeding and hyponitremia.

Table 5 Potentials for drug–drug interactions

	3A4	2D6	1A2	2C19	2C9
Venlafaxine	0	0/+	0	0	0
Citalopram	0	+	+	0	0
Fluoxetine	+ +	+ + +	+	+ +	+ +
Paroxetine	+	+ + +	+	+	+
Escitalopram	0	+	0	0	0
Fluvoxamine	+ +	+	+ + +	+ + +	+ +
Sertraline	+	+	+	+ +	+

0, negligible; +, very weak interaction; + +, moderate interaction; + + +, strong interaction.
3A4: Ca^{+} antagonists, erythromycin, ketoconazole, lidocaine, cancer therapies.
2D6: Antiarrhythmic, β-blockers, haloperidol, neuroleptics.
1A2: caffeine, ciprofloxacin, theophylline, verapamil.
2C19: diazepam, propranolol, moclobemide, imipramine.
2C9: miconazole, phenytoin, S-warfarin, NSAIDs (Greenblatt *et al.*, 1998; Alberts *et al.*, 2000; Von Moltke *et al.*, 2001).

General dosing strategy

The general dosing strategy involves avoidance of frequent dose increases but making contact with the patient every 1–2 weeks, waiting for 2–4 weeks with a total nonresponse (or a partial response that has plateaued) before increasing the dose. The medication can be changed if there is no response after 4 weeks; however, when clinically necessary, the change may have to be made earlier than 4 weeks and wait 8–12 weeks if a gradual response has not plateaued.

Antidepressant treatment trials in patients with chronic medical illness

Major depression is responsive to antidepressant treatment in patients with cancer, chronic tinnitus, chronic obstructive pulmonary disease (COPD), diabetes, inpatient rehabilitation needs, ischemic heart disease, Parkinson's disease, rheumatoid arthritis, stroke, and HIV+ (Katon and Sullivan, 1990).

Formal psychotherapy used in combination with antidepressants

Combination treatment may be useful if either treatment alone is only partially effective. The clinical circumstances suggest two different and discrete targets of therapy (e.g. symptom reduction to be addressed with medication and psychological/social/occupational problems to be addressed with formal psychotherapy). Targeted psychotherapy of depression (e.g. cognitive, behavioral, IPT of depression) does not have the physiological side effects associated with medications. It should be kept in mind that psychotherapy is composed of 70% ventilation, 20% exploration, and 10% suggestion, guidance reassurance.

Brain synchronization therapy and electroconvulsive therapy

ECT provides rapid symptom relief, which is especially useful in severely ill suicidal patients, refractory to other treatments, psychotic, melancholic patients, and when a patient's medical condition makes drug therapy risky.

Treatment of depression in the new millennium

Other potential antidepressants such as tachykinin, glucocorticoid, and corticotropin-releasing factor-1 receptor

antagonists have not fulfilled expectations, although newer mechanisms such as L-arginine-nitric oxidecyclic guanosine monophosphate pathway modulators, sigma-1 receptor modulators, neurosteroids, 5-HT6 and 5-HT7 serotonin receptor antagonists, β3-adrenoceptor antagonists, and vasopressin receptor antagonists, as well as some potentially new herbal antidepressants, have not yet been assessed beyond animal experiments (Kulkarni and Dhir, 2009). Further investigation of these potentially new treatment options is of major importance, in order to provide better strategies for the clinical management of depression.

(1) Cell surface: drugs designed for specific receptors (NRI, noradrenergic and specific serotonergic antidepressant, norepinephrime and dopamine disinhibitors), blockade of 5HTC2 (agomelatine).
(2) Intracellular: drugs acting on second messenger transduction, transcription.
(3) New modalities: drugs to suppress Hypothalamic-Pituitary-Adrenal (HPA) axis hyperactivation, glucocorticoid production Corticotropin- releasing factor (CRF), substance P inhibition (neurokinin-antagonist), β 3 receptors [regulate neural activity in the ventral medial prefrontal cortex (vmPFC)], drugs acting on Brain-Derived Neurotrophic Factor (BDNF).

Conclusion

Improving the quality of life of depressed patients requires the proper diagnosis and differentiating them from normal sadness. The selection of one of the 42 available AD requires the psychiatrist to be abreast of knowledge for treating comorbid physical and mental disorders. The first line of treatment, whether medications or psychotherapy, will determine the well-being of the depressed patients. Psychiatrists nowadays are satisfied with the patient being 'better' but not 'well'. The aim of treatment should be remission. Response is not sufficient. Residual depressive syndrome is common in about 32% of patients and may lead to increased relapse rates, continuing functional impairment, increase in suicide rates, and lower quality of life.

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Conflicts of interest

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