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REVIEW

Monoaminergic system and depression

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Abstract

Major depressive disorder is a severe, disabling disorder that affects around 4.7% of the population worldwide. Based on the monoaminergic hypothesis of depression, monoamine reuptake inhibitors have been developed as antidepressants and nowadays, they are used widely in clinical practice. However, these drugs have a limited efficacy and a slow onset of therapeutic action. Several strategies have been implemented to overcome these limitations, including switching to other drugs or introducing combined or augmentation therapies. In clinical practice, the most often used augmenting drugs are lithium, triiodothyronine, atypical antipsychotics, buspirone, and pindolol, although some others are in the pipeline. Moreover, multitarget antidepressants have been developed to improve efficacy. Despite the enormous effort exerted to improve these monoaminergic drugs, they still fail to produce a rapid and sustained antidepressant response in a substantial proportion of depressed patients. Recently, new compounds that target other neurotransmission system, such as the glutamatergic system, have become the focus of research into fast-acting antidepressant agents. These promising alternatives could represent a new pharmacological trend in the management of depression.

Keywords Antidepressant · Major depression · Monoamines · Augmentation · Multitarget agents

Status MDD

As defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM5), major depressive disorder (MDD) is characterized by depressed mood or loss of interest or pleasure in nearly all activities; changes in appetite or weight; altered sleep and psychomotor activity; a loss of energy; feelings of worthlessness or guilt; difficulty thinking, concentrating, or making decisions; or recurrent thoughts of death or suicidal ideation, or suicide plans or attempts (American Psychiatric Association 2013).

Its high prevalence and the associated loss in health and general functioning make the MDD a substantial clinical, social, economic, and public health challenge. Although its prevalence is subject to cultural differences, gender, and age (Ferrari et al. 2013b), it is estimated that in 2015 more than 320 million people suffered from depression globally, equivalent to 4.7% of the world's population (GBD Disease and

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Injury Incidence and Prevalence Collaborators 2016; World Health Organization 2017). These figures are on the rise, particularly in lower-income countries (GBD Disease and Injury Incidence and Prevalence Collaborators 2016; Lim et al. 2018), and at least one third of symptomatic cases follow a moderate to severe disease course (Ferrari et al. 2013a).

According to World Health Organization (WHO), depression accounts for 10% of the total non-fatal disease burden worldwide and it is globally responsible for more years lost to disability than any other disease (Smith 2014; World Health Organization 2016). Indeed, depressive disorders were the fourth leading cause of disability in 2005 and the third in 2015 (GBD Disease and Injury Incidence and Prevalence Collaborators 2016), leading to the prediction by the WHO that depression will produce the second highest global disease burden by 2020 and it will become one of the priority conditions covered by the WHO's Mental Health Gap Action Programme (World Health Organization 2001). In addition, depression was also recognized as a major contributor to suicide deaths in 2015 (World Health Organization 2017).

Despite this high prevalence and the social impact of this mental illness, our understanding of the pathophysiology of depression is still poor (Krishnan and Nestler 2008). Additionally, current treatments for depression do not effectively or sufficiently reduce the associated morbidity and mortality (Insel and Wang 2009). Indeed, up to 50% of individuals treated with antidepressant medications for MDD do not achieve full remission (Thase et al. 2010). These data highlight the importance of including depressive disorders as a priority in public health programs and of implementing effective interventions that reduce this burden (Ferrari et al. 2013a).

Monoaminergic hypothesis of depression

Studies into the neurobiology and pharmacology of depression commenced in the 1950s, the consequence of three events that led to the formulation of the so-called monoaminergic hypothesis. The first of these was the development of iproniazid for the treatment of tuberculosis and the observation of a mood improvement among depressed tuberculosis patients (Loomer et al. 1957). The second was the appearance of imipramine, a medication first developed as an antipsychotic drug, which was structurally related to chlorpromazine and that produced an antidepressant effect (Kuhn 1957). The third event emanated from the studies carried out during the development of reserpine, an antihypertensive drug, which was appeared to provoke the appearance of depressive symptoms among patients (Lemieux et al. 1956), an effect that was antagonized by imipramine (Domenjoz and Theobald 1959).

Given that these compounds modify the bioavailability of catecholamines, the so-called catecholaminergic hypothesis of depression was that first postulated (Schildkraut 1965). This hypothesis proposed that at least some types of depression would be associated with a decrease in the levels of noradrenaline and dopamine in the synaptic cleft. Indeed, data from further studies on the peripheral and central metabolites of norepinephrine, although with some inconsistencies, were thought to support this hypothesis (Montoya et al. 2016). However, the role of serotonin (5-HT) in the antidepressant response was highlighted soon after (Coppen et al. 1967), driving the more widely accepted "monoaminergic theory of depression," which postulated that the etiological origin of depression is a deficit in monoaminergic neurotransmission (noradrenergic, dopaminergic, and serotonergic). This hypothesis was based on the mechanism of action of the drugs that increase the bioavailability of these monoamines and it represented a breakthrough in the design of new antidepressant drugs.

Current monoaminergic drugs and limitations

The first generation of antidepressant drugs was monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants; these enhance the monoamine levels in the synaptic cleft by impairing monoamine oxidase activity or neurotransmitter transporters, respectively. However, to minimize their severe side effects due to the blockage of certain postsynaptic receptors, more specific and safe antidepressant drugs have since been developed. Thus, the second generation of antidepressants included selective serotonin reuptake inhibitors (SSRIs) like fluoxetine, fluvoxamine, paroxetine, sertraline, or citalopram; selective noradrenaline reuptake inhibitors (SNRIs) like desipramine or reboxetine; dual serotonin and noradrenaline reuptake inhibitors like duloxetine, venlafaxine, and milnacipram; and a multitarget antidepressant, vortioxetine. Finally, other compounds with an atypical mechanism of action but related to the activity of monoamines have been proposed (e.g., bupropion, mirtazapine, or agomelatine). However, among the wide range of antidepressant drugs developed to treat MDD, SSRIs are considered the first-line therapies for these patients (National Institute for Clinical Excellence 2004). Indeed, these drugs are relatively well tolerated and they have a good safety profile, although they are associated with drug-related side effects that may compromise treatment compliance, such as nausea, insomnia, or sexual dysfunction (Lopez-Munoz and Alamo 2009).

Data from clinical trials suggest that these standard monoaminergic antidepressants have response and remission rates of 60% and 40%, respectively (Thase et al. 2001). The partial efficacy of antidepressants is the main limiting factor associated with MDD treatment and it contributes to the negative impact of this mental illness. In addition, the delay in the appearance of the beneficial clinical response also limits the effectiveness of these therapies (Posternak and Zimmerman

2005). Indeed, it takes more than 2 weeks to achieve a significant improvement in the depressive symptomatology, even though the blockade of the reuptake of biogenic amines is almost immediate. The onset of the therapeutic effects of antidepressant drugs is considered to be the period in which crucial neurobiological adaptations occur to restore the brain's network activity. It appears that neurobiological adaptive mechanisms triggered exclusively by chronic treatment are necessary to change from a depressed to a euthymic mood state (Blier and de Montigny 1994).

The limited efficacy of monoaminergic antidepressants along with their delayed effect explains the poor therapeutic outcome in patients with MDD, highlighting the need to search for new drugs or alternative strategies to overcome these limitations.

Strategies to enhance the therapeutic efficacy of monoaminergic antidepressants

Different pharmacological strategies have been adopted to improve overall outcomes when attempting to manage depression in clinical practice, including (i) increasing the dose of the antidepressant drug, (ii) switching the antidepressant agent, (iii) the use of combinations of antidepressants, and (iv) augmentation therapy. These strategies improve the clinical response (Carvalho et al. 2014) and as such, a large-scale study was set up to determine the most effective "next-step" for patients who do not remit after the initial treatment: Sequenced Treatment Alternatives to Relieve Depression (STAR*D). This study used four levels or treatment steps based on switching, combination, or augmentation strategies. These strategies resulted in a cumulative remission rate of 67% after the four sequenced treatments, the two first treatment steps being the most effective (Rush et al. 2006).

One of the early strategies used when patients do not respond satisfactorily to first-choice antidepressant (even at higher doses) is to switch to a different type of antidepressant (e.g., a SNRI, dual antidepressant, or bupropion) or to another SSRI. As such, combining antidepressants is also frequently used by clinicians to increase the therapeutic efficacy in patients who fail to achieve the desired effect with an initial treatment (e.g., SSRI and tricyclic antidepressant) (Carvalho et al. 2014). In addition to improving antidepressant effectiveness, such combination strategies are also used to increase tolerability. For example, bupropion counteracts the sexual dysfunction caused by SSRIs (Moreira 2011).

Augmentation therapies

Augmentation strategy usually implies the use of an adjunctive drug that is not an antidepressant to enhance the efficacy of monoaminergic drugs, and/or to reduce the time required for them to achieve a clinical effect. Based on the available literature, the following augmentation therapies (Fig. 1) merit some attention:

Lithium

Lithium is a monovalent cation used as a mood stabilizer to treat bipolar disorder and it is one of the best studied augmentation therapies to treat non-responder depressed patients. Adjunctive administration of lithium enhances clinical responses in patients who respond inadequately to standard antidepressants and the benefits of its combination with tricyclic antidepressants for refractory depression are well-documented (Bauer et al. 2014). While lithium has multiple targets in a number of neurotransmitter systems, its efficacy in mood regulation appears to be mediated by direct inhibition of glycogen synthase kinase 3β, and its effects on neurotrophic factors (BDNF) or neurotransmitters (facilitation of 5-HT neurotransmission). It is also known to improve the activity of the HPA axis and it influences protein kinase activity (Won and Kim 2017).

Thyroid T3

A commonly employed augmentation strategy involves triiodothyronine (T3) administration, an augmentation therapy that enhances the response and produces a faster therapeutic improvement than antidepressant monotherapy in clinical trials (Altshuler et al. 2001; Aronson et al. 1996). The STAR*D study compared T3 to lithium as an augmentation therapy in patients who failed to remit with at least two prior treatments. While the two approaches did not show a significant difference in terms of remission rates (16% for lithium and 25% for T3), T3 provoked relatively fewer side effects (Nierenberg et al. 2006). Potentiation of monoaminergic neurotransmission may explain the synergistic effect of T3 augmentation, primarily involving the serotonergic system through direct stimulation of gene transcription. Indeed, in combination with antidepressants, T3 dampens the expression of 5-HT1A and 5-HT1B autoreceptors (Lifschytz et al. 2006), receptors that play an important role in the regulation of serotonergic neurotransmission through negative feedback. In fact, the activation of somatodendritic 5-HT1A and terminal 5-HT1B autoreceptors reduces both neuronal electrical activity and serotonin release.

Atypical antipsychotics

The capacity of some atypical antipsychotics to potentiate the efficacy of antidepressant drugs has been tested in clinical trials. As a result, there is evidence that these drugs can enhance the antidepressant effect of monoaminergic antidepressants,

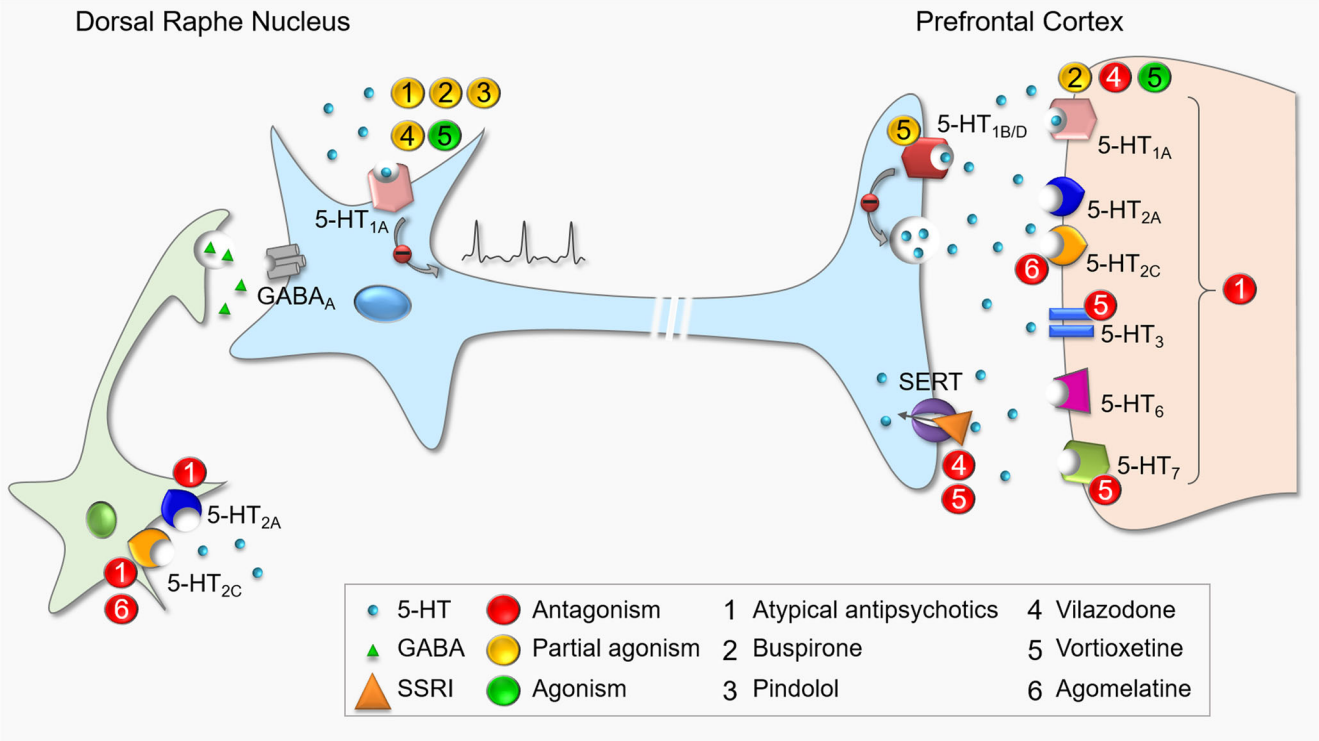

Fig. 1 The potential mechanisms associated with augmentation therapies and multitarget antidepressants that act on serotonergic neurotransmission to the prefrontal cortex. This scheme shows the multiple potential targets on serotonergic and GABAergic neurons in the dorsal raphe nucleus, or on cortical neurons, for augmentation agents and multitarget antidepressants, also indicating their pharmacological effects (antagonism, partial agonism, or agonism). Augmentation strategies (atypical antipsychotics (1), buspirone (2), and pindolol (3)) are based on combining SERT inhibition, commonly using a selective serotonin reuptake inhibitor (SSRI), with other agents that act directly on serotonergic receptors. Although atypical antipsychotics have distinct affinities towards different monoaminergic neurotransmitter receptors, this figure only illustrates the most shared effects on serotonergic receptors. Buspirone and pindolol acts on 5-HT1A receptors, although it should be noted that pindolol has a preferential effect on presynaptic rather than postsynaptic 5-HT1A receptors. The multitarget antidepressants vilazodone (4) and vortioxetine (5) inhibit serotonin reuptake, in addition to their affinity for serotonergic receptors. By contrast, agomelatine (6) has a mixed mode of action, targeting 5-HT2C receptors and the melatoninergic system

increasing approximately a 30% remission rate, although their use may produce additional side effects that need to be considered (Han et al. 2013; Nelson and Papakostas 2009). Although antipsychotics have distinct affinities towards different monoaminergic neurotransmitter receptors, the most relevant mechanism of action in antidepressant augmentation is considered to be the antagonism of 5HT2AC receptors (Han et al. 2013). Nevertheless, how a blockade of postsynaptic 5-HT2AC contributes to such clinical effects remains poorly understood. One possible explanation is that antagonism at 5-HT2AC might boost the 5-HT system due to the inhibition of GABAergic interneurons in the dorsal raphe nucleus or alternatively, this antagonism might directly control cortical activity (Boothman et al. 2006; Celada et al. 2004). As a result, combination with antipsychotics produces a stronger increase in 5-HT bioavailability than that achieved by antidepressant monotherapy. However, atypical antipsychotics have a relatively high affinity for other monoaminergic receptors, which could also contribute to the augmentation effect. For example, some antipsychotics acts as antagonists at 5-HT1A, 5-HT6, 5-HT7, α2-adrenergic, and/or D2/3 receptors, while others also have the capacity to directly inhibit monoamine reuptake due to their affinity towards monoamine transporters (Han et al. 2013).

Buspirone

The non-benzodiacepine anxiolytic drug buspirone is also used as an adjunctive medication to enhance the clinical effect of standard antidepressants. This therapeutic procedure is based on an enhancement of serotonergic tone through the drug's activity as a partial agonist at 5-HT1A receptors. However, there are some doubts about its efficacy and while some clinical trials indicate beneficial effects of buspirone, in particular the STAR*D study that reported a 30% remission rate in patients not responding to first-line treatment, other studies failed to find a significant improvement after adding buspirone (Trivedi et al. 2006).

Pindolol

Pindolol is a partial 5-HT1A agonist and β-adrenoceptor antagonist that has been tested as an augmenting agent (Perez

et al. 1997). Nevertheless, the efficacy of pindolol in enhancing antidepressant responses remains controversial, although it has been seen to accelerate the antidepressant effect of some current antidepressants (Ballesteros and Callado 2004). Pindolol maintains the immediate increase in 5-HT produced by antidepressant drugs by blocking the negative feedback exerted by presynaptic 5-HT1A autoreceptors. Note that pindolol has a higher activity for presynaptic rather than postsynaptic 5-HT1A receptors. Thus, it will preferentially preserve the activation of 5-HT1A receptors located postsynaptically, which seems to be essential for the antidepressant effect. This specific mode of action would explain the faster onset of the antidepressant effect associated with pindolol augmentation therapy relative to other selective 5-HT1A antagonists (Artigas et al. 1996).

Stimulants and related compounds

Psychostimulants like methylphenidate and modafinil, which mainly target the dopaminergic and noradrenergic systems, have been tested as augmentation drugs to refine and improve the efficacy and tolerability of antidepressants. Unfortunately, the associated outcomes have been disappointing, with at best limited improvements produced (McIntyre et al. 2017).

Alternative monoaminergic drugs: multitarget approaches

Based on the encouraging data from the augmentation strategy with pindolol, the challenge for the pharmaceutical industry has been to develop new compounds that target both 5-HT1A receptors and SERT in a single molecule. This has led to the appearance of vilazodone, a compound with a dual mechanism of action that combines the inhibition of serotonin reuptake with partial 5-HT1A agonism (Fig. 1). Despite the promising results expected for vilazodone in the treatment of MDD, there is still limited clinical evidence regarding the efficacy of this antidepressant drug. Moreover, unlike pindolol augmentation therapy, vilazodone failed to produce a faster therapeutic response to other antidepressants (Sahli et al. 2016). Another compound developed that shares this dual mechanism of action was vortioxetine, which did show robust antidepressant efficacy. The clinical efficacy of vortioxetine compared to vilazodone could be explained by its high affinity for other 5-HT receptors, including 5-HT3, 5-HT7, 5-HT1B, and 5-HT1D receptors (Fig. 1) (Sanchez et al. 2015).

Similarly, agomelatine is a compound with a different multitarget mechanism of action that shows antidepressant efficacy. This drug modifies serotonergic neurotransmission through antagonism at 5-HT2C receptors (Fig. 1) and it promotes the effects of melatonin through its agonistic activity at both MT1 and MT2 melatonin receptors (de Bodinat et al. 2010). Melatonin plays a crucial role in sleep regulation and it is closely related to the serotonergic system given that 5-HT is converted to melatonin. Thus, the distinct activity profile of agomelatine can produce a therapeutic effect, as well as improving the sleep disturbances commonly observed in patients with depression. However, the liver damage induced by agomelatine is an important limitation to its use in clinical practice.

New insights into the treatment of depression: alternatives beyond monoaminergic drugs

The arrival of the monoaminergic hypothesis of depression boosted the design of second-generation monoaminergic drugs, which have since become a cornerstone in the treatment of depression. As a consequence, a multitude of strategies and new promising compounds have been tested to potentiate monoaminergic neurotransmission. Indeed, the monoaminergic system is still being targeted by drug companies in the search to find improved antidepressant agents with greater effectiveness and a faster onset of clinical action. Some of these candidate drugs are currently under study, including triple reuptake inhibitors that simultaneously inhibit serotonin, noradrenaline and dopamine transporters, as well as other molecules that act as agonists or antagonists at specific serotonergic receptors (Artigas et al. 2018; Lane 2015). Despite the pharmacological achievements in this field, the existing monoamine-based drugs fail to overcome the limitations of the more standard monoaminergic drugs, particularly regarding the time required to improve the depressive symptomatology. Nonetheless, a rapid antidepressant response has been observed in refractory depressed patients treated with other non-pharmacological antidepressant options, such as electroconvulsive therapy (UK ECT Review Group 2003) or deep brain stimulation (Perez-Caballero et al. 2014). Therefore, it is possible to rapidly switch from a depressive to a euthymic state and maybe, the long-term adaptations produced by monoaminergic drugs could be achieved immediately through other approaches. Indeed, interest in the glutamatergic system has recently been stimulated through the rapid and sustained antidepressant effect evoked in treatment-resistant depressed patients by ketamine, a non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonist (Molero et al. 2018) or its isomer, esketamine. Interestingly, it has recently shown that ketamine cannot exert its acute antidepressant effect without engaging the body's opioid system (Williams et al. 2018), pointing to the important role of the opioid system for mood disorders (Berrocoso et al. 2009). This promising effect could open new possibilities to develop more effective, better tolerated, and faster acting antidepressants to manage depression.

Conclusions

Current monoamine-based drugs form the basis of the armamentarium to treat MDD, despite their still limited therapeutic efficacy, delayed onset of action, and a broad profile of side effects. Nevertheless, the monoaminergic system is still considered the main target to treat depressed patients. However, the promising results associated with the use of glutamatergic drugs could open up a host of new treatments. Certainly, further studies focusing on the mechanisms underlying the antidepressant response could help optimize current antidepressant therapies. Hopefully, these studies could resolve what currently remains as one of the leading neuropsychopharmacological challenges.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

Altshuler LL, Bauer M, Frye MA, Gitlin MJ, Mintz J, Szuba MP, Leight KL, Whybrow PC (2001) Does thyroid supplementation accelerate tricyclic antidepressant response? A review and meta-analysis of the literature. Am J Psychiatry 158:1617–1622

American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders (DSM-5). American Psychiatric Publishing, Arlington

Aronson R, Offman HJ, Joffe RT, Naylor CD (1996) Triiodothyronine augmentation in the treatment of refractory depression. A meta-analysis. Arch Gen Psychiatry 53:842–848

Artigas F, Romero L, de Montigny C, Blier P (1996) Acceleration of the effect of selected antidepressant drugs in major depression by 5-HT1A antagonists. Trends Neurosci 19:378–383

Artigas F, Bortolozzi A, Celada P (2018) Can we increase speed and efficacy of antidepressant treatments? Part I: general aspects and monoamine-based strategies. Eur Neuropsychopharmacol 28:445–456

Ballesteros J, Callado LF (2004) Effectiveness of pindolol plus serotonin uptake inhibitors in depression: a meta-analysis of early and late outcomes from randomised controlled trials. J Affect Disord 79: 137–147

Bauer M, Adli M, Ricken R, Severus E, Pilhatsch M (2014) Role of lithium augmentation in the management of major depressive disorder. CNS Drugs 28:331–342

Berrocoso E, Sanchez-Blazquez P, Garzon J, Mico JA (2009) Opiates as antidepressants. Curr Pharm Des 15:1612–1622

Blier P, de Montigny C (1994) Current advances and trends in the treatment of depression. Trends Pharmacol Sci 15:220–226

Boothman LJ, Mitchell SN, Sharp T (2006) Investigation of the SSRI augmentation properties of 5-HT(2) receptor antagonists using in vivo microdialysis. Neuropharmacology 50:726–732

Carvalho AF, Berk M, Hyphantis TN, McIntyre RS (2014) The integrative management of treatment-resistant depression: a comprehensive review and perspectives. Psychother Psychosom 83:70–88

Celada P, Puig M, Amargos-Bosch M, Adell A, Artigas F (2004) The therapeutic role of 5-HT1A and 5-HT2A receptors in depression. J Psychiatry Neurosci 29:252–265

Coppen A, Shaw DM, Herzberg B, Maggs R (1967) Tryptophan in the treatment of depression. Lancet 2:1178–1180

de Bodinat C, Guardiola-Lemaitre B, Mocaer E, Renard P, Munoz C, Millan MJ (2010) Agomelatine, the first melatonergic antidepressant: discovery, characterization and development. Nat Rev Drug Discov 9:628–642

Domenjoz R, Theobald W (1959) On the pharmacology of tofranil N-(3-dimethylaminopropyl)-iminodibenzyl hydrochloride. Arch Int Pharmacodyn Ther 120:450–489

Ferrari AJ, Charlson FJ, Norman RE, Patten SB, Freedman G, Murray CJ, Vos T, Whiteford HA (2013a) Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. PLoS Med 10:e1001547

Ferrari AJ, Somerville AJ, Baxter AJ, Norman R, Patten SB, Vos T, Whiteford HA (2013b) Global variation in the prevalence and incidence of major depressive disorder: a systematic review of the epidemiological literature. Psychol Med 43:471–481

GBD Disease and Injury Incidence and Prevalence Collaborators (2016) Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 388:1545–1602

Han C, Wang SM, Kato M, Lee SJ, Patkar AA, Masand PS, Pae CU (2013) Second-generation antipsychotics in the treatment of major depressive disorder: current evidence. Expert Rev Neurother 13: 851–870

Insel TR, Wang PS (2009) The STAR*D trial: revealing the need for better treatments. Psychiatr Serv 60:1466–1467

Krishnan V, Nestler EJ (2008) The molecular neurobiology of depression. Nature 455:894–902

Kuhn R (1957) Treatment of depressive states with an iminodibenzyl derivative (G 22355). Schweiz Med Wochenschr 87:1135–1140

Lane RM (2015) Antidepressant drug development: focus on triple monoamine reuptake inhibition. J Psychopharmacol 29:526–544

Lemieux G, Davignon A, Genest J (1956) Depressive states during Rauwolfia therapy for arterial hypertension; a report of 30 cases. Can Med Assoc J 74:522–526

Lifschytz T, Segman R, Shalom G, Lerer B, Gur E, Golzer T, Newman ME (2006) Basic mechanisms of augmentation of antidepressant effects with thyroid hormone. Curr Drug Targets 7:203–210

Lim GY, Tam WW, Lu Y, Ho CS, Zhang MW, Ho RC (2018) Prevalence of depression in the community from 30 countries between 1994 and 2014. Sci Rep 8:2861

Loomer HP, Saunders JC, Kline NS (1957) A clinical and pharmacodynamic evaluation of iproniazid as a psychic energizer. Psychiatr Res Rep Am Psychiatr Assoc 8:129–141

Lopez-Munoz F, Alamo C (2009) Monoaminergic neurotransmission: the history of the discovery of antidepressants from 1950s until today. Curr Pharm Des 15:1563–1586

McIntyre RS, Lee Y, Zhou AJ, Rosenblat JD, Peters EM, Lam RW, Kennedy SH, Rong C, Jerrell JM (2017) The efficacy of psychostimulants in major depressive episodes: a systematic review and meta-analysis. J Clin Psychopharmacol 37:412–418

Molero P, Ramos-Quiroga JA, Martin-Santos R, Calvo-Sanchez E, Gutierrez-Rojas L, Meana JJ (2018) Antidepressant efficacy and tolerability of ketamine and esketamine: a critical review. CNS Drugs

Montoya A, Bruins R, Katzman MA, Blier P (2016) The noradrenergic paradox: implications in the management of depression and anxiety. Neuropsychiatr Dis Treat 12:541–557

Moreira R (2011) The efficacy and tolerability of bupropion in the treatment of major depressive disorder. Clin Drug Investig 31(Suppl 1): 5–17

National Institute for Clinical Excellence (2004) Depression: management of depression in primary and secondary care (National Clinical Practice Guideline No 23). NICE, London

Nelson JC, Papakostas GI (2009) Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. Am J Psychiatry 166:980–991

Nierenberg AA, Fava M, Trivedi MH, Wisniewski SR, Thase ME, McGrath PJ, Alpert JE, Warden D, Luther JF, Niederehe G, Lebowitz B, Shores-Wilson K, Rush AJ (2006) A comparison of lithium and T(3) augmentation following two failed medication treatments for depression: a STAR*D report. Am J Psychiatry 163: 1519–1530

Perez V, Gilaberte I, Faries D, Alvarez E, Artigas F (1997) Randomised, double-blind, placebo-controlled trial of pindolol in combination with fluoxetine antidepressant treatment. Lancet 349:1594–1597

Perez-Caballero L, Perez-Egea R, Romero-Grimaldi C, Puigdemont D, Molet J, Caso JR, Mico JA, Perez V, Leza JC, Berrocoso E (2014) Early responses to deep brain stimulation in depression are modulated by anti-inflammatory drugs. Mol Psychiatry 19:607–614

Posternak MA, Zimmerman M (2005) Is there a delay in the antidepressant effect? A meta-analysis. J Clin Psychiatry 66:148–158

Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, McGrath PJ, Rosenbaum JF, Sackeim HA, Kupfer DJ, Luther J, Fava M (2006) Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 163:1905–1917

Sahli ZT, Banerjee P, Tarazi FI (2016) The preclinical and clinical effects of vilazodone for the treatment of major depressive disorder. Expert Opin Drug Discovery 11:515–523

Sanchez C, Asin KE, Artigas F (2015) Vortioxetine, a novel antidepressant with multimodal activity: review of preclinical and clinical data. Pharmacol Ther 145:43–57

Schildkraut JJ (1965) The catecholamine hypothesis of affective disorders: a review of supporting evidence. Am J Psychiatry 122:509–522

Smith K (2014) Mental health: a world of depression. Nature 515:181

Thase ME, Entsuah AR, Rudolph RL (2001) Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. Br J Psychiatry 178:234–241

Thase ME, Nierenberg AA, Vrijland P, van Oers HJ, Schutte AJ, Simmons JH (2010) Remission with mirtazapine and selective serotonin reuptake inhibitors: a meta-analysis of individual patient data from 15 controlled trials of acute phase treatment of major depression. Int Clin Psychopharmacol 25:189–198

Trivedi MH, Fava M, Wisniewski SR, Thase ME, Quitkin F, Warden D, Ritz L, Nierenberg AA, Lebowitz BD, Biggs MM, Luther JF, Shores-Wilson K, Rush AJ, Team SDS (2006) Medication augmentation after the failure of SSRIs for depression. N Engl J Med 354: 1243–1252

UK ECT Review Group (2003) Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. Lancet 361:799–808

Williams NR, Heifets BD, Blasey C, Sudheimer K, Pannu J, Pankow H, Hawkins J, Birnbaum J, Lyons DM, Rodriguez CI, Schatzberg AF (2018) Attenuation of antidepressant effects of ketamine by opioid receptor antagonism. Am J Psychiatry:appiajp201818020138

Won E, Kim YK (2017) An oldie but goodie: lithium in the treatment of bipolar disorder through neuroprotective and neurotrophic mechanisms. Int J Mol Sci 18

World Health Organization (2001) The world health report 2001: mental health: now understanding, new hope. World Health Organization, Geneva

World Health Organization (2016) Out of the shadows: making mental health a global development priority. World Health Organization, Washington

World Health Organization (2017) Depression and other common mental disorders: global health estimates. World Health Organization, Geneva