.Major depressive disorder (invited review)

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REVIEW ARTICLE

MECHANISMS OF DISEASE

Major Depressive Disorder

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Depression is related to the normal emotions of sadness and bereavement, but it does not remit when the external cause of these emotions dissipates, and it is disproportionate to their cause. Classic severe states of depression often have no external precipitating cause. It is difficult, however, to draw clear distinctions between depressions with and those without psychosocial precipitating events.[1] The diagnosis of major depressive disorder requires a distinct change of mood, characterized by sadness or irritability and accompanied by at least several psychophysiological changes, such as disturbances in sleep, appetite, or sexual desire; constipation; loss of the ability to experience pleasure in work or with friends; crying; suicidal thoughts; and slowing of speech and action. These changes must last a minimum of 2 weeks and interfere considerably with work and family relations. On the basis of this broad definition, the lifetime incidence of depression in the United States is more than 12% in men and 20% in women.[2] Some have advocated a much narrower definition of severe depression, which they call melancholia or vital depression.[3]

A small percentage of patients with major depression have had or will have manic episodes consisting of hyperactivity, euphoria, and an increase in pleasure seeking. Although some pathogenetic mechanisms in these cases and in cases of major depressive disorder overlap, a history of mania defines a distinct illness termed bipolar disorder.[4]

Depression is a heterogeneous disorder with a highly variable course, an inconsistent response to treatment, and no established mechanism. This review presents the major current approaches to understanding the biologic mechanisms of major depression.

GENETICS

Studies comparing concordance rates for major depression between monozygotic and dizygotic twins suggest a heritability of about 37%,[5] which is much lower than the heritability of bipolar disorder or schizophrenia. Some aspects of the normal personality, such as avoidance of harm, anxiousness, and pessimism, are also partly heritable.[6] Kendler et al.[7] showed that although depression is due in part to heritable depression-prone personality traits, it is also the result of heritable factors that are independent of personality. Early-onset, severe, and recurrent depression may have a higher heritability than other forms of depression.[8] It is clear from studies of families that major depression is not caused by any single gene but is a disease with complex genetic features. Studies of pedigrees with multiple cases of major depression have identified chromosomal regions with linkage to the disorder, and some of these loci have been replicated in more than one study, although no single chromosomal region has been replicated in every family study of genetic linkage in depression. Holmans et al.[9] found

evidence of linkage of recurrent, early-onset depression to chromosome 15q25-q26, but the population attributable risk was small.

No specific molecular risk factor has been reliably identified. One common polymorphic variant of the serotonin-transporter–linked polymorphic region (5-*HTTLPR*), which affects the promoter of the serotonin-transporter gene, causes reduced uptake of the neurotransmitter serotonin into the presynaptic cells in the brain.[10] Some studies have shown that this polymorphism confers a predisposition to depression,[11] but it also confers a predisposition to an anxious and pessimistic personality.[10] Brain imaging reveals functional differences in emotion-related areas of the brain among carriers of the different common polymorphisms of 5-*HTTLPR*,[12] although a direct relation to depression is unclear. In a large, prospective epidemiologic study, Caspi et al.[13] found that 5-*HTTLPR* predicted depression only in association with defined life stresses. Some environmental factors could confer a predisposition to depression by affecting the genome epigenetically — for example, increased maternal care in rodents causes an epigenetic change in the promoter region of the glucocorticoid-receptor gene.[14]

THE MONOAMINE-DEFICIENCY HYPOTHESIS

The noradrenergic and serotonergic systems originate deep in the brain and fan out over almost the entire brain, suggesting a system capable of modulating many areas of feeling, thinking, and behaving. The early antidepressants blocked the reuptake of norepinephrine and serotonin by the presynaptic neuron. The immediate effects of this pharmacologic action are to increase the availability of norepinephrine and serotonin in the synapse and to increase stimulation of the postsynaptic neuron. Inhibitors of the enzyme monoamine oxidase were also discovered to have antidepressant properties. This enzyme catabolizes norepinephrine and serotonin in their respective presynaptic neurons, and such inhibition could be expected to increase the availability of neurotransmitters. These discoveries led to a major theory of depression known as the monoamine-deficiency hypothesis. Numerous studies of norepinephrine and serotonin metabolites in plasma, urine, and cerebrospinal fluid, as well as postmortem studies of the brains of patients with depression, have yet to identify the purported deficiency reliably. However, a newly discovered form of the enzyme tryptophan hydroxylase, designated TPH-2, is specific to the brain[15] and could explain why previous postmortem studies of total enzyme activity did not show differences in tryptophan hydroxylase activity between patients with depression and controls.[16] A recent positron-emission tomographic study using a ligand for brain monoamine oxidase showed a 30% increase of the enzyme in a subgroup of patients with depression.[17] A study measuring differences in monoamine metabolites between the internal jugular vein and the brachial artery showed lower production by the brain of norepinephrine metabolites in patients with depression than in controls.[18] The monoamine-deficiency hypothesis continues to stimulate research whenever a new technical window into the brain is opened.

Serotonin and norepinephrine can be depleted experimentally in humans by oral treatments.[19] A drink containing all amino acids except tryptophan stimulates the liver to synthesize proteins and rapidly depletes the plasma (and therefore the brain) of tryptophan. Tryptophan is rate-limiting for serotonin synthesis in the brain. Such oral tryptophan depletion does not induce depression in healthy subjects but will cause a relapse of depression in patients who have been successfully treated with a serotonin-reuptake inhibitor.[19] Similarly, α-methyl paratyrosine inhibits tyrosine hydroxylase, the rate-limiting step in catecholamine synthesis. Treatment with α-methyl paratyrosine does not induce depression in normal subjects but will induce a relapse in patients who have been treated successfully with a norepinephrine-reuptake inhibitor.[19] These findings suggest that norepinephrine and serotonin have critical roles in the mechanisms of these treatments of depression but that additional neurochemical factors are necessary to cause depression.

Because direct measurements of monoamine neurotransmission did not yield definitive findings in relation to depression, the downstream effects of monoamine neurotransmission were explored (Fig. 1). The serotonin-1B receptor is located presynaptically and regulates the release of serotonin by feedback inhibition. Postmortem studies show that the levels of p11, a protein that enhances the efficiency of serotonin-1B receptor signaling, are decreased in the brains of patients with depression.[20] The serotonin-1A receptor is located both presynaptically and postsynaptically to regulate

serotonin function (Fig. 1). The receptor can be evaluated in patients with depression by injecting specific agonists and measuring specific neuroendocrine responses, such as elevation of the prolactin level.[21] Results suggest that the sensitivity of this receptor is reduced in patients with depression.[21] The α_2-noradrenergic receptor, which is usually presynaptic, modulates norepinephrine release by feedback inhibition (Fig. 1). Heightened receptor sensitivity has been described in patients with depression,[22] which is consistent with reduced norepinephrine release.

It is conceivable that the second-messenger systems for serotonergic and noradrenergic neurotransmission malfunction in depression, and for this reason the phosphatidylinositol and cyclic AMP second-messenger systems have been extensively evaluated. Reduced inositol levels have been found in postmortem studies of the brains of persons who have died by suicide[23] and in magnetic resonance spectroscopic studies of the frontal cortex in patients with depression.[24] A blunted cyclic AMP response to stimulation was found in postmortem studies of the brains of patients with depression.[25] These reductions in second-messenger function may impair neurotransmitter function even without changes in monoamine levels or receptor numbers. These data indirectly support elaborations of the original monoamine-deficiency hypothesis of depression (Fig. 1).

G proteins that mediate signaling between receptors and second-messenger systems have also been investigated in patients with depression, both in postmortem studies of the brain[26] and in studies of peripheral-blood cells.[27] Although these systems are clearly affected, no consistent picture has emerged because there are numerous forms of G proteins that vary in different areas of the brain. The cyclic AMP response element–binding protein (CREB) is a transcription factor affected by cyclic AMP in the cell. In an animal model of depression, rats with overexpression of CREB in the dentate gyrus behaved similarly to rats treated with antidepressants, but the opposite effect was found when CREB was overexpressed in the nucleus accumbens.[26,28] Thus, the role of CREB in depression is specific to the region of the brain. Most but not all studies show that long-term treatment with antidepressants stimulates CREB function, possibly depending on the type of drug and the dosage.[28] Levels of CREB and phospho-CREB were reduced in postmortem studies of the cortexes of patients who had a major depressive disorder and had not taken antidepressants, as compared with controls.[26,28] Many studies of second-messenger systems and transcription factors in depression were inspired by the belief that it takes several weeks before antidepressant treatment has an effect; consequently, the studies were designed to detect time-dependent biochemical changes in the cell. New meta-analyses suggest that antidepressant effects begin rapidly, however,[29] thereby supporting the classic monoamine-deficiency hypothesis.

A strong point of the monoamine theory has been its predictive power. Almost every compound that has been synthesized for the purpose of inhibiting norepinephrine or serotonin reuptake has been proved to be a clinically effective antidepressant. A behavioral model of depression has been developed in which a rodent is placed in a glass cylinder filled with water, the sheer wall offering no chance of escape. The animal struggles for a while and then floats passively (the forced swim test). A single prior injection of antidepressant increases the struggling time; results in this model have excellent predictive validity for new antidepressants. Other animal models have been developed by selective breeding of rats for depression-like behavior, and these genetically susceptible rodents also have a response to antidepressants.[30] Still other models that can be studied biochemically induce depression with the use of long-term mild stress or learned helplessness. However, no animal model of depression captures the periodic change of behavior into and out of depression that is seen in patients with depression.

Molecular techniques such as gene knockout partially support the monoamine theory of depression. The serotonin-reuptake–transporter knockout mouse is excessively anxious and characterized by increased immobility in the forced swim test.[31] This effect is similar to that of the low-activity polymorphic variant of the serotonin receptor on human personality[10] but is the opposite of the expected effects of serotonin-reuptake–inhibitor antidepressants. However, this inconsistency could be explained by the difference between a chronic monoamine abnormality during brain development[31] and the hypothesized acute monoamine depletion in an adult with depression. Table 1 shows the effects in mice of knocking out genes related to monoamine neurotransmitters.

The effects of stimulants on mood indirectly

support the monoamine-deficiency hypothesis of depression and show that mood can be altered rapidly. Cocaine and amphetamines are powerful releasers of monoamines into the synapse as well as inhibitors of reuptake. Their mood-elevating effects are immediate, but in patients with severe depression they have often been reported to cause agitation rather than relief of depression. This finding could reflect the ability of these stimulants to deplete the presynapse of monoamines and thus cause a "crash" into depression. Recent studies support the theory that an acute response to a single dose of amphetamine predicts a patient's longer-term response to monoamine-reuptake inhibitors.[46]

The role of dopamine deficiency in depression is suggested by the frequency of depression in patients with Parkinson's disease and the effect of reserpine, which depletes serotonin, norepinephrine, and dopamine, causing a hypoactive state in animals. The antidepressant agent buproprion inhibits the reuptake of dopamine. Some direct dopamine-receptor agonists, such as pramipexole, have been reported to be efficacious in the treatment of depression, even though they were developed for Parkinson's disease.[47]

A major liability of the monoamine-deficiency hypothesis is its derivation from the mechanism of currently available antidepressants. Approximately two thirds of patients have a clinical response to these agents, whereas one third have a response to placebo.[48] Perhaps the mechanism of depression is not related to monoamines in two of three cases.

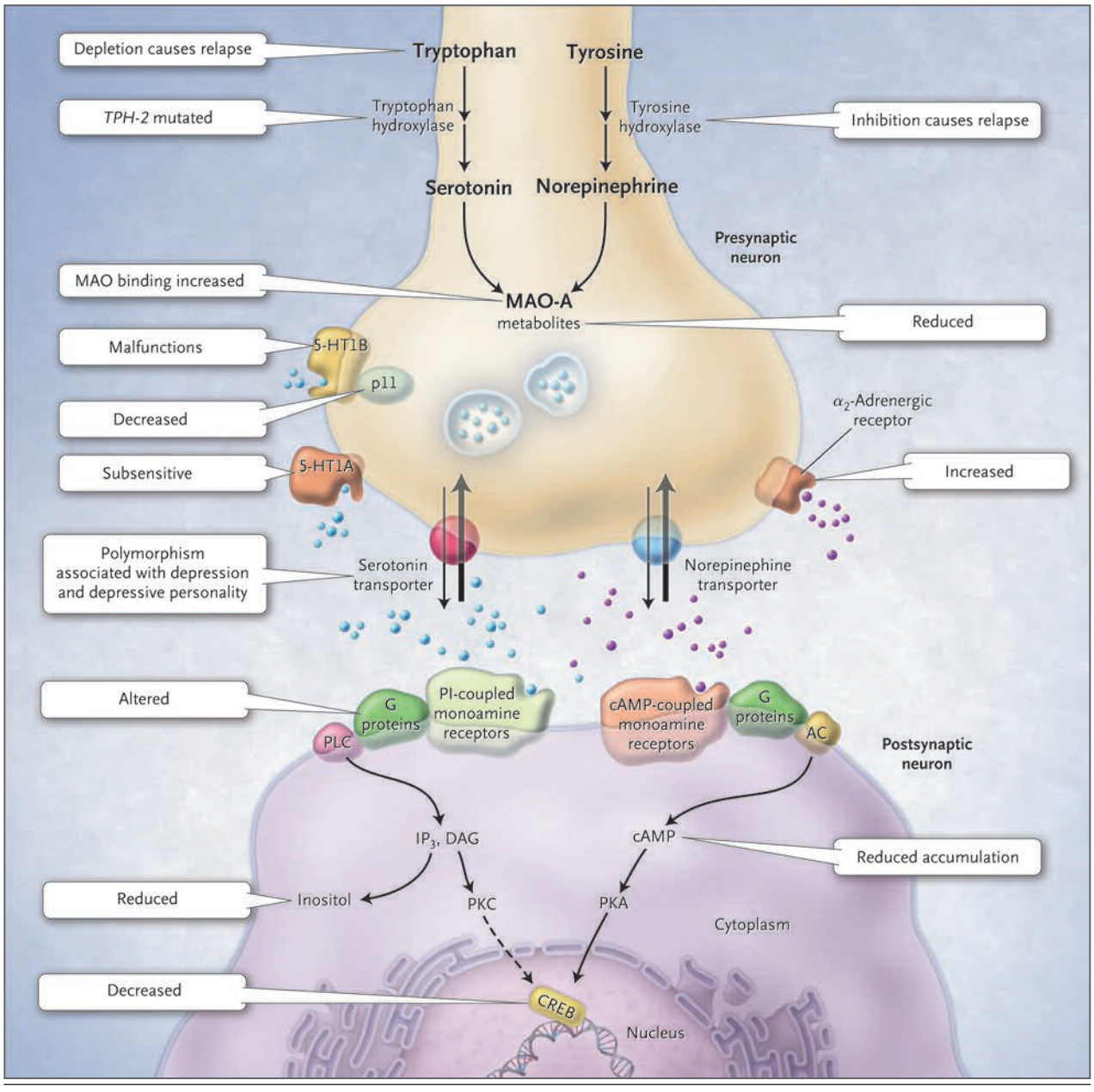
STRESS, THE HYPOTHALAMIC–PITUITARY–ADRENAL AXIS, AND GROWTH FACTORS

Stress[49] is perceived by the cortex of the brain and transmitted to the hypothalamus, where corticotropin-releasing hormone (CRH) is released onto pituitary receptors. This stimulus results in the secretion of corticotropin into plasma, stimulation of corticotropin receptors in the adrenal cortex, and release of cortisol into the blood. Hypothalamic cortisol receptors respond by decreasing CRH production to maintain homeostasis (Fig. 2).

There is considerable evidence that cortisol and its central releasing factor, CRH, are involved in depression.[50,51] Patients with depression may have elevated cortisol levels in plasma,[38] elevated CRH levels in cerebrospinal fluid,[50] and increased levels of CRH messenger RNA and protein in limbic brain regions.[50] In studies using dexamethasone to evaluate the sensitivity of the hypothalamus to feedback signals for the shutdown of CRH release, the normal cortisol-suppression response is absent in about half of the most se-

Figure 1 (facing page). The Monoamine-Deficiency Hypothesis Extended.

The monoamine hypothesis of depression postulates a deficiency in serotonin or norepinephrine neurotransmission in the brain. Monoaminergic neurotransmission is mediated by serotonin (5-hydroxytryptamine 1A [5-HT1A] and 5-hydroxytryptamine 1B [5-HT1B]) or norepinephrine (noradrenaline) released from presynaptic neurons (serotonergic neuron, shown on the left side, and noradrenergic neuron, shown on the right side [condensed virtually]). Serotonin is synthesized from tryptophan, with the first step in the synthetic pathway catalyzed by tryptophan hydroxylase; norepinephrine is synthesized from tyrosine, with the first step catalyzed by tyrosine hydroxylase. Both monoamine transmitters are stored in vesicles in the presynaptic neuron and released into the synaptic cleft, thereby affecting both presynaptic and postsynaptic neurons. Cessation of the synaptic action of the neurotransmitters occurs by means of both reuptake through the specific serotonin and norepinephrine transporters and feedback control of release through the presynaptic 5-HT1A and 5-HT1B regulatory autoreceptors for serotonin and the α2-noradrenergic autoreceptors for norepinephrine. Monoamine oxidase A (MAO-A) catabolizes monoamines presynaptically and thereby indirectly regulates vesicular content. The protein p11, which interacts with 5-HT1B receptors, increases their function. Postsynaptically, both serotonin and norepinephrine bind two kinds of guanine nucleotide triphosphate–binding protein (G protein)–coupled receptors: cyclic AMP (cAMP)–coupled receptors, which activate adenylate cyclase (AC) to generate cAMP, and phosphatidylinositol (PI)–coupled receptors, which activate phospholipase C (PLC). PLC generates inositol triphosphate (IP_3) and diacylglycerol (DAG); cAMP activates protein kinase A (PKA), and IP_3 and DAG activate protein kinase C (PKC). The two protein kinases affect the cAMP response element–binding protein (CREB). Findings in patients with depression that support the monoamine-deficiency hypothesis include a relapse of depression with inhibition of tyrosine hydroxylase or depletion of dietary tryptophan, an increased frequency of a mutation affecting the brain-specific form of tryptophan hydroxylase (TPH-2), increased specific ligand binding to MAO-A, subsensitive 5-HT1A receptors, malfunctioning 5-HT1B receptors, decreased levels of p11, polymorphisms of the serotonin-reuptake transporter associated with depression, an inadequate response of G proteins to neurotransmitter signals, and reduced levels of cAMP, inositol, and CREB in postmortem brains.



verely depressed patients.[52] Antidepressant-induced clinical remission is accompanied by reversal of some of these abnormalities.[52]

Adults with a history of physical or sexual abuse as children have increased levels of CRH in cerebrospinal fluid.[53] Adult rodents that were separated from their mothers or abused as pups show increased immobility in the forced swim test, which is reversed by antidepressant treatment.[54] Mice with region-specific knockout of the glucocorticoid receptor at an adult age have increased activity of the hypothalamic–pituitary–adrenal axis and increased immobility in the forced swim test, both of which are reversed by antidepressants.[55] Increased levels of monoamines in the synapse affect the hypothalamic–pituitary–adrenal axis[56] and reverse some of the long-term effects of stress.[56] It is possible that antidepressants relieve depression by reducing the secondary stress caused by a painfully dispirited mood rather than by directly elevating mood. An antistress mechanism could explain the general usefulness of antidepres-

Table 1. Monoamine-Related Gene Knockouts That Affect Depression-Related Behavior in Mice.*

Gene or Protein	Function	Depression-Related Changes	Corroboration of Monoamine-Deficiency Hypothesis	Other Behavior Elicited by Knockout of Gene
sert	Serotonin transporter	Increased depressive behavior, reduced serotonin level, desensitized postsynaptic 5-HT1AR, and reduced presynaptic 5-HT1AR function[32]	No	Excessive anxiety[32]
net	Norepinephrine transporter	Reduced depressive behavior, prolonged norepinephrine clearance, elevated extracellular norepinephrine levels[33]	Yes	Increased locomotion response to amphetamines and cocaine[33]
5-ht1ar	Serotonergic 1A receptor (presynaptic autoreceptor and postsynaptic)	Reduced depressive behavior, normal serotonin level and release, impaired SSRI-induced neurogenesis[32]	No	Excessive anxiety, impaired hippocampal learning[32]
5-ht1br	Serotonergic 1B receptor (presynaptic autoreceptor and postsynaptic)	Reduced response to SSRI in forced swim test, reduced serotonin level and increased serotonin release, increased SSRI-induced serotonin release, decreased serotonin-transporter expression[32]	Yes	Increased aggressiveness, reduced anxiety, increased exploration, increased use of cocaine[32]
p11 (protein)	Interacts with and enhances signaling efficiency of 5-HT1BR	Increased depressive behavior, increased serotonin turnover[20]	No	Not reported[20]
5-ht2ar	Serotonergic 2A receptor	No change[34]	No	Reduced inhibition in conflict-anxiety paradigms[34]
5-ht7	Serotonergic 7 receptor (possibly presynaptic autoreceptor and postsynaptic)	Reduced depressive behavior and REM sleep duration[35]	No	Normal locomotion[35]
$\alpha_{2a}ar$	α_{2A}-Adrenergic receptors (presynaptic autoreceptor)	Reduced norepinephrine levels, presynaptic inhibition of release,[36] increased depressive behavior[37]	No	Altered sympathetic regulation,[36] impaired motor coordination
$\alpha_{2c}ar$	α_{2C}-Adrenergic receptors (presynaptic autoreceptor restricted to central nervous system)	Reduced depressive behavior[38]	Yes	Increased aggressiveness,[32] increased locomotion response to amphetamines[36]
mao-a	Monoamine oxidase A	Increased brain serotonin and epinephrine levels[39]	No	Increased aggressiveness and response to stress,[30] decreased exploration[32]
ac VII (heterozygotes)	Adenylyl cyclase type 7	Reduced depressive behavior[40]	No	Unchanged anxiety[40]
impa1	Inositol monophosphatase 1	Reduced depressive behavior, unaltered brain inositol levels[41]	Yes	Increased hyperactivity and sensitivity to pilocarpine-induced seizures[41]
smit1	Sodium-*myo*-inositol transporter 1	Reduced depressive behavior and brain inositol levels[42]	Yes	Increased sensitivity to pilocarpine-induced seizures[42]
creb	Cyclic AMP–response element–binding protein	Reduced depressive behavior, normal antidepressant-induced behavior[43]	No	No increase in BDNF after long-term use of antidepressants[43]
bdnf				
Male mice	Brain-derived neurotrophic factor	No depressive behavior[44]	No	Increased aggressiveness, hyperphagia,[45] hyperactivity[44]
Female mice	Brain-derived neurotrophic factor	Increased depressive behavior[44]	Yes	Increased aggressiveness, hyperphagia[45]

* BDNF denotes brain-derived neurotrophic factor, 5-HT1AR 5-hydroxytryptamine 1A receptor, 5-HT1BR 5-hydroxytryptamine 1B receptor, REM rapid eye movement, and SSRI selective serotonin-reuptake inhibitor.

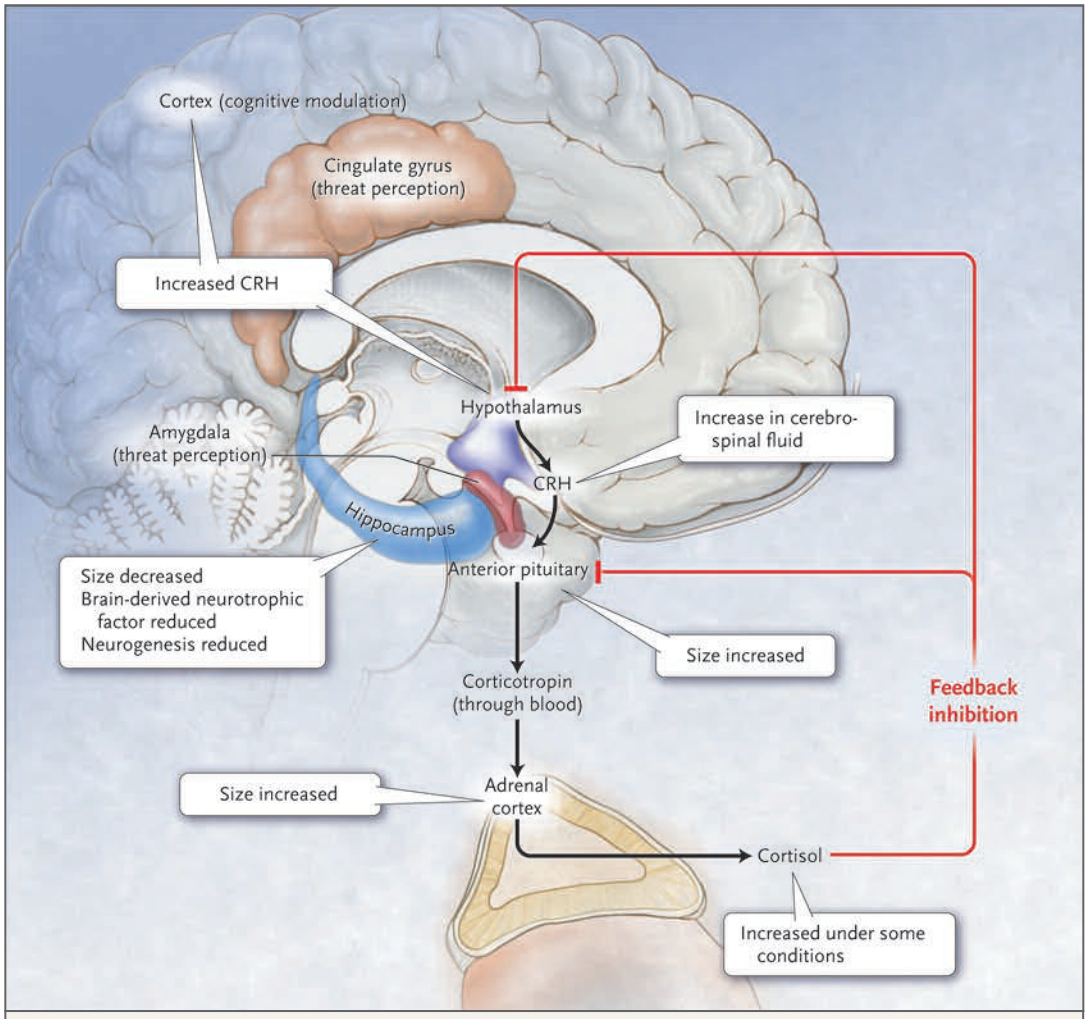


Figure 2. The Hypothalamic–Pituitary–Cortisol System in Depression.

The hypothalamic–pituitary–cortisol hypothesis of depression postulates that abnormalities in the cortisol response to stress may underlie depression. The black arrows show that in response to stress, which is perceived by the brain cortex and the amygdala and transmitted to the hypothalamus, corticotropin-releasing hormone (CRH) is released, inducing the anterior pituitary gland to secrete corticotropin into the bloodstream. Corticotropin stimulates the adrenal cortexes to secrete the glucocorticoid hormone cortisol. The red lines show that cortisol, in turn, induces feedback inhibition in the hypothalamus and the pituitary, suppressing the production of CRH and corticotropin, respectively. Findings in patients with depression that support the hypothalamic–pituitary–cortisol hypothesis include the following: cortisol levels are sometimes increased in severe depression, the size of the anterior pituitary and adrenal cortex is increased, and CRH levels in the cerebrospinal fluid and CRH expression in the limbic brain regions are increased. Hippocampal size and the numbers of neurons and glia are decreased, possibly reflecting reduced neurogenesis due to elevated cortisol levels or due to reduced brain-derived neurotrophic factor.

sants for a wide variety of psychiatric conditions, including panic disorder, post-traumatic stress disorder, bulimia, premenstrual syndrome, and obsessive–compulsive disorder. CRH-receptor antagonists show antidepressant activity in animal models,[57] but the results of large clinical trials have been disappointing. A compound that blocks the glucocorticoid receptor has been reported to be efficacious in depression, but only the most severe and psychotic type.[58]

A single test for the cortisol level in blood does not contribute to the diagnosis of depression, since levels of cortisol vary markedly in a circadian rhythm[38] and because the overlap between values in patients and those in controls is considerable. Mild stress induced in the laboratory, such as

Table 2. Additional Biologic Theories of the Pathophysiology of Depression.*

Theory	Supporting Evidence	Contradictory Evidence
Altered glutamatergic neurotransmission	Glutamate and glutamine levels in the prefrontal cortex are reduced[91]	Glutamate levels in the occipital cortex are increased[92,93]
	Intravenous ketamine, an NMDA antagonist, induces rapid, sustained antidepressant effect[94]	Ketamine binds to high-affinity-state D2 dopamine receptors[95]
	Cortical messenger RNA levels of glutamate transporters and of the enzyme that converts glutamate to glutamine are reduced[96]	It is not clear whether antidepressants affect AMPA receptors in the brain[97]
Reduced GABAergic neurotransmission	Levels of GABA in plasma, cerebrospinal fluid, the dorsolateral prefrontal cortex, and the occipital cortex are reduced[91-93]	GABA occurs in more than 30% of brain synapses, suggesting nonspecificity
	GABA-modulating agents have effects in animal models of depression[98]	There is a lack of difference in prefrontal cortex GABA levels on MRS in depression[99]
	Antidepressants affect GABAergic function[98]	GABA neurotransmission may be related to symptoms of anxiety in depression
	GABA neuron immunoreactivity is reduced in the prefrontal cortex[100]	
Abnormal circadian rhythms	Sleep deprivation and light therapy have antidepressant effects[101,102]	The association between clock-related genes and depression is inconsistent[103]
	Some patients with depression have circadian abnormalities of mood, sleep, temperature, and neuroendocrine secretion[104]	
	Rodents active during the day become depressed when daylight is shortened[105]	
Deficient neurosteroid synthesis	Cholesterol levels are low in plasma and the brain during depression[106]	The findings in schizophrenia are similar[107]
	DHEA has antidepressant effects in patients with depression[108]	Neurosteroids (neuroactive steroids in the brain that modulate neurotransmitter receptors) mostly affect memory and sleep
Impaired endogenous opioid function	δ-Opioid–receptor agonists have antidepressant-like effects in rodents and up-regulate levels of BDNF in the brain[109]	Although early reports suggested that opiates may be effective in treating depression,[110] data from large, controlled, randomized trials are lacking
	Capacity for cortical μ-opioid–receptor binding is decreased in response to sustained sadness[111]	
Monoamine–acetylcholine imbalance	Depressed mood can be induced in humans by administration of physostigmine, an acetylcholinesterase inhibitor[112]	Mecamylamine, a nicotinic acetylcholine receptor antagonist, reduced symptoms of depression[113]
	Nicotinic acetylcholine receptor antagonists potentiate antidepressants[114]	Many antidepressants are not anticholinergic
Cytokine-mediated cross-talk between the immune system and the brain	Depression is common in infectious and autoimmune diseases[115]	Most studies are correlative[116]
	Exposure to cytokines induces depressive symptoms, and cytokine secretion is increased in major depression[115]	Cytokine-induced depressive symptoms are temporary and not replicated in all studies[117]
	Antidepressants have antiinflammatory effects[115]	Substance P antagonists are not therapeutic in depression
	Cytokines affect the hypothalamic–pituitary–adrenal axis and monoamines[115]	

Thyroxine abnormalities	Levels of transthyretin are reduced in the cerebrospinal fluid in patients with depression[118]	
	Thyroid hormones modulate the serotonergic system in the brain[119]	Thyroxine monotherapy is ineffective
	Brain neurogenesis is decreased after the administration of thyroxine in adult rats with hypothyroidism[120]	Hypothyroidism is not manifested in most patients with depression
	Rate of response to triiodothyronine is increased during depression[121]	
Dysfunction of specific brain structures and circuits	Transcranial magnetic stimulation of the prefrontal cortex[122] and deep-brain stimulation of the anterior cingulate affect mood[123]	Implicated brain areas differ from study to study
	Glucose use is reduced in the prefrontal cortex[124] and subgenual prefrontal cortex[125]	Inconsistent findings with respect to blood flow, volumetric, glucose utilization, and postmortem methodologies[63,124,126]
	Circuit dynamics in the hippocampus are altered in a rat model of depression[127]	

* AMPA denotes alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, BDNF brain-derived neurotrophic factor, DHEA dehydroepiandrosterone, GABA γ-aminobutyric acid, MRS magnetic resonance spectroscopy, and NMDA *N*-methyl-D-aspartic acid.

stress associated with mental arithmetic calculations or simulated public speaking, results in greater changes in plasma cortisol levels than most reported differences between the values in patients with depression and those in controls.[38] It is possible that chronic mild elevations of cortisol, especially at night, when cortisol levels in normal subjects are very low, have a pathogenic role in depression. It is also possible that peripheral cortisol elevations are only a reflection of central disturbances in CRH signaling, which mediate the effects of environmental stress on mood.[59] A major liability of the hypothalamic–pituitary–adrenal axis theory of depression is the difficulty of defining the relationship of stress to depression. Some patients have a single lifetime depressive episode, whereas a larger proportion have a recurrent or even chronic course. Various types of acute stress, early childhood trauma, or long-term psychosocial problems may be involved and may lead to different responses of the stress system. Stress may be causative in some cases and secondary to depressed mood in others.

Severe stress in rodents does not necessarily model the common stresses of childhood. The association of abuse in childhood with psychopathologic disorders, including depression, in adulthood could be due to common factors linking family perpetrators of abuse and their victims, including not only shared genes but also a shared environment of poverty, poor nutrition, and poor prenatal care. Depression is not uncommon in people with no psychosocial risk factors. Most patients treated for depression have no evidence of hypothalamic–pituitary–adrenal dysfunction, just as most such patients have no direct evidence of brain monoamine deficiency.

The classic teaching is that neurons do not divide in the adult mammalian brain, but studies have shown that neurogenesis occurs in several areas of the brain, especially the hippocampus. Neurogenesis is more prominent in rodents than in primates,[60] and some have questioned whether it occurs in the human cortex.[61] Elevated levels of glucocorticoids can reduce neurogenesis, and this has been suggested as a mechanism for the decreased size of the hippocampus on magnetic resonance images of the brain in many patients with depression.[62] In postmortem studies of patients with depression, cell loss in the subgenual prefrontal cortex, atrophy in the dorsolateral prefrontal cortex and the orbitofrontal cortex, and

increased numbers of cells in the hypothalamus and the dorsal raphe nucleus have been reported.[63] These effects resemble the atrophic changes in the brain in patients with Cushing's disease[64] and in rodents treated with glucocorticoids.[65] However, cortisol elevations in depression are much lower than in Cushing's disease.

Restraint in a small container induces stress in rodents, suppressing neurogenesis, and this effect is countered by antidepressant treatment.[66] Antidepressants also enhance neurogenesis in nonhuman primates.[67] Santarelli et al.[68] irradiated the hippocampus in mice and abolished neurogenesis. They found that the radiation also abolished the ability of the animals to respond behaviorally to antidepressant treatment in the forced swim test, but this phenomenon does not occur in every mouse strain studied.[69] Henn and Vollmayr summarized other studies providing evidence that decreased neurogenesis is a result of stress and anxiety but may not be behaviorally relevant.[70] The relevance of animal models of neurogenesis to clinical studies of depression has been questioned by analogy with studies of neuroprotection strategies in stroke, for which numerous findings in animal models have not been replicated in human studies.[71]

Brain-derived neurotrophic factor (BDNF), a neurotrophic peptide, is critical for axonal growth, neuronal survival, and synaptic plasticity,[72] and its levels are affected by stress[73] and cortisol.[74] A postmortem study of patients with depression who had committed suicide showed that BDNF was reduced in the hippocampus.[75] Antidepressant drugs and electroconvulsive therapy up-regulate BDNF and other neurotrophic and growth factors[75,76]; a single bilateral infusion of BDNF into the dentate gyrus has antidepressant-like effects.[77] One study showed that the hippocampus was smaller than normal in patients with depression who carried a met166 BDNF allele.[78] In an animal model of depression, epigenetic histone methylation mediated down-regulation of *BDNF* transcripts and antidepressant treatment reversed this effect.[79] These studies suggest that BDNF is the link among stress, neurogenesis, and hippocampal atrophy in depression. However, a genetic association of the BDNF val166met polymorphism with depression has not been replicated in most studies,[74] and BDNF may be related not only to depression but to multiple psychiatric disorders.[74] BDNF-knockout mice have behaviors unrelated to depression.[45] Reduced BDNF levels in the peripheral blood of patients with depression seem to derive almost entirely from blood platelets,[80] and many artifacts must therefore be considered in interpreting these findings. Inflammation in the brain and some neurotoxins increase brain BDNF levels, suggesting that the actions of BDNF are not uniformly therapeutic.[81] Castrén[82] has proposed that antidepressant treatments may increase synaptic sprouting and allow the brain to use input from the environment more effectively to recover from depression. This hypothesis highlights the role that cognition may play in depression and suggests that biochemical mechanisms may be nonspecific.

Strong epidemiologic data point to an association between major depressive disorder and increased cardiovascular morbidity and mortality.[83] In many patients, cardiovascular disorders precede depression, and in others, depression precedes the cardiovascular disorder. Both n–3 fatty acid deficiency[84] and elevated plasma homocysteine levels[85] have been implicated in cardiovascular disease and in depression. Elevated cortisol levels in depression could increase the risk of coronary artery disease, since cortisol increases visceral fat.[64,86] Antidepressant treatment increases the survival rate among patients who become depressed after coronary occlusion.[86] Endothelial-cell signaling plays a crucial role in brain neurogenesis,[87] and these cells secrete BDNF; thus, both depression and cardiovascular disease could be examples of an endothelial disorder. Signs of inflammatory processes have been described in major depression[88] and in cardiovascular disease. Some data suggest that exercise has protective or therapeutic effects in depression.[89] Rodent models support this possibility.[90]

OTHER POSSIBLE MECHANISMS

Table 2 summarizes possible pathophysiological mechanisms of depression other than those based on the monoamine-deficiency hypothesis or the roles of stress, cortisol, and neurogenesis. Many of these other proposed mechanisms have also been implicated in psychiatric and neurologic disorders other than depression. Since the components of the brain are highly interconnected, it is not difficult to find possible integrative frameworks between two or more of the various theories. Testing the theories in a manner that can re-

ject the null hypothesis has been more difficult. Research in depression has sometimes been sequentially imitative of dominant ideas in related fields, such as neurogenesis, glutamate neurotransmission, and nicotinic receptors, instead of progressing on its own path.

SUMMARY

It would be appealing to attempt to categorize depression in terms of monoamine-depletion forms that are perhaps related to genes coding for enzymes involved in neurotransmission and cortisol-related forms that are characterized by a more long-term course, hippocampal atrophy, and a history of psychosocial stress. However, the clinical data do not fall into such neat categories, since monoamine-based antidepressants are most effective in patients with severe depression when cortisol levels remain high after the administration of dexamethasone.

Major depressive disorder is likely to have a number of causes. Middle-aged or elderly patients presenting with depression may have a disorder related to cardiovascular disease and originating from endothelial dysfunction.[128] Patients in their late teens or early 20s who have severe depression may have important genetic risk factors and a high risk of manic episodes.[8] In patients with an anxious and depressive personality, depression may be due to genetically determined personality factors[11] or adverse childhood experiences.[129]

Avoidance of premature closure on any one scientific theory of the mechanism of depression will best serve the search for new, more effective treatments. It is likely that the pathogenesis of acute depression is different from that of recurrent or chronic depression, which is characterized by long-term declines in function and cognition. Mood can be elevated (by stimulants,[46] by brain stimulation,[123] or by ketamine[94]) or depressed (by monoamine depletion[19] in recovered patients) for short periods, but longer-term improvement may require reduction of the abnormal glucocorticoid function induced by stress or increases in brain neurotrophic factors.

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Molecular Brain

REVIEW Open Access

Depression research: where are we now?

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Abstract

Extensive studies have led to a variety of hypotheses for the molecular basis of depression and related mood disorders, but a definite pathogenic mechanism has yet to be defined. The monoamine hypothesis, in conjunction with the efficacy of antidepressants targeting monoamine systems, has long been the central topic of depression research. While it is widely embraced that the initiation of antidepressant efficacy may involve acute changes in monoamine systems, apparently, the focus of current research is moving toward molecular mechanisms that underlie long-lasting downstream changes in the brain after chronic antidepressant treatment, thereby reaching for a detailed view of the pathophysiology of depression and related mood disorders. In this minireview, we briefly summarize major themes in current approaches to understanding mood disorders focusing on molecular views of depression and antidepressant action.

Introduction

Mood disorders such as major depression and bipolar disorders are the most common psychiatric disorders in modern society. About 16% and 1% of the population are estimated to be affected by major depression and bipolar disorder one or more times during their life time, respectively [1]. The presence of the common symptoms of these disorders are collectively called 'depressive syndrome' and includes a long-lasting depressed mood, feelings of guilt, anxiety, and recurrent thoughts of death and suicide [2]. The genetic contribution to the manifestation of depression has been estimated as 40-50% [3]. However, combinations of multiple genetic factors may be involved in the development of depression, because a defect in a single gene usually fails to induce the expression of multifaceted symptoms of depression [4]. Also, various non-genetic factors such as stress, affective trauma, viral infection, and neurodevelopmental abnormalities increase the complexity of the pathogenesis of the disease. Thus, extensive studies have led to a variety of hypotheses for the molecular mechanism of depression, but a definite pathogenic mechanism has yet to be defined.

The 'monoamine hypothesis,' which suggests a deficiency or imbalances in the monoamine neurotransmitters, such as serotonin, dopamine and norepinephrine, as the cause of depression has been the central topic of depression research for approximately the last 50 years. This hypothesis has been initiated and supported by the fact that early versions of antidepressants including tricyclics and monoamine oxidase inhibitors have the common effect of acutely enhancing monoamine function [5-7]. Recent development of the selective serotonin reuptake inhibitors (SSRIs) as effective antidepressants has further strengthened the hypothesis [6,8]. However, unresolved complexity of the current antidepressants remains. First, antidepressants are effective in less than 50% of patients, and recently discovered drugs have failed to enlarge the extent of applicable patients [2]. Second, chronic treatment with antidepressants is required for clinical effects, and the reason for this is unknown [9]. Third, depression medications as well as mood stabilizers show a wide spectrum of undesired side effects.

In particular, because clinical effects of antidepressants that acutely modify monoamine systems are significantly delayed, it is now believed that an adaptation of downstream events, including lasting changes in gene expression by chronic treatment, underlie the antidepressant efficacy [10]. This phenomenon suggests that there is probably not a simple relationship between biogenic amines and depression postulated by classical monoamine hypothesis. The complexity may be due to multiple factors, which is likely because depression is a group of disorders with several underlying pathologies. Also, expression of depression symptoms may require disturbances in certain neurotransmitter systems that are

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functionally interconnected to each other at multiple levels. Taken together, while it still has to be emphasized that the initiation of antidepressant efficacy may be mediated by acute changes in monoamine systems, apparently, the focus of current research is moving toward molecular mechanisms that underlie long-lasting downstream changes in the brain after chronic antidepressant treatment, thereby reaching for a detailed view to the pathophysiology of depression and related mood disorders. In this minireview, we summarize major themes in current approaches to understanding depression and related mood disorders.

Gene-environment interactions

As a way to discovering genes predisposing to depression, geneticists have long been searching for gene variants that play a role in the response to life stresses, a critical environmental factor for the onset of depression, which would be an example of 'gene-environment interaction': whereby an environmental factor is filtered through the activity of a gene to confer differential susceptibility to depression among individuals. To this end, polymorphisms in the serotonin transporter (5-hydroxyltryptamine transporter, 5-HTT) gene have been extensively analyzed. It has been reported that the expression level of 5-HTT from the 5-HTT gene is influenced by polymorphisms in the 5'-flanking region (5-HTT gene-linked polymorphic region, 5-HTTLPR) and in the variable number tandem repeat (VNTR) of the second intron [11,12]. In particular, a short variant of 5-HTTLPR appears to be associated with repressed transcriptional activity of the promoter, decreased 5-HTT expression, and decreased 5-HT uptake when compared with a long variant of 5-HTTLPR [13]. Significantly, genetic studies have shown that these polymorphisms are associated with major depressive disorder in human [14]. Moreover, a longitudinal study with 847 New Zealanders has shown that a short allele of 5-HTTLPR variants is associated with an increase in susceptibility to depression in response to life stresses such as job losses or divorces [15]. Strikingly, in this study, the polymorphism is influential only when the subjects are in significant life stresses, suggesting that 5-HTT may be a connecting point between individual's genetic makeup and environmental triggers of depression. These observations were further strengthened by study showing that increased depression scores in maltreated children without social supports are associated the short allele of 5HTTLPR [16].

However, the insight from these studies does not appear to be fully supported by other studies. The association of allelic variation in VNTR of 5-HTT gene with the susceptibility to depression was not consistently detected in some analyses [17,18]. A meta-analysis showed that polymorphisms in 5-HTTLPR and the second intron are actually found in depressed patients but the strength of association does not reach a statistical significance [19]. An extensive study using 1206 twins also failed to find a main effect of 5-HTTLPR, or an interaction between the 5-HTTLPR genotype and stressful life events on major depression [20]. Moreover, a recent meta-analysis using 14 comparable studies has yielded no evidence that the serotonin transporter genotype alone or in interaction with stressful life events is associated with an elevated risk of depression [21]. The mixed results from these studies reveal the potential weakness of the 'candidate gene' approach focusing on a specific gene variant to elucidate gene-environment interactions, and thus add importance on unbiased whole-genome scan approach, especially when a disease with polygenic nature, such as depression and related mood disorders, is concerned.

Stress response circuits

Chronic stress is an important component in depression even though it does not seem to function as a necessary or sufficient factor. From this point of view, the hypothalamic-pituitary-adrenal (HPA) axis, a core neuroendocrine circuit for managing stress in the body, has been a topic of interest in depression research [22]. Corticotrophin-releasing factor (CRF) secreted from the paraventricular nucleus of the hypothalamus enhances secretion of adrenocorticotrophin (ACTH) from the pituitary [22,23], and subsequently, glucocorticoid is secreted from the adrenal cortex, impacting neurobehavioral functions of various brain regions [2]. The HPA axis forms a feedback loop via certain brain regions such as the hippocampus and amygdala [24]. It was reported that hypercortisolemia, a persistent upregulation of blood glucocorticoid levels, increases the excitotoxicity of CA3 pyramidal neurons in the hippocampus, resulting in dendritic atrophy, reduction in spinogenesis, apoptosis of neurons, and possibly inhibition of adult neurogenesis [25]. These functional abnormalities of hippocampal neurons caused by chronic stress can reduce the inhibitory tone on the HPA-axis, which results in hyperactivity of the HPA-axis [23]. Notably, hyperactivity of HPA-axis is evident in approximately half of depressed patients and chronic treatment with antidepressants often reverses this phenomenon [23,26]. Furthermore, evidence from animal studies suggests that chronic treatment with antidepressants appears to contribute to the recovery of the abnormal function of the hippocampus by increasing neurogenesis [27,28].

In this regard, one research direction is to evaluate the therapeutic potentials of weakening of the functions of the HPA axis. The obvious targets are CRF receptors expressed in the pituitary and glucocorticoid receptors

expressed in the hippocampus and other brain regions, because those receptors are core components in the HPA axis and the associated feedback loop [24,29-32]. In a similar context, vasopressin receptors have also emerged as alternative targets [33,34]. Vasopressin is a neuropeptide that enhances CRF function and works through vasopressin receptors expressed in the amygdala and other parts of the limbic system. Also, a single nucleotide polymorphism (SNP) of vasopressin 1b (V1b) receptor has protective effects against major depressive disorder [35]. Intriguingly, antagonism of CRF receptors, glucocorticoid receptors, and vasopressin receptors appear to exhibit antidepressant effects in experimental animals. The applicability to human patients remains to be further refined.

Neurotrophic factors

Long-term stress appears to reduce the expression level of brain derived neurotrophic factor (BDNF) in the hippocampus [36]. Also, in a post-mortem study of depressed patients, a reduction in BDNF expression was reported [37]. In addition, polymorphisms of BDNF gene are associated with neuroticism, a personality trait linked to increased susceptibility to depression [38]. A family-based association study showed that polymorphisms in BDNF genes are related to bipolar disorders [39]. Conversely, a chronic treatment with antidepressants not only enhances the BDNF level but also increases the stress resistance in animals [40,41]. These observations provided a basis for 'neurotrophism theory' stating that depression is caused by a deficit in neurotrophic factors, and antidepressants neutralize this deficit. This theory may be intimately related to neuronal damages in the hippocampal region caused by hyperactivity of stress response circuits aforementioned. Because BDNF is known to enhance synaptic plasticity in various brain regions [42,43], it is reasonable to postulate that improving BDNF function may be beneficial to the hippocampal neurons that are susceptible to stress-induced damages. Supporting this idea, direct injection of BDNF into the hippocampus of experimental animals induces behavioral changes similar to antidepressant treatment [41]. Thus, BDNF and its receptor TrkB, have become promising targets of novel-type antidepression therapies.

Despite these observations, a possible causative relationship between BDNF function and the pathogenesis of depression or antidepressant efficacy requires further clarification. For example, while the antidepressant efficacy is suppressed in experiments using inducible BDNF knock-out mice, depression-related behaviors are only seen in females, showing significant gender differences [36]. Moreover, forebrain-specific conditional TrkB receptor knockout mice do not exhibit depression-related behaviors such as increased behavioral despair in the forced swim test [44], whereas it has been demonstrated that activation of TrkB receptor is required for antidepressant-induced behavioral effects [45]. Thus, the relationship between the loss of BDNF activity and the expression of depressive symptoms is not in a simple correlation. Nevertheless, the potential value of the neurotrophic theory as a basis for the design of new form of anti-depression therapies cannot be excluded by the complexity of the current experimental results.

Histone modifications

One poorly understood characteristic of antidepressants is the long delay before the onset of positive effects in patients [10]. This phenomenon is often attributed to the slow development of adaptation in the relevant neurons that underlies the beneficial effect of the drugs. The identity of the adaptation is not clear yet, but enduring changes in the state of chromatin are thought to be involved. Chronic electro-convulsive shocks that are effective for some depressed patients also induce changes in wide range of the histone modification patterns in experimental animals [46]. One locus with prominent changes is BDNF, and in conjunction with the suggestion of BDNF as a potential target for design of new antidepressants, the epigenetic control of BDNF expression has been extensively analyzed in the context of the expression of depression and chronic antidepressant treatments. In the rat hippocampus, chronic electro-convulsive shocks increase acetylated histone H3 at the BDNF promoters 3 and 4, and these modifications appear to be correlated with increased expression of BDNF and CREB [46]. This upregulation has been linked to the effects of antidepressants in animal studies [28,47]. Moreover, chronic defeat stress, an experimental model for depression, elicits selective downregulation of some BDNF splice variants, in the hippocampus [28]. This downregulation appears to be due to induction of H3-K27 dimethylation, a histone code for transcriptional repression [28,48]. Conversely, an antidepressant treatment reverses repression of BDNF expression likely by inducing H3 acetylation and H3-K4 methylation, acting as histone codes for transcriptional activation, at the BDNF promoter region [49]. During this whole process, roles for histone deacetylases (HDACs) seem to be crucial because chronic antidepressant treatment downregulates HDAC5, and overexpression of HDAC5 in the hippocampus prevents its antidepressant effect [28].

HDAC inhibitors have thus received attention for their potentials as promising therapeutics for depression and related mood disorders. HDAC inhibitors are members of four families: the short chain fatty acids (e.g. sodium butyrate (SB), phenylbutyrate, and valproic acid (VPA)), the hyroxamic acids (e.g. TSA and suberoylanilide

hydroxamic acid (SAHA)), the epoxyketones (e.g. trapoxin), and the benzamides. One of the most widely used mood stabilizers is VPA. As VPA is known to have an inhibitory activity on HDAC1 and presumably other HDACs [50], it has been proposed that its mood stabilizing efficacy may be mediated at least in part by histone modifications. Another study showed that HDAC inhibitors such as VPA, SB, and TSA increase BDNF expression in the brain [51]. Thus, epigenetic mechanisms, especially histone modification, seem to have the potential to provide new mechanistic insights into the expression of depression and novel treatments for depression and related mood disorders.

Adult hippocampal neurogenesis

Brain imaging studies showing reduced hippocampal volume in depressed patients have provided a platform for investigating adult neurogenesis in the context of the pathogenesis of depression [52]. The hypothesis states that chronic stresses and other depression-inducing stimuli decrease neurogenesis [53-55], whereas antidepressant efficacy may rely on an increase in neurogenesis [54-56]. Adult neurogenesis is restricted to the subventricular zone and subgranular zone of the hippocampus [57], and this emphasizes the potential importance of hippocampal neurogenesis during the onset as well as during the treatment of depression. Supporting this idea, various animal models of depression, such as learned helplessness, chronic mild stress, and psychosocial stress, are associated with reductions in hippocampal neurogenesis [58-60]. Conversely, chronic antidepressant treatment not only increases neurogenesis but also supports survival of newborn neurons [61]. It has also been shown that the antidepressant efficacy of tricyclics, imipramine, and SSRIs requires hippocampal neurogenesis in rodents [58,62,63]. Furthermore, chronic fluoxetine treatment appears to increase the number of synapses in the pyramidal cell layers and block the decrease in spine density in the dentate gyrus and other hippocampal cell layers [64]. Notably, enriched environments, which is known to enhance hippocampal neurogenesis [65], decrease depression-related behaviors in rodents [66,67].

The expression level of BDNF deserves attention when examining the molecular mechanisms underlying the antidepressant-mediated increase in neurogenesis. As described above, in various animal models of depression, the BDNF level is decreased [40], whereas chronic antidepressant medication and electro-convulsive shocks increase the levels in the hippocampus [28,46]. A recent study showed that CREB, a transcription factor that regulates expression of CRE-containing target genes including BDNF, is also upregulated and activated in hippocampus by chronic antidepressant treatment [2,53,68,69]. However, the cause and effect relationship among the induction of CREB and BDNF, the neurogenesis, and behavioral effects of antidepressants remains to be further investigated.

Recent studies demonstrated that long-term administration of mood stabilizers such as lithium, valproic acid, and carbamazepine also enhances adult hippocampal neurogenesis [70-72]. Lithium directly inhibits glycogen synthase kinase-3 (GSK-3) and inositol signaling [73]. VPA enhances gene expression likely by inhibiting HDACs, indirectly blocks GSK-3 activity, and suppresses inositol signaling [71,74-76]. Although it remains unclear whether the GSK-3 and inositol signaling are actually linked with clinical effects of mood stabilizers, the data suggest a common molecular pathway constituting the pathophysiology of depression and related mood disorders that converges on adult hippocampal neurogenesis.

Substance withdrawal

Various drugs such as alcohol, psychostimulants, opiates and *N*-methyl-D-aspartate (NMDA) receptor antagonists generate a physiological response called withdrawal symptoms during abstinence in humans and experimental animals [77-80]. The characteristics of affective symptoms caused by drug withdrawal and major depressive disorder are strikingly similar [80]. Depressed mood and anhedonia are commonly present with both drug abstinence and depressive disorders [81]. Hyperphagia, hypersomnia, feelings of fatigue, and suicidal ideation are also observed in both conditions [82,83]. Disruptions of the HPA axis are also seen during drug withdrawal, and are accompanied by increased levels of cortisol and elevated cerebrospinal levels of CRF [84]. In addition, elevated levels of cortisol, ACTH and β-endorphin during early cocaine withdrawal resemble those in depressed patients [85]. Brain-imaging studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have revealed that methamphetamine withdrawal induces decreased glucose metabolism in the anterior cingulate cortex and insula, and increased metabolic activity in the amygdala and orbitofrontal cortex, all of which are frequently observed in clinical depression [86].

Much evidence shows that depression and related mood disorders are accompanied by abnormalities in dopaminergic transmission in the nucleus accumbens (NAc) and ventral tegmental area (VTA), regions that are core parts of the brain reward circuit [87]. It is well established that depressed patients have difficulties in the expression of pleasure and acquisition of motivation, which are mainly governed by a normal NAc-VTA dopamine circuit [88]. Consistently, it has been shown that a deregulation of dopamine D2 receptor signaling

results in depression-like behaviors in experimental animals [89], and that neuronal nitric oxide synthase (nNOS) knockout mice with altered dopamine D1 receptor signaling exhibit decreased depression-related behaviors [90]. Because nearly all drugs of abuse directly or indirectly activate monoaminergic neurotransmission in the limbic system, resulting in reward sensations [91,92], it has been postulated that counter-adaptations may occur in opposition to the reward effects with chronic drug intake, generating cognitive, motivational, and affective impairments, including depression-like symptoms during the drug withdrawal period [93].

As described above, in many ways, depressive mood subsequent to drug withdrawal shares common characteristics, such as neuro-hormonal changes, regional brain activity, and pharmacological responses, with clinical depression. However, it needs to be emphasized that the onset, course, duration, and other factors such as involvement of substances diagnostically distinguishes substance-induced mood disorders from major depressive disorders [94,95]. Some experimental data also hint at differences between these conditions at the molecular level, demanding cautions when interpreting the related observations. For example, dopamine transporter densities are increased in the striatum in both cases [96], but serotonin transporter densities are elevated in the brainstem during the early stage of cocaine abstinence [97], but not in clinical depression [98]. Also, some abstinent drug addicts have been treated with antidepressant drugs to reduce drug craving, but the positive effect of these drugs needs further validation [99]. Nonetheless, insights from these views not only tell us that brain reward circuits composed of the mesolimbic system are potentially important in understanding depression, but also provide a useful behavioral readout for depressive mood in experimental animals.

Circadian rhythms

Circadian rhythm is a roughly 24-hour cycle of biochemical, physiological, and behavioral processes under control of internal clock [100-102]. From the clinical point of view, a potential link between circadian rhythms and depression or related mood disorders has long been postulated. For example, it is relatively well known that insufficient length of light phase to entrain the circadian rhythm can be causative for the development of seasonal affective disorders [103,104]. Also, abnormal regulation of sleep/wake cycles, body temperature, blood pressure, and various endocrine functions under the control of circadian clock are prominent symptoms of mood disorders [102,105-110]. However, molecular mechanisms underlying the link are still largely unknown.

Recently, interesting observations have been made in the mutant mouse that has a deletion of 19th exon of *Clock* gene, a core component of molecular clock. The mouse exhibits hyperactive VTA dopaminergic neurons and behavioral phenotypes that are reminiscence of mania seen in bipolar disorder patients [111,112]. Moreover, lithium, a mood stabilizer for bipolar depression patients, effectively inhibits GSK3β, a core regulatory component in the molecular clock. Lithium also has an effect on the nuclear entry of Period-Cryptochrome heterodimers, a key process to form a negative loop in the molecular clock, likely through an inhibition of GSK3β activity. Furthermore, lithium appears to regulate activity of Rev-erb α that links the negative loop to the positive loop in the biological clock [113-116].

Potential links between circadian rhythm and the monoamine system are also reported. The synthesis and/or secretion of monoamine neurotransmitters and the function of their receptors are under influence of circadian rhythms. The circadian rhythmicity of dopamine transporter and tyrosine hydroxylase expression in dopaminergic neurons is also disrupted when the suprachiasmatic nucleus of the hypothalamus, the central part of endogenous clock, is damaged [117]. Moreover, monoamine oxidase-A (MAO-A) expression is regulated by dimer formation of Clock and Bmal1, and MAO-A activity accordingly shows a circadian rhythmicity [118]. Conversely, the expression of circadian genes such as *Clock, Per1*, and *Bmal1* is stimulated when dopamine D1 receptor is activated, and suppressed when dopamine D2 receptor is activated in the limbic area [119]. Collectively, the molecular clock appears to be tightly interconnected with monoamine systems, which might explain symptomatic correlation between circadian rhythm and depression at the molecular level.

Although the relationship among the daily variations of mood, endogenous molecular clock, and the expression of depressive symptoms is complicated, normalization of the biological rhythms of a depressive individual could have a beneficial effect. In this regard, the recent development of agomelatine as an antidepressant is of great interest. Agomelatine is a potent agonist for melatonin receptors and has capacity to reset the internal circadian clock [120,121]. Intriguingly, it also exhibits antagonistic activity on 5-HT_{2C} receptor, thereby indirectly enhancing the dopamine and norepinephrine neurotransmission [122-124]. Moreover, agomelatine affects differentially various stages of neurogenesis in the dorsal and ventral hippocampus [125]. Further understanding of the molecular basis of agomelatine action and its efficacy may provide interesting insight into the interface between circadian rhythm and pathophysiology of depression.

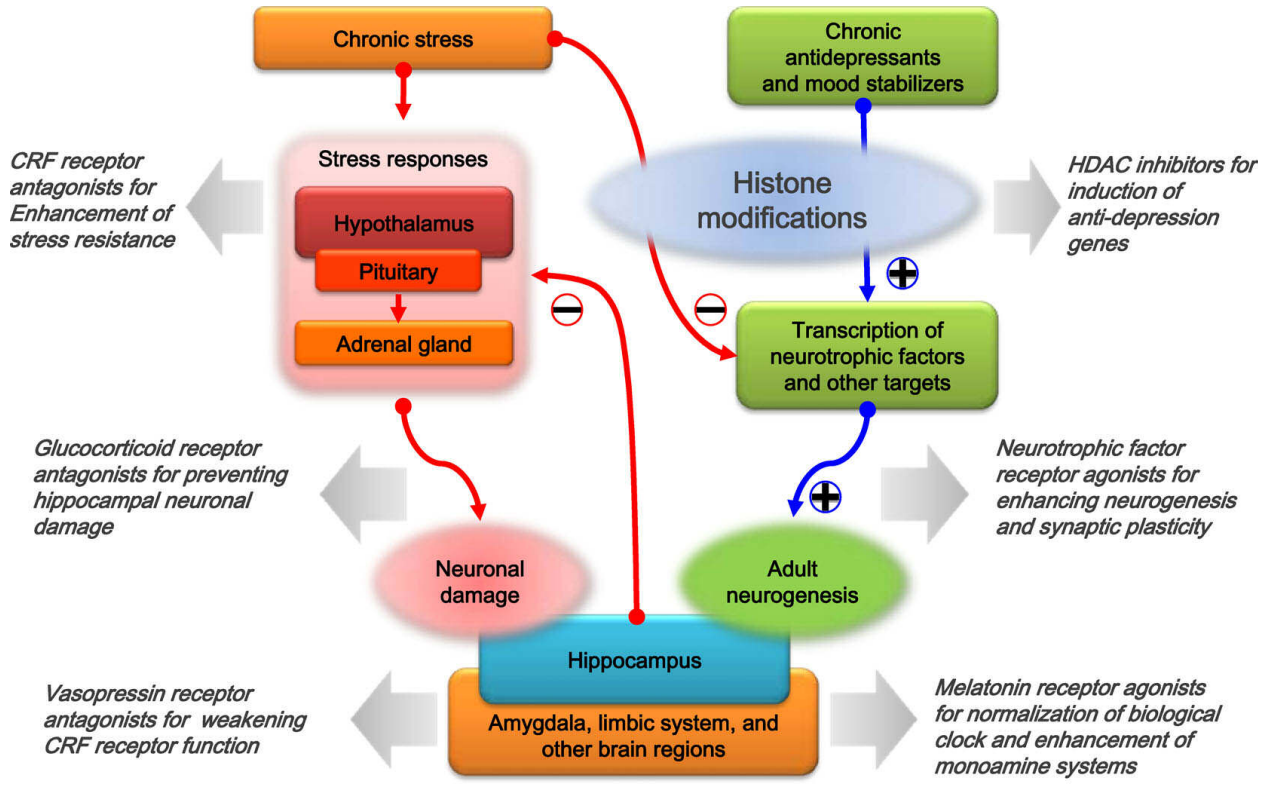

Figure 1 Approaches to the development of antidepressants targeting non-monoaminergic components. Chronic stress can cause hypercortisolemia which results in neuronal damages in the hippocampus, thereby weakening the feedback inhibition on HPA axis. Chronic stress also can inhibit the expression of neurotrophic factors through epigenetic mechanisms. On the other hand, chronic treatment of antidepressants and mood stabilizers can establish epigenomic environments that favor the expression of anti-depression genes. The targets may include genes for neurotrophic factors which prevent neuronal damages and enhance hippocampal neurogenesis. Some of approaches to the development of antidepressants targeting non-monoaminergic components are also shown.

Functional anatomy

Information on brain regions and neural circuitry responsible for the expression and progression of a disease is an important platform to better diagnose the disease and to properly interpret the observations obtained from molecular, cellular, and tissue experiments in the clinically relevant context. While various brain regions are known to be involved in regulation of mood or emotion, definite information on central neural circuits responsible for mood disorders is still incomplete, mainly because anatomical lesions in patients have been less consistently found relative to other various neurological disorders such as some neurodegenerative diseases. However, there are neuropathological and neuroradiological studies that have established interesting associations between mood disorders and structural abnormalities in the brain. For example, glial reduction was observed in anterior cingulate gyrus and neuronal abnormalities were detected in the dorsolateral prefrontal cortex in postmortem neuropathological studies of mood disorder patients [126,127]. Radiological studies using MRI also revealed reduced volumes of orbitofrontal and subgenual anterior cingulate cortex [128-130], electrical stimulation of which correlatively elicits an antidepressant effect [131]. Most notably, reductions in hippocampal volume in depressed elderly patients were reported [132,133].

Recent brain imaging studies mainly using fMRI are adding information on brain regions that play important roles in depressive symptoms at the functional level [134]. Functional changes in brain regions such as prefrontal/cingulate cortex, hippocampus, striatum, amygdala, and thalamus are correlated with depression [52]. The neocortex and hippocampus also appear to play critical roles in the symptoms related to the cognitive deficits that are prevalent in depressed patients [55], and the nucleus accumbens and amygdala seem to be core regions for anhedonia and emotional memory-related symptoms [135,136]. The functional changes in the hypothalamus are also linked to sleep- and appetite-associated symptoms [137]. Research on these topics is now being accelerated by fast advances in brain imaging technologies, and the outcome, in combination with the information from the conventional anatomical studies, is

driving the generation of a higher-resolution picture of the neural circuitry relevant to depression.

Conclusion

A prerequisite for effective control of depression and related mood disorders is to understand their detailed molecular pathways. Although the classical stress model of depression and current understanding of antidepressant action appears to be partially linked via epigenetic mechanisms and hippocampal neurogenesis (Figure 1), obviously, the current picture of the pathophysiology of depression is largely incomplete, and thus many potential hypotheses are being generated and tested, forming fragmented neurobiological views of depression and related mood disorders. One major task in the field must be to integrate the relevant hypotheses to formulate a bigger picture of the pathophysiology of depression and related disorders. A key step may be to define the high-resolution neural circuitry of depression, which will provide a platform to better interpret the observations obtained from molecular, cellular, and tissue experiments at the organism level. Another critical step will be to identify 'depression genes' that are causative for depression. This will help us generate genetic animal models that may not only be critical for clarifying many issues in depression research using experimental animals, but may also be useful for assessing the potential efficacy of candidate antidepressants. Finally, the most challenging task in the field is to overcome the limitations of current therapies, which are only effective in a fraction of patients. It has long been expected that novel antidepressants targeting non-monoamine systems would enlarge the extent of treatable patients (Figure 1), but the progress still falls short of expectations, thereby leaving it as a pressing task in the field.

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Authors' contributions

SL, JJ, and YK collected information and participated in drafting the manuscript. SKP wrote the manuscript and coordinated the drafting process. All authors read and approved the final form of the manuscript.

Competing interests

The authors declare that they have no competing interests.

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CONTINUING MEDICAL EDUCATION

Treatment of Depressive Disorders

Tom Bschor, Mazda Adli

SUMMARY

Introduction: A confusing variety of options are available for the treatment of depressive disorders.

Method: Selective literature review under consideration of current guidelines.

Results: The treatment of depression can be divided into acute, maintenance and prophylactic phases. The basic forms of treatment are pharmacotherapy, psychotherapy, and supportive strategies. The approximately 30 antidepressants currently on the market differ mainly with respect to their side effect profiles. Of the specific types of psychotherapy, cognitive behavioral therapy, psychodynamic therapy, and psychoanalysis are funded by the statutory health insurance providers in Germany. All treatment strategies (except for sleep deprivation) show a latency of onset of several weeks and a nonresponse rate of about 30% to 50%. In clinical practice it is essential to follow a stepwise procedure and to perform a standardized evaluation of response after the latency period. In the event of nonresponse, the next step of treatment should be initiated.

Discussion: Depressive disorders have a good prognosis provided one takes best advantage of the available treatment options. Preconditions are continuation of treatment for an appropriate length of time (for antidepressants ca. 4 to 6 weeks, for psychotherapy ca. 4 to 12 weeks) and standardized evaluation of response thereafter.

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Key words: depression, antidepressants, stepwise antidepressant treatment, treatment algorithm, psychotherapy

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The diagnostic evaluation of depressive disorders and their classification as mild, moderate, or severe was presented a short while ago in an earlier issue of *Deutsches Ärzteblatt* (1). If depression has been correctly diagnosed, numerous effective treatment options are currently available. The prognosis of a depressive disorder is good if it is treated appropriately and consistently.

The learning aims of this article are

- knowing the fundamentals of the treatment of depressive disorders (indication, setting, treatment phases, treatment steps)
- learning the principles of establishment of the physician-patient relationship
- acquiring basic knowledge about pharmacotherapy with antidepressants
- acquiring knowledge about treating depression with different forms of psychotherapy.

This continuing medical education article is based on a selective review of the literature, combined with the authors' own extensive experience in the ambulatory and in-hospital treatment of depressed patients. It presents the current state of the therapy of depressive disorders, with an emphasis on treatments that can be provided by general practitioners and family physicians.

Evidence of a depressive episode requiring treatment, as opposed to appropriate grief, can include the following:

- Duration of the depressive syndrome > 2 weeks
- Persistently depressed affect that cannot be lightened even by positive experiences
- A sense of paucity of emotion (the patient does not consider himself or herself to be sad, but rather feels "turned to stone" or "dead within")
- Typical circadian fluctuations, with a morning low and improvement toward evening
- Somatic symptoms without any organic cause

Prognosis

Depressive disorders have a favorable prognosis if the available treatments are applied consistently and thoroughly.

- Inappropriate feelings of guilt, or even depressive delusions
- Suicidality
- Previous episodes of severe depression
- A family history of severe depressive disorders.

The treatment setting

Depression is a very common condition (1). Therefore, its diagnosis and treatment, at least in uncomplicated cases, are tasks not just for the psychiatrist, but for the general practitioner and family physician as well.

- The indications for referral to a psychiatrist are
  - diagnostic uncertainty
  - psychiatric comorbidity (e.g., addiction, dementia, personality disorder)
  - severe depressive manifestations
  - delusional depression
  - depression in the setting of a bipolar affective disorder (bipolar depression)
  - suicidality
  - chronified depression
  - intractability, i.e., nonresponse to one or two treatments that have been carried out appropriately
  - need for psychotherapy or for an intensity of care that cannot be delivered in the setting of a family practice.

- The indications for referral for inpatient psychiatric treatment are
  - acute suicidality or other type of self-endangerment (e.g., refusal of food)
  - severe delusional or other psychotic manifestations
  - depressive stupor
  - the inability, because of illness or other causes, to participate in outpatient treatment on a regular basis (e.g., because of a lack of drive)
  - imminent neglect of oneself because of the lack of an adequately supportive social network
  - external living conditions that would impair the success of outpatient treatment, e.g., severe familial conflicts
  - lack of response to outpatient treatment.

Phases and objectives of treatment

The treatment of depression is divided into three phases (2, 3). The goal of acute therapy is complete or near-complete remission of the depressive manifestations. Because the speed of response of depressive disorders to treatment varies, acute therapy may need to be given for no more than a few weeks or for many months.

After the acute phase, maintenance therapy is given, with the main goal of preventing an early relapse. Its duration varies from 6 to 12 months. Maintenance therapy is indicated during this period because there is a high chance of relapse regardless of the form of treatment that was used to induce remission in the acute phase (4). In general, the form of treatment that led to remission is continued unchanged into the maintenance phase. A further goal of maintenance therapy is complete functional recovery, i.e., the patient's complete return to his or her premorbid level of function at home, in the workplace, and elsewhere.

Prophylactic therapy is indicated only in patients whose illness has taken a recurrent course, depending on the likelihood of recurrence in the individual case. The latter can best be judged from the number of prior depressive episodes and from the intervals of time between them. If prophylactic therapy is thought to be indicated, it should be started without any temporal endpoint in view (4). This review article will mainly deal with acute therapy.

Principles of treatment

The three main types of treatment for depression are

- pharmacotherapy,
- psychotherapy, and
- supportive measures.

Because of the considerable rate of spontaneous remission, particularly in milder cases of depression (untreated episodes last for an average of 6 to 8 months), the physician and the patient may agree on a two- to four-week period of "watchful waiting" before any treatment is given (5).

The initial treatment of mild or moderate depression should consist of monotherapy, either with a single medication or with psychotherapy, depending on availability and on the patient's preference. In severe, recurrent, or chronified depression, as well as for elderly depressed patients, a primary combination of these two treatment modalities may be advantageous.

Basic treatment strategy

The foundation of any treatment for depression, including but not restricted to specific forms of psychotherapy, is conversation with an empathic and understanding physician in the framework of a stable therapeutic alliance. The patient should sense the physician's acceptance of his or her worries and fears and should feel relieved as a

Depression—a common disorder

The recognition and treatment of depression, at least in cases with an uncomplicated course, is a task not just for psychiatrists, but for general practitioners as well.

The basis of treatment

The treatment of depression is based on conversation with an empathetic and understanding physician and on a stable therapeutic alliance.

result of the therapeutic interview, particularly with respect to feelings of guilt and inadequacy. The physician should inspire optimism by assuring the patient that depression is treatable and has a good prognosis. To this end, it often helps to instruct patients with a biological model of their condition, making it possible for them—particularly in the acute stage—to understand their depressive manifestations as the expression of an illness and thus as a legitimate, temporary dispensation from the duties of everyday life. A biological explanation can often also take away the inexplicable and threatening character of depression. Chronically depressed patients, on the other hand, need stepwise activation and promotion of their individual responsibility and initiative. Over-challenged family members often react with reproaches, trivializations ("everything will be OK soon enough, it's not really so bad"), or exhortations to "pull yourself together." All of these are unhelpful, yet they underscore the necessity of educating the patient's family, too, about depression as a treatable illness and of enlisting them in the effort to bring about recovery. Patients and their families can be motivated to participate in a self-help or family group *(see German Internet addresses listed at the end of this article)*. Written patient information can be useful as well *(see Internet addresses)*.

A special danger of depressive disorders is suicidality. 3% to 15% of persons suffering from depression commit suicide (e1), while 40% to 70% of suicide victims had suffered from depression (6).

The issue of suicidality should always be addressed repeatedly over the course of treatment. Patients almost always feel relieved when this topic is discussed. For concrete management, see the article by Rudolf et al. (1). Most suicides are announced beforehand in some way, either directly or indirectly.

Important steps to be taken for suicidal patients are the following:

- The immediate commencement of a psychotherapeutic crisis intervention. A stable physician-patient relationship is the most effective protective factor; thus, the family physician plays a central role in such situations.
- Referral to a specialized psychiatrist
- Short-term follow-up at close intervals and clear, unambiguous agreement on the time and place of the next session—no vague offers such as, "give me a call if things are not going well."
- A concrete, 24-hour offer of help: telephone number of the psychiatric crisis service or rescue center
- Obtain the patient's agreement to put off any thoughts of harming himself or herself and have the patient commit to an anti-suicide pact. The latter is an agreement between the physician and the patient in which the patient promises not to harm himself or herself within a specified period of time.
- Inpatient referral or involuntary commitment, if necessary, in accordance with the relevant laws
- For acute suicidality, give benzodiazepine when indicated.

Because there is no single treatment method to which all patients will respond, depression is treated, as a rule, in sequential therapeutic steps (7). The duration of each step should be long enough to give the method used a chance to be effective, yet also short enough to avoid treating the patient ineffectively for any longer than necessary. Four weeks (or six, for elderly patients) has generally been found to be an appropriate period for treatment with antidepressant medications, four to twelve weeks for specific forms of psychotherapy.

At the end of this period, the patient's response to treatment should be evaluated in a standardized fashion. To this end, a detailed documentation of the patient's disease manifestations at the outset of the treatment step is essential. The established, easy-to-use depression severity scales are also helpful—both external assessment scales (e.g., the Hamilton Depression Scale [8]) and self-assessment scales (e.g., the Beck Depression Inventory [9]). A "response" in terms of these scales is generally said to have occurred when the overall score has gone down by at least half during the treatment step in question (10). If this is the case, further treatment should be aimed at a complete remission of the disease manifestations. In case of nonresponse, on the other hand, a transition should be made to the next treatment step.

Pharmacotherapy

Antidepressants

The antidepressants play a central role in the pharmacotherapy of depression. Approximately 30 substances in this class are approved for use in Germany. All are about equally effective (5), with a nonresponder rate of one-third to one-half. All antidepressants have a similar latency until the onset of their therapeutic effect: for practical clinical purposes, a latency of two to four weeks can be assumed (EBM level A [Ia]).

Suicidality

A special danger of depressive disorders is suicidality. 3% to 15% of persons suffering from depression commit suicide, while 40% to 70% of suicide victims had suffered from depression.

The treatment of depression

As a rule, depression should be treated in successively applied therapeutic steps, because not all patients respond to every kind of treatment.

With very few exceptions, all available antidepressants work mainly by raising the synaptic concentration of serotonin and/or noradrenaline in the central nervous system. They differ only in the precise mechanism by which they do this (11) *(table 1)*.

TABLE 1

The mechanism of action of antidepressants

Mechanism	Pharmacological group
Inhibition of serotonin and/or noradrenaline reuptake	• Tri- and tetracyclic antidepressants (TCA) • Selective serotonin and noradrenaline reuptake inhibitors (SNRI) • Selective serotonin reuptake inhibitors (SSRI) • Selective noradrenaline reuptake inhibitors (reboxetine)
Inhibition of monoamine oxidases	• Reversible monoamine oxidase inhibitors • Irreversible monoamine oxidase inhibitors
Inhibition of presynaptic autoreceptors	• Presynaptic receptor antagonists

Phytotherapy (St. John's wort)

Phytotherapy with St. John's wort preparations is very popular in Germany in particular. The scientific evidence with regard to the efficacy of this agent is mixed at present, with many studies fraught with severe methodological deficiencies. A current meta-analysis (5) comes to the conclusion that St. John's wort is probably effective for the treatment of mild and moderate depression. The more than 40 St. John's wort preparations that are now available on the German market contain extremely variable concentrations of more than 400 individual chemical substances (5).

It is not widely known, yet highly clinically relevant, that St. John's wort carries with it a major risk of interactions with other medications: by inducing isoenzymes of the cytochrome P450 system, it can weaken the effect of many medications, including oral contraceptives, anticoagulants, digoxin, theophylline, other antidepressants, cyclosporine, and anti-HIV agents. Likewise, when a patient stops taking St. John's wort, the serum concentrations of these drugs will rise.

Benzodiazepines

Benzodiazepines have no antidepressant effect in the strict sense of the term, yet they have an acute sedative and anxiolytic effect and their use may thus be indicated for severely depressed and suicidal patients for a period no longer than 14 days. Such treatment is often needed because of the long latency of effect of the antidepressants, which was already mentioned above. The risks and contraindications of the benzodiazepines must, however, be taken into account. For instance, a history of addiction may be a risk that contraindicates benzodiazepine use.

Neuroleptics

Neither the older nor the newer neuroleptics have been shown to be effective as monotherapy for unipolar depression. Neuroleptics are indicated only for the treatment of delusional depression and should only be prescribed by a psychiatrist. Studies have shown that some of the atypical neuroleptics are effective when given in addition to an antidepressant (augmentation therapy), but neuroleptics have not been approved for this indication. Weekly injections of fluspirilene should not be given because of the risk of tardive dyskinesia.

Lithium

So-called lithium augmentation plays a role in the acute treatment of depression that has not responded to antidepressants (12). Furthermore, lithium as monotherapy is effective for prophylactic treatment in recurrent depression. Treatment with lithium requires special knowledge and precautionary measures and should thus be prescribed only by experienced physicians.

The course of pharmacotherapy

Patient education and shared decision-making

Thorough patient instruction about the effect, duration, and possible side effects of treatment is an integral component of pharmacotherapy. Patients must also be informed that maintenance therapy will be needed after the acute phase of treatment. When discussing these matters with the patient, the physician must address widespread misgivings and ungrounded fears, e.g., of addiction or a change of personality. Patient compliance with psychiatric medication is often inadequate but can be improved by informing the patient about the latency of the antidepressant effect and by describing possible side effects in advance. Shared decision-making (13) means that the well-informed patient should be able to decide for or against taking any proposed antidepressant medication in tandem with the physician. Letting the

St. John's wort

St. John's wort is likely to be effective for the treatment of mild or moderately severe depression. The available preparations are, however, of variable composition and can lower the effectiveness of many types of concomitantly taken medications.

Patient education and shared decision-making

A thorough orientation of the patient about the effect, duration, and possible side effects of treatment is an integral component of pharmacotherapy. Patients must also be informed that maintenance therapy will be necessary after the acute phase of treatment.

TABLE 2

Antidepressants

Substance group, substances	Initial dose (mg/d)	Standard dose (mg/d)	High dose*1 (mg/d)	Side effect, risk, and interaction profile (selected)	Neurochemical properties
Tricyclic antidepressants: amitriptyline, clomipramine, desipramine, doxepine, imipramine, lofepramine, nortriptyline, trimipramine **Tetracyclic antidepressant:** maprotiline	25–50	150	300	Anticholinergic effects (dry mouth, constipation, impaired accommodation, urinary retention, delirium, cognitive impairment); orthostatic hypotension; sedation, increased appetite, weight gain (esp. with amitriptyline, doxepine, and trimipramine); heart block, cardiac arrhythmia; potentially lethal toxicity with overdose: beware of accidental (impaired memory) or suicidal overdoses	Inhibition of serotonin and noradrenaline reuptake; also, blockade of muscarinic acetylcholine receptors, histamine$_1$ receptors, and α_1-adrenergic receptors
MAO inhibitors: Irreversible: tranylcypromine Reversible: moclobemide	10 150	10–30 300–600	80 900	For tranylcypromine, pay close attention to drug information (a low-tyramine diet is necessary—beware of hypertensive crises! Danger of serotonin syndrome when combined with serotonergic medications, or given at too short an interval before or after them!). Side effects: sleep disturbance, orthostatic hypotension, dry mouth.	Tranylcypromine: irreversible MAO-A and MAO-B inhibition; Moclobemide: reversible MAO-A inhibition
SSRI: Citalopram, fluoxetine, paroxetine Escitalopram Fluvoxamine, sertraline	20 10 50	20–40 10–20 50–150	not indicated	Nausea, inner unrest, sleep disturbance, sexual dysfunction, SIADH*2. With fluoxetine, paroxetine, and fluvoxamine, beware of the major risk of interactions with many other drugs because of inhibition of cytochrome P450 isoenzymes!	Selective inhibition of serotonin reuptake
SNRI: Venlafaxine Duloxetine	75 60	150–225 60	375 120	Nausea, inner unrest, sexual dysfunction, rise in blood pressure (esp. venlafaxine), SIADH*2, dry mouth, diaphoresis	Selective inhibition of serotonin and noradrenaline reuptake
Autoreceptor blockers: Mianserine Mirtazapine	30 15	60–120 15–45	180 80	Sedation, increased appetite, weight gain; mianserin: risk of changes in blood count (check periodically!)	Blockade of presynaptic autoreceptors and thus inhibition of negative feedback
Other: Trazodone	50–100	200–400	600	Sedation, sleep disturbance, increased appetite, weight gain, orthostatic hypotension, priapism (inform patient!)	Blockade of serotonin$_2$ receptors and presynaptic autoreceptors, moderate inhibition of serotonin reuptake
Bupropion	150	150–300	450	Unrest, sleep disturbance, headache, rise in blood pressure, dry mouth	Inhibition of dopamine and noradrenaline reuptake
Reboxetine	8	8	10	Tachycardia, orthostatic hypotension, inner unrest, sleep disturbance, dry mouth, diaphoresis, urinary retention	Selective inhibition of noradrenaline reuptake

*1High-dose treatment requires more frequent monitoring, sometimes on an inpatient basis, and will predictably result in a higher rate of undesired effects.
*2SIADH, syndrome of inappropriate ADH secretion

patient's family take part in this process also improves compliance.

The choice of antidepressant

The choice of an antidepressant for acute treatment is largely based on the side-effect profile, as the agents used for acute treatment are all comparably effective *(table 2)*. If a particular antidepressant has already been used effectively to treat a previous episode, then this agent should be preferred.

Sedation is a side effect that may be either undesired or beneficial if the patient suffers from sleep disturbance.

Tricyclic antidepressants should be avoided in a number of situations (5):

- In prostatic hyperplasia, glaucoma, cognitive impairment/dementia, constipation, and co-medication

The choice of antidepressant
The choice of an antidepressant for acute treatment is largely based on the side-effect profile, as the agents used for acute treatment are all comparably effective.

Effectiveness
The effectiveness of antidepressants can only be assessed after they have been given for two to four weeks in standard doses.

with other anticholinergically active substances, because of their anticholinergic side effects;
- In patients with pre-existing heart disease, because they may cause cardiac conduction abnormalities or arrhythmias;
- In suicidal or cognitively impaired patients (risk of deliberate or accidental overdose), because of their greater overdose toxicity compared to other antidepressants.

A reasonable and well-established practice is to give, during the maintenance phase, the same antidepressant that led to remission in the acute phase (4), even though venlafaxine is the only substance officially approved in Germany for maintenance pharmacotherapy. Either antidepressants or, alternatively, lithium can be used for prophylactic therapy in recurrent depression.

Dosing

Each antidepressant has a minimal effective dose; these standard doses are listed in *table 2*, as are the differing starting doses of preparations that must be given initially in a slowly increasing dose. For elderly patients, but for no others, lower than standard doses may already be effective and may, indeed, be indicated because they cause fewer complications. The same antidepressant dose should be prescribed in the maintenance phase of treatment that induced a remission in the acute phase (4). It is very difficult to recommend specific doses for prophylactic treatment at present because of the limited data that are currently available. For prophylactic treatment, too, the standard dose used for acute treatment is probably more effective than a lower dose.

Monitoring

In the first four weeks of acute therapy, the patient should be seen in follow-up at least once a week. At each follow-up appointment, the patient's toleration of the medication should be evaluated, and any concerns on the patient's part should be addressed. The response should be evaluated after four weeks of treatment.

The following tests are recommended for follow-up:
- Before treatment with an antidepressant, complete blood count and transaminases
- If a tricyclic antidepressant (TCA) is used, an ECG as well
- If a TCA or selective serotonin and noradrenaline reuptake inhibitor (SNRI) is used, blood pressure measurement
- Over the course of treatment, repeated complete blood count and transaminases, as well as (in the situations mentioned above) ECG and blood pressure measurement, particularly if the dose is raised
- If selective serotonin reuptake inhibitors (SSRI) are used, then the serum electrolytes should be measured over the course of treatment because of the risk of hyponatremia, particularly in elderly patients.

What to do in case of nonresponse

If the patient's disease manifestations do not respond to treatment with antidepressants in adequate doses for an adequately long trial period, the treatment strategy should be changed. In this situation, a number of options are available.

A reasonable first step consists of measuring the serum concentration of the antidepressant being used. This is called therapeutic drug monitoring (TDM) and is a helpful check on patient compliance as well as a means of detecting any metabolic particularities that may cause an inadequate serum level in the individual patient when taking a standard dose. Blood must be drawn before the medication is taken. For many newer antidepressants, however, there is still no reliably established connection between a therapeutic serum level and a clinical response; thus, TDM is mainly recommended if the agent being used is either a tricyclic antidepressant or venlafaxine. More information on therapeutic levels, the degree of evidence upon which they are based, and the laboratories that measure them can be found on the Internet *(please see list of German-language websites at the end of this article)*.

A common strategy after nonresponse to initial antidepressant treatment is to switch to another antidepressant; choosing an agent from another antidepressant class is usually recommended. There is, however, no scientific evidence for the effectiveness of this strategy (14). Thus, the antidepressant should not be changed more than once in the acute phase, and, if the second antidepressant also fails to bring about a response, another strategy should be used.

High-dose antidepressant treatment *(table 2)* is a sensible option for most antidepressants (15). The SSRIs are an exception: these agents have no clear dose-response relationship, so dose escalation of SSRIs lacks a theoretical basis (15). Antidepressants given in high doses can be expected to produce more severe side effects. ECG checks at closer intervals are

For acute therapy

In the first four weeks of acute therapy, the patient should be clinically reassessed at least once per week.

In case of resistance to treatment

- measure the serum concentration of antidepressant
- change the antidepressant (no more than once)
- give the antidepressant in a high dose (exception: SSRI)

obligatory when tricyclic antidepressants are given in high doses; with venlafaxine, the blood pressure must be checked at close intervals. The possible response to high-dose therapy should be evaluated no sooner than about four weeks after it has been initiated because of the known latency until the treatment effect sets in.

A further reasonable treatment strategy after non-response to antidepressant monotherapy is combination therapy with two antidepressants. The effectiveness of combination therapy, however, has only been documented for one specific type of combination, namely that of a reuptake inhibitor (tricyclic antidepressant or SSRI) together with a presynaptic autoreceptor blocker (mirtazapine, mianserin, or trazodone) (16).

Lithium augmentation is the administration of lithium in addition to an antidepressant that has been used hitherto for monotherapy without effect. Adding on lithium can bring about a response in a considerable number of patients, as has been shown in numerous studies and meta-analyses (12).

Psychotherapy

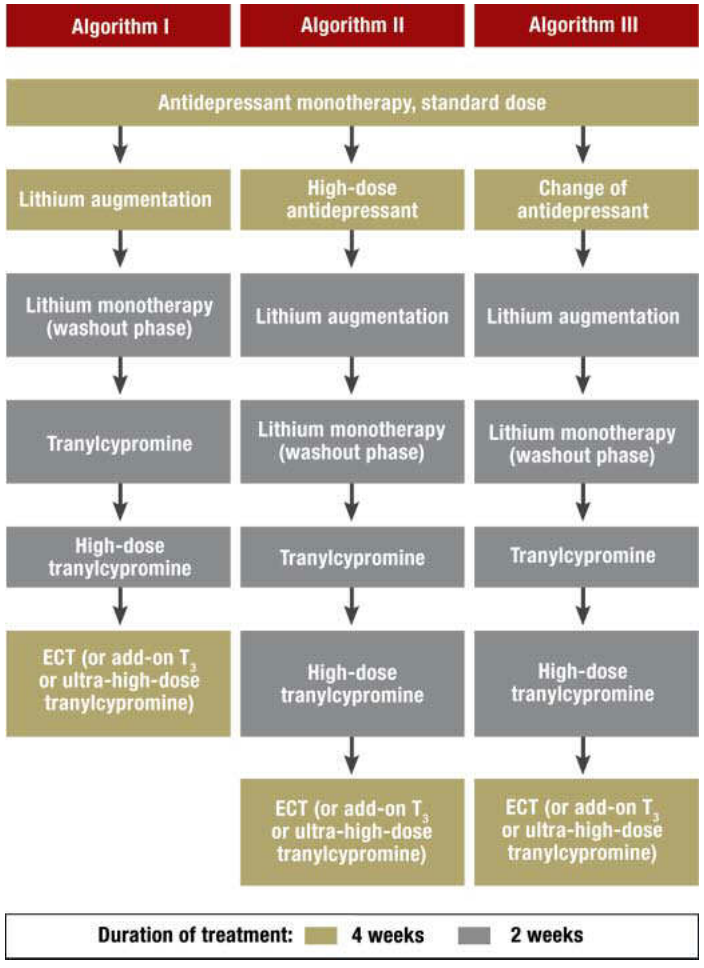
The effectiveness of various forms of psychotherapy in depression has been well documented. Most of the therapeutic effect seems to be due to common, non-specific factors that may also be at work in medical care outside the specifically psychotherapeutic setting. The most important among these factors is a systematically established therapeutic relationship with an accepting, actively listening, and empathetic physician. The physician himself or herself thereby becomes a potent "therapeutic agent," whose importance can scarcely be underestimated.

Most psychotherapeutic approaches to the treatment of depression involve the following strategies:

- Resource activation (identification and reinforcement of the patient's current abilities)
- Problem actualization (directed addressing of particular areas of conflict)
- Problem coping (supporting the patient with emotional, cognitive, or active solution strategies)
- Motivational clarification (recognition of problematic modes of perception and behavior and dysfunctional cognitions).

As in pharmacotherapy, patients should be regularly re-evaluated for the possible emergence of side effects, and therapeutic efficacy should be assessed after an adequate period of treatment.

FIGURE



Algorithm-based flowchart for stepwise treatment of depression. The flowchart shows the three arms of the algorithm study of the German Competence Network on Depression, because neither the result of the study (supported by the German Federal Ministry of Education and Research) nor the relevant literature permits any definite recommendation to be made. Whether the patient goes on to the next step in any of the three algorithms is a function of the decision procedure. The severity of depression is assessed at the end of each step with the Hamilton Depression Rating Scale (HAM-D, 21-item version).

T_3, triiodothyronine

- HAM-D $\leq$ 9: remission → clinical reassessment in 2 weeks to confirm remission, if confirmed → transition to maintenance therapy, if not confirmed → next step
- HAM-D decreased by at least 8 points (and overall score > 9): partial response → prolongation of the current step by 2 weeks (no more than once per step)
- HAM-D decreased by less than 8 points: non-response → next step

Psychotherapy in the treatment of depression

- Resource activation
- Problem actualization
- Problem coping
- Motivational clarification

Algorithm-based stepwise treatment

There are a number of different stepwise algorithms for the treatment of depression. The current state of the data does not permit any definite recommendation to be made.

Specific psychotherapeutic techniques

Psychotherapy for depression can be carried out in an outpatient or inpatient setting, individually or in groups, and with or without the participation of the patient's family. In Germany, the statutory health insurance carriers currently reimburse ambulatory behavioral therapy and deep psychology–based and analytic psychotherapy as so-called guideline techniques.

Cognitive behavioral therapy

Cognitive behavioral therapy (CBT) is based on the assumption that dysfunctional cognitions can lead to disturbed emotions and behavior, and vice versa. A lack of positive reinforcement owing to depression worsens the patient's depressive manifestations. CBT thus involves both cognitive and behavioral approaches. Its treatment strategies aim at overcoming the patient's lack of positive reinforcement, social withdrawal, and conviction of his or her own helplessness. The "cognitive errors" that are often identified among depressed patients include inappropriate generalizations, personalization, emotional thinking, and black-and-white thinking. Etiological importance is also attached to "depressiogenic" cognitive schemata that are learned early on in life and may be reactivated by critical life events; a typical example is the so-called "cognitive triad" of automatic negative assumptions about oneself, the environment, and the future. Cognitive therapy aims to correct these dysfunctional cognitions with structured and directed short-term therapy consisting of an average of 20 sessions. The efficacy of ambulatory CBT against depression has been very well studied and has also been confirmed by meta-analyses (17, e2–e4).

Deep psychology–based and psychoanalytic psychotherapy

Classical psychoanalytic treatment is performed with the patient lying on a couch, several times weekly, over a long period of time. Deep psychology–based psychotherapy is based on central fundamental assumptions and principles of psychoanalysis, but it is usually performed with the patient sitting in a chair, only once per week, and over a shorter period of time. Both of these types of psychotherapy are based on the assumption that depressive disorders are largely due to unconscious processes whose roots typically lie in the patient's childhood. Depressed persons, in particular, often suffer from uncertainties in their relationships and a negative bonding style with increased vulnerability to losses and affronts. More than in other types of psychotherapy, the therapist-patient relationship itself becomes an object of treatment, because the patient's typical relationship pattern and anxieties are reproduced in this relationship and can be addressed within it.

The currently available data from controlled studies of efficacy are less extensive than for CBT. More structured, short-term deep psychological psychotherapy in mildly or moderately depressed patients has been the type most frequently studied (e5). Other studies and meta-analyses have involved patients with a mixture of diagnoses, so that it is difficult to draw any specific conclusions about the effectiveness of these types of treatment for depression (e6, 18).

Interpersonal psychotherapy (IPT)

IPT is a type of short-term psychotherapy that was developed specifically for the treatment of depression. It consists of 12 to 20 hours of semi-structured psychotherapy, generally in weekly sessions, and focuses on the psychosocial and interpersonal aspects of depressive disorders. Thus, it places particular emphasis on coping with grief, role switching, life changes, and interpersonal conflicts.

Although much evidence for the efficacy of IPT is available from controlled studies and meta-analyses (19), in which it was used alone or in combination with antidepressants, IPT is currently not reimbursed by the statutory health insurance carriers in Germany.

Supportive measures

The importance of involving the patient's family has already been mentioned more than once. The only treatment for depression that has an immediate therapeutic effect is sleep deprivation, which can be done on an inpatient or outpatient basis. The patient is required either to do without sleep for an entire night (complete sleep withdrawal) or simply to get up between 1 a.m. and 2 a.m. (partial sleep deprivation), without making up for the missed sleep either in advance or afterward. It is crucial for the success of this treatment that the patient should not take even a short nap during periods of wakefulness. About 60% of patients so treated have a marked improvement of mood the day after.

The main disadvantage of sleep deprivation treatment is that its beneficial effect lasts no more than 1 or 2 days in about 80% of patients. If the treatment is effective, it can be repeated once every 3 to 4 days. An absolute contraindication is a history of epileptic seizures; relative

Cognitive behavioral therapy

The effectiveness of cognitive behavioral therapy in the outpatient setting has been very well studied and has also been confirmed by meta-analyses.

Supportive measures

Roughly 60% of patients undergoing sleep withdrawal therapy experience a marked improvement of mood for 1 to 2 days thereafter.

contraindications include bipolar or psychotic forms of depression.

The effectiveness of light therapy with special apparatus has been unequivocally documented only for seasonal depression (winter depression) (e7). Physical activity probably has a beneficial effect on the resolution of depression and can be recommended as a supplementary treatment, even though the scientific data to support this are as yet inadequate (e8). Treatments that are currently under investigation include aerobic training and endurance training (treadmill running) (20).

The most effective of all treatments for depression is probably electroconvulsive therapy (ECT), for which the current main indication is treatment-resistant depression (21, 22). Because of the specialized personnel and apparatus that this form of treatment requires, and also because of persistent, widespread misgivings about it, ECT is used only when multiple previous therapeutic attempts have failed, or when the patient explicitly requests it. Its beneficial effect typically appears after one to three weeks of treatment with three ECT sessions per week. Its major clinical drawback is the high rate of early recurrences in the first 16 weeks—up to 75% of patients who are not subjected to continuing treatment. With good maintenance therapy, the percentage of early recurrences can be reduced to about 35%, but such recurrences cannot be eliminated.

Conclusion

Depression can be treated effectively at present because multiple forms of treatment are available that complement each other or can be given in combination. Most of them have been well documented as effective in properly designed, controlled studies. No single form of treatment can be considered superior to all of the others, and a relatively high nonresponder rate is a common feature of all of them. Thus, the art of treating depression consists of a methodical and exhaustive use of the available therapeutic options within the framework of an algorithm-based stepwise treatment regimen *(figure)*, in which each sequential step of treatment is carried out for an adequate length of time and is then evaluated for effectiveness in standardized fashion. Randomized comparative studies have shown that stepwise treatment leads to more frequent and more rapid treatment responses than unstructured treatment, while simultaneously reducing the amount of psychoactive medication that must be prescribed as well as the frequency of changes in treatment strategy (7).

High nonresponder rate

The treatment of depression must make thorough use of all of the currently available therapeutic options in accordance with a stepwise treatment algorithm.

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For e-references please see:
www.aerzteblatt-international.de/ref4508

For a case illustration relating to this article,
see the following website:
www.aerzteblatt-international.de/0812

German-language websites for further information:
– Self-help and family groups:
www.nakos.de
– Written information for patients:
www.akdae.de/45/Depression.pdf
www.kompetenznetz-depression.de
– Information about therapeutic serum levels of antidepressants and grades of supportive evidence:
www.agnp.de →Arbeitsgruppen →AG Therapeutisches Drug-Monitoring

Further Information

This article has been certified by the North Rhine Academy for Postgraduate and Continuing Medical Education.

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The solutions to the following questions will be published in volume 1–2/2009.

The CME unit "Hereditary Cancer Syndromes" (volume 41/2008) can be accessed until 21 November 2008.

For volume 49/2008 we plan to offer the topic "Tonsillectomy in Childhood."

Solutions to the CME questionnaire in volume 37/2008:

Kainer F, Hasbargen U: Emergencies Associated With Pregnancy and Delivery: Peripartum Hemorrhage:

1/c, 2/d, 4/c, 5/b, 7/d, 8/c, 9/c, 10/e. All answers to questions 3 and 6 were counted as correct.

Please answer the following questions to participate in our certified Continuing Medical Education program. Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

What is the objective of maintenance therapy for depressive disorders?

(a) Phase prophylaxis
(b) Remission
(c) Response
(d) Relief of symptoms
(e) The prevention of an early relapse

Question 2

In what respect do the roughly 30 antidepressants that are currently available in Germany differ from one another most markedly?

(a) Their side-effect profiles
(b) Their nonresponder rates
(c) Their addictive potential
(d) Their latency of onset
(e) Their potency

Question 3

A 68-year-old woman in whom you have diagnosed moderately severe depression will only accept St. John's wort as the sole pharmacotherapeutic agent against depression. What should be your particular concern if you prescribe her a preparation containing this substance?

(a) The potential for morbid obesity
(b) The ECG
(c) Any medications she is concomitantly taking
(d) Renal function
(e) Possible addiction

Question 4

A 59-year-old bus driver presents to you with a history of depression that began two months ago. You are considering treatment with a tricyclic antidepressant. Which of the following comorbidities would lead you not to prescribe a drug of this type?

(a) Bronchial asthma
(b) Gout
(c) Prostatic hyperplasia
(d) Psoriasis
(e) Rheumatoid arthritis

Question 5

What is the most rapidly acting treatment for depression?

(a) Depression-specific psychotherapy
(b) Electroconvulsive therapy (ECT)
(c) Light therapy
(d) Pharmacotherapy with antidepressants
(e) Sleep deprivation

Question 6

According to the theory underlying psychotherapy based on deep psychology, what psychological phenomenon is more common in depressed people?

(a) Borderline personality structure
(b) Latent homosexuality in a parent
(c) Penis envy
(d) Increased vulnerability to loss
(e) Documented above-average intelligence

Question 7

Which of the following antidepressive treatments has been well documented to be effective by multiple controlled studies and meta-analyses?

(a) Physical activity
(b) Neuroleptic monotherapy
(c) High-dose SSRI treatment
(d) Outpatient cognitive behavioral therapy
(e) Changing the antidepressant in case of nonresponse

Question 8

What is meant by an algorithm-based stepwise treatment regimen for depression?

(a) Alternation between psycho- and pharmacotherapeutic techniques until a remission occurs
(b) Choice of treatment according to the classification of the patient's depression as mild, moderate, or severe, on the basis of a systematic evaluation
(c) Treatment of depression with monotherapy or with a combination of two, three, or four therapeutic methods, depending on the systematically assessed degree of resistance to treatment
(d) Determination of the treatment plan with the aid of treatment software that processes the data of the individual patient on the basis of a response probability matrix
(e) Determination of a multi-step treatment plan at the beginning of treatment with a standardized response evaluation at the end of each step, whose results determine the transition to the next treatment step

Question 9

Which of the following is a basic assumption of cognitive behavioral therapy?

(a) Placing the overwhelming emphasis on cognition, rather than emotion, is a central element in the pathogenesis of depression.
(b) Depressive disorders are based to a large extent on unconscious processes.
(c) Dysfunctional cognitions lead to disturbed emotions and behavior.
(d) Cognitive ego-splitting lies at the heart of depressive disorders.
(e) Excessive positive reinforcement in the consumer society is the main cause of depression.

Question 10

What tests are advisable before the beginning of treatment for depression and regularly over the course of treatment?

(a) Stress ECG for sertraline treatment
(b) Blood pressure checks for venlafaxine treatment
(c) EEG for citalopram treatment
(d) Metabolizer status checks for amitriptyline treatment
(e) Serum level determinations for treatment with reboxetine

CONTINUING MEDICAL EDUCATION

Treatment of Depressive Disorders

Tom Bschor, Mazda Adli

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CONTINUING MEDICAL EDUCATION

Treatment of Depressive Disorders

Tom Bschor, Mazda Adli

Case

Treatment of Depressive Disorders

A 46-year-old office worker went to his family physician, accompanied by his wife, complaining of persistent headaches. When questioned more closely, he described a dull pressure in the entire head that had been present continuously, though at varying intensity, for approximately the past four weeks. His chronic back pain had worsened in the same period. Because of these problems, he had first stopped attending his weekly chess night and then stopped going on his usual weekend excursions with his family. Over the course of time, he had stopped performing any tasks at all for his family and household. He had stayed home from work for the past three days. A thorough physical examination revealed no abnormality.

Only on directed questioning did the patient state that he had felt exhausted and bereft of energy all the time for the past few weeks, that he had lost interest in his usual activities, and that he no longer enjoyed the things that used to give him pleasure. His food no longer tasted good to him, and he had already lost 2.5 kg of weight. Most recently, he had begun to have difficulty falling asleep and to wake up every morning between 4 and 5 a.m.; he attributed this to the headaches. His wife, on directed questioning, said that her husband often seemed sad and that she had seen tears in his eyes for no apparent reason on multiple occasions. Nor could she understand why her husband, who was normally very conscientious about his work, now continually worried about the possible implications of his current three-day absence for his job security and the family's financial future.

The addiction history and past psychiatric history were negative. There was, however, a positive family history: the patient's paternal grandfather had committed suicide, for unknown reasons.

The family physician diagnosed a first depressive episode, informed the patient and his wife of her diagnosis in two separate interviews, and stressed both the nature of the symptoms as a disease and the good prognosis for recovery.

She declared him unable to work for two weeks and urged him to take a one- to two-hour walk each morning, but to take on no further tasks or activities. The patient was able to accept the temporary, passive role of an ill person only when acute depression was explained to him through an analogy to acute pneumonia. The patient and his family physician agreed that he would take antidepressive medication; she prescribed nortriptyline (150 mg/day), an agent with both serotonergic and noradrenergic properties, because such agents can be expected to have an additional beneficial effect in pain. Other than dry mouth, the medication was well tolerated. The patient and his family physician saw each other weekly. Three weeks after the onset of treatment, the patient came for the first time without his wife accompanying him and reported that he had just begun working in the garden again on his own initiative. After a total of five weeks of treatment, he was practically free of symptoms and returned to work. The patient and his family physician agreed that he would continue taking nortriptyline for six months as maintenance therapy.