Beyond monoamines towards the development of novel antidepressants

Oltre le monoamine al fine di sviluppare nuovi farmaci antidepressivi

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Summary

Objective

Herein, a concise review is presented on the current and most promising antidepressant pharmacological agents for management of depression.

Materials and methods

A PubMed search (1966 - February 2012) was performed using the following keywords or their combination: "depression"; "major depressive disorder": "antidepressants"; "novel antidepressant targets"; "monoamine"; "novel antidepressants". Additional literature sources, including most authoritative and updated edited books or pamphlets were examined accordingly.

Results

All relevant literature sources written in English were evaluated giving priority to RCTs and meta-analyses. At present, the pharmacological management of depression appears is characterized by a wide variety of different augmentation or switching approaches (Fig. 1). Nonetheless, response rates remain substantially unsatisfactory, thus prompting for the development of novel agents with different mechanisms of action.

Conclusions

Shifting the interest for novel antidepressant drugs beyond the monoaminergic modulation represents (Tables I-III) an intriguing opportunity to enhance response rates of depression, although other issues, including revision of current nosological boundaries, should also be considered.

Key words

Monoamines • Antidepressant drugs • Novel targets

Introduction

Depression is one of the most prevalent psychiatric disorders, and has unfavourable prognosis with considerable suicide risk [1]. Its lifetime prevalence rate in the United States is estimated to be 16.6%, affecting over 30 million people, with more than 80% of these individuals experiencing recurrent episodes [2 3]. Nonetheless, despite the clinical and social relevance of the phenomenon, depression still faces considerable unsatisfactory response rates, thus soliciting the exploration of novel therapeutic targets to develop more effective interventions.

Concerning the pharmacological treatment of depression, currently the cornerstone of clinical management, numerous agents from different classes have been proposed since the 1950s, when the mood-enhancing properties of two anti-tuberculosis agents, isoniazid and iproniazid [4 5] and imipramine, also a tricyclic compound [6] were serendipitously observed. Unfortunately, at that time the number of people diagnosed with "depression" who would benefit from these "new" agents was very low, so that the development of antidepressants was not the high priority of pharmaceutical companies [7]. The situation changed in 1988, when the introduction of fluoxetine, a selective serotonin reuptake inhibitor (SSRI) approved for the treatment of major depressive disorder (MDD) [8], alternatively generically labelled as "depression", marked the beginning of a "golden era" of the pharmacological treatment of the disorder [9]. In fact, although not as effective as the previously introduced tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAO-Is) [10 11], the SSRIs and the latter introduced classes of antidepressants, still ensured substantial remission rates compared to placebo while providing a better tolerability profile (although not completely devoid of side-effects), thus contributing to the widespread pharmacological management of depression [12 13]. Nonetheless, the need for higher response rates for the antidepressant treatment solicited the introduction of novel compounds as well the implementation of enhanced augmentation or switching strategies for currently available drugs.

In this review, the prominent pharmacological opportunities for the treatment of depression are briefly outlined, focusing on novel non-monoaminergic compounds.

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Materials and methods

Considered sources included all PubMed results written in English (updated to February 2012) systematically retrieved using the following keywords or their combination: "depression"; "major depressive disorder": "antidepressants"; "novel antidepressant targets"; "monoamine"; "novel antidepressants". Additional literature sources, including most authoritative and updated edited books or pamphlets were evaluated accordingly.

Results

Two hundred and eighty nine randomized clinical trials (RCTs) or meta-analyses were assessed, while non-controlled studies were used only when controlled data unavailable. Finally, studies performed in humans were prioritized, while pre-clinical or animal investigations have been cited only in the absence of corresponding evidence in human samples.

The monoamine hypothesis of depression and beyond

Since its first conceptualization, [14-16] the "monoamine hypothesis of depression" largely influenced the development of novel antidepressant drugs and prescribing attitudes of clinicians toward MDD [17]. This hypothesis essentially focuses on increasing the levels and synaptic effects of three monoamines, namely dopamine (DA), norepinephrine (NE) and the indole amine 5-hydroxytryptamine (5-HT) or serotonin, to induce an antidepressant response [18-20]. Within the past decades, this hypothesis has undergone extensive revision, leading to the observation that such synaptic modifications would be due to blockade of monoamine transporters, including the dopamine transporter (DAT), the norepinephrine transporter (NET) and the serotonin transporter (SERT) [19]. However, monoamine levels can increase rapidly following blockade of these transporters, much earlier than onset of clinical action, if ever [21 22]. The "neurotransmitter receptor sensitivity hypothesis" of depression can explain this lag phase [23], and is also in agreement with the neurotransmitter receptor hypothesis focusing on the abnormal up-regulation of receptors during the course of depression [24]. Nonetheless, it is likely that modifications in receptor number and/or sensitivity following antidepressant treatment require alterations in gene expression, transcription, translation and production of various neurotrophic factors as the brain derived neurotrophic factor (BDNF) [25 26]. Thus, in addition to modulating monoamine and receptor levels, the final common pathway of all antidepressants should involve the regulation of various trophic factors, rather than just the monoamine balance. As a major implication, this possibility has suggested that other antidepressant targets should be explored.

The need for novel antidepressant drugs: the increasingly crowded antidepressant scenario

Both pharmacological and clinical considerations concerning the efficacy, safety, tolerability and costs influence compliance and outcome of the depressed patient, soliciting novel antidepressant interventions.

The need for an anticipated onset of action

A lag phase of at least 3-4 weeks prior to the onset of an antidepressant effect is commonly seen with current antidepressant drugs [27], in contrast with an almost immediate increase in monoamine extracellular levels evident just few hours initiation of therapy.

At least two types of 5-HT auto-receptors are present on the serotonergic neuron. Activation of 5-HT1A receptors, present in the somatodendritic area, reduces neuronal firing, resulting in less serotonin release from the axon terminal. On the other hand, activation of 5-HT1B receptors causes direct inhibition of serotonin release. 5-HT1A is also related to control of serotonergic release through a large feedback loop from terminal to the cell body region [28]. It is likely that these auto-restraining processes counteract the initial effect of SSRIs as well as other classes of antidepressant drugs that primarily act by serotonergic modulation, and chronic administration of these agents is reported to desensitize both presynaptic and postsynaptic 5-HT1A receptors [29].

Similarly, complex pre- and post-synaptic modulations concern norepinephrinergic modulation. The alpha-2 norepinephrinergic auto-receptors, located both on axon terminals and cell bodies, establish an effective self-regulation system similar to that in serotonergic neurons, which is also believed to become supersensitive during depression [30], while the beta-adrenoceptors are located post-synaptically. Up-regulation of these receptors has been observed in the course of depression, whereas down-regulation of these latter has been related to antidepressant activity [31]. Nonetheless, despite the discovery of the mechanisms held to be responsible, overcoming the lag phase of antidepressant drugs remains an unaddressed need [32].

The need for more effective antidepressants: beyond the SSRIs

The SSRIs are still the most commonly prescribed antidepressant drugs [13]. Nonetheless, their efficacy has highly debated, especially for most severe cases of depression [33], which have favoured the use of serotonin norepinephrine

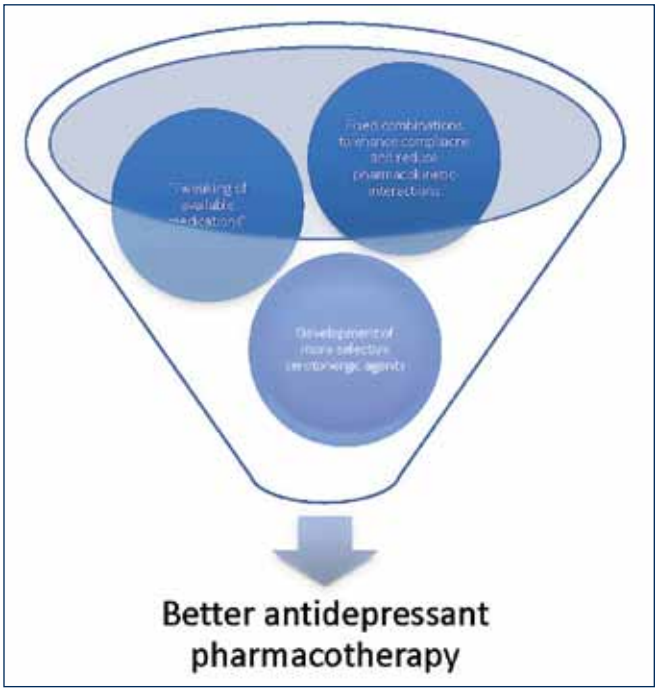

FIGURE 1.
Switching and augmentation of strategies are part of routine psychopharmacological practice of the treatment of depression, especially for less responsive cases. Other optimizations include the development of novel formulations of older medications to enhance tolerability and compliance (e.g. controlled release formulation of trazodone with milder anti-alpha-1 effect is waiting approval for a new high-dose, 300-450 mg once-daily formulation; similarly, desvenlafaxine, the main metabolite of venlafaxine, under-metabolized by the kidney, appears to have the antidepressant effects of its parent compound with a more favourable pharmacokinetic profile) [50 51]. More selective serotonergic antidepressants are also being considered, including the following: Lu AA21004, a SSRI with anti-nausea and anti-anxiety 5-HT3 antagonism plus 5-HT1A action [52], vilazodone or SB 659746A acting as SSRI/5-HT1A partial agonist [53], gepirone ER and PRX 00023 as 5-HT1A partial agonists [54 55], VPI 013 or OPC 14523 acting as a sigma-1/5-HT1A partial agonist [56], TGW-00-AD/AA as 5-HT1A agonist and 5-HT2A antagonist, TGBA-01-AD as SRI/5-HT2/5-HT1A/5-HT1D modulator, elzasonam as 5-HT1B/D antagonist [31] and agomelatine acting as 5-HT2C and weak 5-HT2B antagonist and MT1/MT2 melatonergic agonist [38]. Additional 5-HT1A/5-HT1B modulation could be provided by non-antidepressant augmentation strategies, including the following: the beta-blocker pindolol acting as 5-HT1A partial agonist and the thyroid hormone triiodothyronine (T3) modulating 5-HT1B receptors [57] as well as some triptans providing 5-HT1A and/or 5-HT1D and/or 5-HT1F agonist effects. Many more agents, including 5-HT2C/5-HT2A blockers, lithium and atypical antipsychotics are under consideration [31]. *Le strategie di passaggio o di aggiunta sono parte della prassi psicofarmacologica antidepressiva, specie nei casi meno responsivi. Altre strategie di ottimizzazione riguardano lo sviluppo di nuove formulazioni di vecchi farmaci allo scopo di aumentarne la tollerabilità e quindi l'aderenza al trattamento (es. formulazioni a rilascio controllato di trazodone, con minor effetto anti-alfa1 è in attesa dell'approvazione per la nuova formulazione a dosaggio elevato, 300-450 mg una volta al giorno; parimenti, la desvenlafaxina, il principale metabolita della venlafaxina, sotto-metabolizzata dal rene, pare mantenere lo stesso effetto antidepressivo del farmaco sorgente ma con un profilo farmacocinetico più favorevole) [50 51]. Altri farmaci selettivi serotoninergici sono ugualmente oggetto di considerazione, inclusi i seguenti: Lu AA21004, un SSRI con attività anti-nausea ed anti-ansia legate all'antagonismo 5-HT3 più azione 5-HT1A [52], vilazodone o SB 659746A attivo quale SSRI parziale agonista 5-HT1A [53], gepirone a rilascio esteso e PRX 00023 quali parziali agonisti 5-HT1A [54 55], VPI 013 o OPC 14523 agente quale parziale agonista sigma-1/5-HT1A [56], TGW-00-AD/AA come 5-HT1A agonista e 5-HT2A antagonista, TGBA-01-AD quale modulatore SRI/5-HT2/5-HT1A/5-HT1D, elzasonam come 5-HT1B/D antagonista [31] ed agomelatina agente come antagonista 5-HT2C e blando bloccante 5-HT2B nonché come agonista melatoninergico MT1/MT2 [38]. L'ulteriore modulazione 5-HT1A/5-HT1B potrebbe esser fornita inoltre da strategie di "augmentation" con farmaci non antidepressivi, tra cui i seguenti: il beta-bloccante pindololo che agisce come parziale agonista 5-HT1A e l'ormone tiroideo Triiodotironina (T3) che modula I recettori 5-HT1B [57] come pure alcuni triptani che forniscono effetti di agonismo 5-HT1A e/o 5-HT1D e/o 5-HT1F. Molti altri agenti, inclusi i bloccanti 5-HT2C/5-HT2A, litio e antipsicotici atipici sono anch'essi considerati [31].*

reuptake inhibitors (SNRIs) such as duloxetine and venlafaxine, characterized by a more comprehensive pharmacological profile and higher antidepressant efficacy in most cases [34]. Efficacy and tolerability concerns have partially shifted prescribing patterns towards novel pharmacological agents, including the norepinephrine selective serotonin sntagonists (NaSSA) mirtazapine, or dopaminergic modulators such as the norepinephrine dopamine reuptake inhibitor (NDRI) bupropion. These aim to enhance the anhedonic, cognitive, metabolic and sexual profile of depression frequently seen as part of disease or as SSRIs-induced effects [35].

Additional strategies to enhance the efficacy of current antidepressant drugs include targeting specific monoamine receptors or "tweaking" the posology of current drugs (Fig. 1).

When "two is not enough": triple reuptake inhibitors

Dual reuptake inhibitors offered clinicians effective and patient-oriented SSRIs alternatives, substantially reducing the need for TCAs or MAO-Is and their unpleasant anticholinergic and anti-histaminergic side effects or even potentially life-threatening complications. Nonetheless, response rates did not increase to a satisfactory level, thus suggesting further strengthening of the antidepressant

TABLE I.
Sample triple reuptake inhibitors proposed for MDD [58 59]. *Esempio di triple del reuptake della serotonina proposte per MDD [58 59].*

Compound	Stage of development	Mechanism
GSK 372475	Phase II	Triple reuptake inhibitor (TRI)
Boehringer NS 2330 (Tesofensine)	Undetermined	TRI
DOV 216303	Phase II	TRI
NS 2360	Preclinical	TRI
Lu AA24530	Phase II	TRI and specific 5-HT2C, 5-HT3, 5-HT2A, alpha1 modulator
Lu AA37096	Phase I	TRI and specific 5-HT6 modulator
Lu AA34893	Phase II	TRI and specific 5-HT2A, alpha1 and 5-HT6 modulator
Sepracor SEP 225289	Phase II	TRI
DOV 21947	Phase II	TRI
JNJ 7925476	Undetermined	TRI

pharmacological profile by concomitant administration of multiple antidepressants with different mechanisms of action or by the development of novel, triple reuptake inhibitors (TRIs) enhancing transmission of 5-HT, NE and DA at once [36].
Remarkably, no TRI is currently available for prescription over the counter either in Europe neither in the US (Table I), and the expectations toward these novel agents still await clinical confirmation. What might be expected, however, is a reduced need for augmentation therapies and total number of daily medications, lower potential for pharmacokinetic interactions and, finally, better patient compliance.

Beyond monoamines: present and future directions

Depression has been conceptualized as the clinical expression of a broader "stress" condition underlined by immune and neuroendocrine imbalances [37], thus further shifting the interest for novel potential antidepressant targets beyond monoamines (Table II). This is confirmed by the recent clinical interest toward agomelatine, acting both as 5-HT2C antagonist and as a melatonergic (MT) type I and type II agonist [38], as well as and increasing attention toward anti-oxidative stress modulators and pro-inflammatory cytokines. Rebalance of an overactive hypothalamic-pituitary-adrenal

TABLE II.
Examples of novel HPA modulators being considered for MDD [31 60-62]. *Esempi di nuovi modulatori HPA considerati per MDD [31 60-62].*

Compound	Stage of development	Mechanism
GSK 561679	Phase II	Corticotropin releasing factor-1 receptor (CRF1) antagonist
GSK 586529	Phase I	CRF1 antagonist
ONO 233M	Preclinical	CRF1 antagonist
R121919	Phase I	CRF1 antagonist
CP316,311	Phase II	CRF1 antagonist
BMS 562086 (Pexacerfont)	Phase II	CRF1 antagonist
GW876008	Undetermined	CRF1 antagonist
SSR125543	Phase I	CRF1 antagonist
JNJ19567470; TS041	Preclinical	CRF1 antagonist
SSR126374	Preclinical	CRF1 antagonist
Schering Plough SCH 900635 (org34517)	Phase II	Glucocorticoid Receptor (GR) antagonist
Corcept Mifiprestone	Phase III	GR II antagonist
Sanofi SSR 149415	Phase II	Vasopressin b1 antagonist

(HPA) axis and subsequent glucocorticoid receptor (GRs) overstimulation [39], commonly found in course of depression [40], via corticotropin releasing factor (CRF) 1 receptor (CRF1) antagonists [41] also represents a promising opportunity to the development of novel non-monoaminergic antidepressants. In addition to CRF, vasopressin (V) is also involved in regulating HPA axis activity, with its b1 receptors positively stimulating adrenocorticotropic hormone (ACTH) release induced by CRF, thus suggesting a Vb1 antagonist may be useful as an antidepressant.

Besides HPA modulators, the central nervous system (CNS) peptide neurokinin (NK) substance P (SP) receptors (SN_{1-3}) are also potential antidepressant targets. In fact, since NK1 antagonists may increase 5-HT transmission, decreasing 5-HT1A auto-receptors sensitivity in the dorsal raphe nucleus, this would induce tonic stimulation of hippocampal 5-HT1A post-synaptic receptors [42 43], thus their antidepressant role is being considered especially for the painful somatic and emotional symptoms often present during the course of depression [44]. The need for better management of depression has also renewed interest in acetylcholine (Ach) modulators for commonly associated cognitive symptoms. Ach transmission is negatively regulated by Ach esterase (AchE), which metabolizes acetylcholine into choline; nicotinic receptors expressed by DA neurons at the ventral tegmental area increase the responsiveness of DA system to reward-related stimuli [45], therefore, AchE inhibitors as galantamine [46] and similar future agents should also have a place in the antidepressant armamentarium. Further focusing on the cognitive symptoms of depression, N-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) glutamate receptors have been considered as potential antidepressant targets (Table III).

Discussion

Since the introduction of newer antidepressant drugs in the past decade, there has been an increase in the diagnosis and treatment of MDD, perhaps in part related to the introduction of "treatments for the diagnosis", "treatment-oriented observation bias" or Klerman's "pharmacocentric view of the world" [47]. Nonetheless, with the exception of agomelatine [38], yet still characterized by a substantial serotonergic activity eventually accounting for most of its antidepressant effects, innovative non-monoaminergic antidepressants are still lacking, and most of the needs for the treatment of major depression remain unmet, especially concerning residual symptomatology and the subsequent risk for recurrence and/or relapse.

Moreover, the antidepressants that already reached the market were produced in the early 1990s and subsequently redeveloped. There are several reasons why the field has been in a relative drought [48]. The first problem that arose in the 1990s was the eagerness of industry to get their candidate antidepressants quickly to market at the expense of performing solid pivotal trials. A second problem persisting in the field is the inadequate dosing of the candidate compounds in clinical trials. A third difficulty is the limited period of patent protection, especially in the presence of financial drain exerted by generic medications. On one hand, industry has to be kept in check to ensure that novel medications are not sold at exorbitant prices, still making enough profits to ensure that their pipelines are not depleted. Additionally, the cost to bring an antidepressant to market is massive, and on occasion medications have to be discontinued due to unexpected adverse events even after they have become "blockbuster".

Shifting the targets of novel antidepressant drugs toward the modulation of monoamine is therefore an ambitious goal from pharmacological, clinical and financial standpoints.

TABLE III.
Examples of nonmonoaminergic, non-HPA-ergic modulators proposed for MDD [63-71]. *Esempi di non monoaminergici, non HPA-ergici modulatori proposto per la MDD [63-71].*

Compound	Stage of development	Mechanism
CPP	Undetermined	NMDA antagonist
Org 26576	Preclinical	Positive AMPA allosteric modulator
Enhancers of sleep and anxiety proposed as SSRI augmentation strategies for MDD		GABAA stimulant GABAB antagonist
Enhancers of sexual impairment during course of MDD		Phosphodiesterase (PDE) inhibitors
Amibegron	Undetermined	Beta-3 antagonists
SA 4503	Undetermined	Sigma-1 agonist
SSR 411298	Undetermined	Fatty acids amide hydrolase derivate
Celecobix	Preclinical	Cyclooxygenase-2 (COX-2) inhibitor

Conclusions

The clinical management of depression remains a major concern for clinicians. In fact, despite the associated burden and a number of therapeutic options, including non-pharmacological interventions, response rates remain low. Therefore, shifting the interest on the development of novel antidepressants beyond monoaminergic modulation is attentively evaluated both by pre-clinical researchers and practitioners. Nonetheless, greater insights on the aetiology of depression are needed, along with more accurate nosological constructs to allow a more focused exploration of potential novel antidepressant targets, with a special attention to sub-threshold bipolarity as potential, insidious, responsible of "pseudo"-resistance in the pharmacological treatment of depression [49 72].

References

1 Terra JL. *Suicide risk and depression*. Rev Prat 2008;58:385-8.

2 Burcusa SL, Iacono WG. *Risk for recurrence in depression*. Clin Psychol Rev2007;27:959-85.

3 Kessler RC, Berglund P, Demler O, et al. *The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R)*. JAMA 2003;289:3095-105.

4 Salzer HM, Lurie ML. *Anxiety and depressive states treated with isonicotinyl hydrazide (isoniazid)*. AMA Arch Neurol Psychiatry 1953;70:317-24.

5 Scanlon WG, White WM. *Iproniazid (marsilid): its use in office treatment of depression*. Am J Psychiatry 1958;114:1036-7.

6 Kuhn R. *The treatment of depressive states with G 22355 (imipramine hydrochloride)*. Am J Psychiatry 1958;115:459-64.

7 Healy D. *The three faces of the antidepressants: a critical commentary on the clinical-economic context of diagnosis*. J Nerv Ment Dis 1999;187:174-80.

8 Poe TE. *Fluoxetine. A new antidepressant*. N C Med J 1988;49:391-2.

9 Preskorn SH. *CNS drug development. Part I: The early period of CNS drugs*. J Psychiatr Pract 2010;16:334-9.

10 Hanada K, Umemura S. *Tricyclic antidepressants*. Nippon Rinsho 2000;58(Suppl 2):633-7.

11 Howland RH. *MAOI antidepressant drugs*. J Psychosoc Nurs Ment Health Serv 2006;44:9-12.

12 Owens MJ. *Selectivity of antidepressants: from the monoamine hypothesis of depression to the SSRI revolution and beyond*. J Clin Psychiatry 2004;65(Suppl 4):5-10.

13 Ferguson JM. SSRI *Antidepressant medications: adverse effects and tolerability*. Prim Care Companion J Clin Psychiatry 2001;3:22-7.

14 Schildkraut JJ. *The catecholamine hypothesis of affective disorders: a review of supporting evidence*. Am J Psychiatry 1965;122:509-22.

15 Coppen A, Shaw DM, Farrell JP. *Potentiation of the antidepressive effect of a monoamine-oxidase inhibitor by tryptophan*. Lancet 1963;1:79-81.

16 McClure DJ. *The role of dopamine in depression*. Can Psychiatr Assoc J 1973;18:309012.

17 Hirschfeld RM. *History and evolution of the monoamine hypothesis of depression*. J Clin Psychiatry 2000;61(Suppl 6):4-6.

18 Kicey CA. *Catecholamines and depression: a physiological theory of depression*. Am J Nurs 1974;74:2018-20.

19 Nutt D, Demyttenaere K, Janka Z, et al. *The other face of depression, reduced positive affect: the role of catecholamines in causation and cure*. J Psychopharmacol 2007;21:461-71.

20 Potter WZ, Manji HK. *Catecholamines in depression: an update*. Clin Chem 1994;40:279-87.

21 Sulser F, Vetulani J, Mobley PL. *Mode of action of antidepressant drugs*. Biochem Pharmacol 1978;27:257-61.

22 Wade A, Friis Andersen H. *The onset of effect for escitalopram and its relevance for the clinical management of depression*. Curr Med Res Opin 2006;22:2101-10.

23 Charney DS, Menkes DB, Heninger GR. *Receptor sensitivity and the mechanism of action of antidepressant treatment. Implications for the etiology and therapy of depression*. Arch Gen Psychiatry 1981;38:1160-80.

24 Werner FM, Covenas R. *Classical neurotransmitters and neuropeptides involved in major depression: a review*. Int J Neurosci 2010;120:455-70.

25 Wager-Smith K, Markou A. *Depression: a repair response to stress-induced neuronal microdamage that can grade into a chronic neuroinflammatory condition?* Neurosci Biobehav Rev 2011;35:742-64.

26 Wolkowitz OM, Reus VI. *Neurotransmitters, neurosteroids and neurotrophins: new models of the pathophysiology and treatment of depression*. World J Biol Psychiatry 2003;4:98-102.

27 Machado-Vieira R, Baumann J, Wheeler-Castillo C, et al. *The timing of antidepressant effects: a comparison of diverse pharmacological and somatic treatments*. Pharmaceuticals 2010;3:19-41.

28 Bosker F, Vrinten D, Klompmakers A, et al. *The effects of a 5-HT1A receptor agonist and antagonist on the 5-hydroxytryptamine release in the central nucleus of the amygdala: a microdialysis study with flesinoxan and WAY 100635*. Naunyn Schmiedebergs Arch Pharmacol 1997;355:347-53.

29 Cremers TI, Spoelstra EN, de Boer P, et al. *Desensitisation of 5-HT autoreceptors upon pharmacokinetically monitored chronic treatment with citalopram*. Eur J Pharmacol 2000;397:351-7.

30 Charney DS, Heninger GR, Sternberg DE, et al. *Presynaptic adrenergic receptor sensitivity in depression. The effect of long-term desipramine treatment*. Arch Gen Psychiatry 1981;38:1334-40.

31 Stahl S, editor. *Stahl's Essential Psychopharmacology*. Third Edition. San Diego, CA: Cambridge University Press 2008.

32 Payne JL, Quiroz JA, Zarate CA, Jr, et al. *Timing is every-*

thing: does the robust upregulation of noradrenergically regulated plasticity genes underlie the rapid antidepressant effects of sleep deprivation? Biol Psychiatry 2002;52:921-6.

33 Sonawalla SB, Fava M. *Severe depression: is there a best approach?* CNS Drugs 2001;15:765-76.

34 Lam RW, Kennedy SH, Grigoriadis S, et al.; Canadian Network for Mood and Anxiety Treatments (CANMAT). *Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. III. Pharmacotherapy*. J Affect Disord 2009;117(Suppl 1):S26-43.

35 Cascade E, Kalali AH, Kennedy SH. *Real-world data on SSRI antidepressant side effects*. Psychiatry (Edgmont) 2009;6:16-8.

36 Dell'Osso B, Bareggi SR, Palazzo MC, et al. *Dai composti ad azione duale a quelli a triplice azione: considerazioni sullo sviluppo di una nuova classe di antidepressivi*. Giorn Ital Psicopat 2010;16:114-5.

37 Miller AH. *Neuroendocrine and immune system interactions in stress and depression*. Psychiatr Clin North Am 1998;21:443-63.

38 Fornaro M, Prestia D, Colicchio S, et al. *A systematic, updated review on the antidepressant agomelatine focusing on its melatonergic modulation*. Curr Neuropharmacol 2010;8:287-304.

39 Catena Dell'Osso M, Bellantuono C, Consoli G, et al. *Inflammatory and neurodegenerative pathways in depression: a new avenue for antidepressant development?* Curr Med Chem 2011;18:245-55.

40 Pariante CM, Lightman SL. *The HPA axis in major depression: classical theories and new developments*. Trends Neurosci 2008;31:464-8.

41 Chopra K, Kumar B, Kuhad A. *Pathobiological targets of depression*. Expert Opin Ther Targets 2011;15:379-400.

42 Gobbi G, Blier P. *Effect of neurokinin-1 receptor antagonists on serotoninergic, noradrenergic and hippocampal neurons: comparison with antidepressant drugs*. Peptides 2005;26:1383-93.

43 Blier P, Gobbi G, Haddjeri N, et al. *Impact of substance P receptor antagonism on the serotonin and norepinephrine systems: relevance to the antidepressant/anxiolytic response*. J Psychiatry Neurosci 2004;29:208-18.

44 Madaan V, Wilson DR. *Neuropeptides: relevance in treatment of depression and anxiety disorders*. Drug News Perspect 2009;22:319-24.

45 Mansvelder HD, Mertz M, Role LW. *Nicotinic modulation of synaptic transmission and plasticity in cortico-limbic circuits*. Semin Cell Dev Biol 2009;20:432-40.

46 Elgamal S, MacQueen G. *Galantamine as an adjunctive treatment in major depression*. J Clin Psychopharmacol 2008;28:357-9.

47 Ghaemi SN, Sachs GS, Chiou AM, et al. *Is bipolar disorder still underdiagnosed? Are antidepressants overutilized?* J Affect Disord 1999;52:135-44.

48 Blier P. *The well of novel antidepressants: running dry*. J Psychiatry Neurosci 2010;35:219-20.

49 Fornaro M, Giosue P. *Current nosology of treatment resistant depression: a controversy resistant to revision*. Clin Pract Epidemiol Ment Health 2010;6:20-4.

50 Sheehan DV, Croft HA, Gossen ER, et al. *Extended-release trazodone in major depressive disorder: a randomized, double-blind, placebo-controlled study*. Psychiatry (Edgmont) 2009;6:20-33.

51 Pae CU. *Desvenlafaxine: a new antidepressant or just another one?* Expert Opin Pharmacother 2009;10:875-87.

52 Adell A. *Lu-AA21004, a multimodal serotonergic agent, for the potential treatment of depression and anxiety*. IDrugs 2010;13:900-10.

53 Howland RH. *Vilazodone: another novel atypical antidepressant drug*. J Psychosoc Nurs Ment Health Serv 2011;49:19-22.

54 Feiger AD, Heiser JF, Shrivastava RK, et al. *Gepirone extended-release: new evidence for efficacy in the treatment of major depressive disorder*. J Clin Psychiatry 2003;64:243-9.

55 de Paulis T. *Drug evaluation: PRX-00023, a selective 5-HT1A receptor agonist for depression*. Curr Opin Investig Drugs 2007;8:78-86.

56 Bermack JE, Debonnel G. *Effects of OPC-14523, a combined sigma and 5-HT1a ligand, on pre- and post-synaptic 5-HT1a receptors*. J Psychopharmacol 2007;21:85-92.

57 Lifschytz T, Segman R, Shalom G, et al. *Basic mechanisms of augmentation of antidepressant effects with thyroid hormone*. Curr Drug Targets 2006;7:203-10.

58 Lucas MC, Weikert RJ, Carter DS, et al. *Design, synthesis, and biological evaluation of new monoamine reuptake inhibitors with potential therapeutic utility in depression and pain*. Bioorg Med Chem Lett 2010;20:5559-66.

59 Marks DM, Pae CU, Patkar AA. *Triple reuptake inhibitors: the next generation of antidepressants*. Curr Neuropharmacol 2008;6:338-43.

60 Kamiyama H, Matsumoto M, Otani S, et al. *Mechanisms underlying ketamine-induced synaptic depression in rat hippocampus-medial prefrontal cortex pathway*. Neuroscience 2011;177:159-69.

61 Wulsin AC, Herman JP, Solomon MB. *Mifepristone decreases depression-like behavior and modulates neuroendocrine and central hypothalamic-pituitary-adrenocortical axis responsiveness to stress*. Psychoneuroendocrinology 2010;35:1100-12.

62 Breuer ME, van Gaalen MM, Wernet W, et al. *SSR149415, a non-peptide vasopressin V1b receptor antagonist, has long-lasting antidepressant effects in the olfactory bulbectomy-induced hyperactivity depression model*. Naunyn Schmiedebergs Arch Pharmacol 2009;379:101-6.

63 Davies J, Evans RH, Herrling PL, et al. *CPP, a new potent and selective NMDA antagonist. Depression of central neuron responses, affinity for [3H]D-AP5 binding sites on brain membranes and anticonvulsant activity*. Brain Res 1986;382:169-73.

64 Jordan GR, McCulloch J, Shahid M, et al. *Regionally selective and dose-dependent effects of the ampakines Org 26576 and Org 24448 on local cerebral glucose utilisation in the mouse as assessed by 14C-2-deoxyglucose autoradiography*. Neuropharmacology 2005;49:254-64.

65 Kalueff AV, Nutt DJ. *Role of GABA in anxiety and depression*. Depress Anxiety 2007;24:495-517.

66 Borsook D, Richardson GS, Moore-Ede MC, et al. *GABA and circadian timekeeping: implications for manic-depression and sleep disorders*. Med Hypotheses 1986;19:185-98.

67 Nurnberg HG, Seidman SN, Gelenberg AJ, et al. *Depression, antidepressant therapies, and erectile dysfunction: clinical trials of sildenafil citrate (Viagra) in treated and untreated patients with depression*. Urology 2002;60(Suppl 2):58-66.

68 Overstreet DH, Stemmelin J, Griebel G. *Confirmation of antidepressant potential of the selective beta3 adrenoceptor agonist amibegron in an animal model of depression*. Pharmacol Biochem Behav 2008;89:623-6.

69 Stahl SM. *The sigma enigma: can sigma receptors provide a novel target for disorders of mood and cognition?* J Clin Psychiatry 2008;69:1673-4.

70 Naidu PS, Varvel SA, Ahn K, et al. *Evaluation of fatty acid amide hydrolase inhibition in murine models of emotionality*. Psychopharmacology (Berl) 2007;192:61-70.

71 Chen CY, Tzeng NS, Chen YC. *Maintenance therapy of celecoxib for major depression with mimicking neuropsychological dysfunction*. Gen Hosp Psychiatry 2010;32:647 e7-9.

72 Fornaro M, Aguglia E, Dell'Osso L, et al. *Could the underestimation of bipolarity obstruct the search for novel antidepressant drugs?* Expert Opin Pharmacother 2011;12:2817-31.

These tricyclic and monoamine oxidase inhibitor antidepressants were subsequently found to promote serotonin or noradrenaline function in the brain. Newer agents are more specific but have the same core mechanisms of action in promoting these monoamine neurotransmitters. This is unfortunate, because only âˆ¼50% of individuals with depression show full remission in response to these mechanisms. This review summarizes the obstacles that have hindered the development of non-monoamine-based antidepressants, and provides a progress report on some of the most promising current strategies. Early antidepressant medications e.g. tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) are effective because they enhance either noradrenergic or serotonergic mechanisms, or both. Unfortunately, these compounds block cholinergic, histaminergic and alpha-1-adrenergic receptor sites, interact with a number of other medications and bring about numerous undesirable side effects. Several chemically unrelated agents have been developed and introduced in the past decade to supplement the early antidepressants.Â An important new development has been the emergence of potential novel mechanisms of action beyond the monoaminergic synapse. The World Health Organization estimates that depression is the fourth leading cause of disability worldwide, with a lifetime prevalence of about 15â€“20% [1]. The ï¬rst reports of antidepressant treatments date back to the early 1950s, when researchers in the United States Next Generation Antidepressants: Moving Beyond Monoamines to Discover Novel Treatment Strategies for Mood Disorders, ed.Â Based on the monoamine hypothesis of depression, which posits a lack in monoamines in various brain regions of depressed patients, the development of antidepressant medications has focused on increasing the levels and synaptic eï¬€ects of three monoamines: the