REVIEW

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The Noradrenergic Action in Antidepressant Treatments: Pharmacological and Clinical Aspects

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SUMMARY

Even though noradrenaline has been recognized as one of the key neurotransmitters in the pathophysiology of major depression (MD), noradrenergic compounds have been less extensively utilized in clinical practice, compared to selective serotonin reuptake inhibitors (SSRIs). The development of the first selective noradrenergic reuptake inhibitor (NRI), Reboxetine, has not substantially changed the state of the art. In addition, Atomoxetine, a relatively pure NRI used for the treatment of ADHD, has shown mixed results when administered in augmentation to depressed subjects. Through a Medline search from 2000 to 2010, the present article provides an updated overview of the main pharmacological and clinical aspects of antidepressant classes that, partially or selectively, act on the noradrenergic systems. The noradrenergic action plays an important clinical effect in different antidepressant classes, as confirmed by the efficacy of dual action antidepressants such as the serotonin noradrenaline reuptake inhibitors (SNRIs), the noradrenergic and dopaminergic reuptake inhibitor (NDRI) Bupropion, and other compounds (e.g., Mianserin, Mirtazapine), which enhance the noradrenergic transmission. In addition, many tricyclics, such as Desipramine and Nortriptyline, have prevalent noradrenergic effect. Monoamine oxidase inhibitors (MAOIs), moreover, block the breakdown of serotonin, noradrenaline, dopamine and increase the availability of these monoamines. A novel class of antidepressants—the triple reuptake inhibitors—is under development to selectively act on serotonin, noradrenaline, and dopamine. Finally, the antidepressant effect of the atypical antipsychotic Quetiapine, indicated for the treatment of bipolar depression, is likely to be related to the noradrenergic action of its metabolite Norquetiapine. Even though a pure noradrenergic action might not be sufficient to obtain a full antidepressant effect, a pronoradrenergic action represents an important element for increasing the efficacy of mixed action antidepressants. In particular, the noradrenergic action seemed to be related to the motor activity, attention, and arousal.

Introduction

It is well established that many antidepressant compounds with proven clinical efficacy act also on noradrenergic pathways. The catecholamine hypothesis of major depression (MD), in fact, indicates noradrenaline as one of the key neurotransmitters involved in the pathophisiology of the disorder on the basis of different neurobiological and neurochemical issues [1,2]. Actually, it is now well established that catecholamines (dopamine, noradrenaline, and serotonin) [3,4] are not the only agents involved in the pathophysiology of MD with many other neurotransmitters (e.g., glutamate, gamma-Aminobutyric acid [GABA]) [5,6], and different systems (e.g., neuroimmune, hypothalamic-pituitary axis, second messengers, altered neuroplasticity [7–10]) also playing an important role [11,12]. With respect to central neurotransmitter systems, moreover, it is now believed that alterations are associated with specific behaviors and symptom dimensions rather than directly with MD [13]. For instance, research in the field has indicated that abnormalities in the serotonin transmission are associated with impulsivity, aggressive, and anxious behaviors [14–16], whereas different noradrenergic concentrations with motor activity, attention, and arousal [15,17]. Therefore, in reviewing the noradrenergic action of currently available antidepressants and summarizing main nauroanatomic, neurochemical, and pharmacological bases of the noradrenergic transmission, it is worthwhile to stress that effects in these systems are not specifically associated with an antidepressant effect but, more properly, to a specific action over behavioral dimensions and clusters of symptoms.

Neuroanatomy of Noradrenergic Transmission

The main noradrenergic brain circuits are located in the locus coeruleus, which consists of a major group of noradrenergic neurons in the periventricular and periaqueductal gray matter, connecting the cerebral cortex, the cerebellum, and the brainstem. The locus coeruleus is basically involved in the responsiveness to external conditions and vigilance, providing pathways descending to the spinal cord and projecting throughout the limbic system and diencephalon as well to the cortex [18,19]. Other noradrenergic neurons are usually located in the medulla and pons, connecting to the nucleus ambiguous, the nucleus of the solitary tract, and the dorsal motor vagal nucleus. Noradrenergic pathways interact with many other neurotransmitter systems. For instance, gabaergic and cholinergic systems are supposed to be involved in the pathophysiology of mood disorders exciting noradrenergic cells of the locus coeruleus acting on muscarinic receptors [20]. In addition, noradrenergic and serotonergic systems overlap at several levels and are far away to be independent, both distributing to broad cortical areas [21]. In fact, serotonergic neurons appear to show noradrenergic receptors and vice versa and there is a consistent cross-talk of their second messengers [22].

Biochemistry

Noradrenaline is a cathecholamine with a hormonal role increasing the glycogenolysis, heart rate, and blood flow: these actions result on a global arousal state in the stress response. Noradrenaline is synthesized in the adrenal medulla starting from the aminoacid tyrosine that is oxidated into diidroxiphenilalanine or L-DOPA. L-DOPA is then decarboxylated into dopamine and a final β-oxydation converts dopamine into noradrenaline. Noradrenaline is released in the blood bound to noradrenaline transporter (NAT). NAT is a sodium-dependent protein that carries noradrenaline and dopamine from the synapse back to cytosol, from which other vescicolar monoamine transporters sequester the two monoamines into vesicles for later storage and release. Noradrenaline has multiple receptor which can be divided into four types (2 alpha and 2 beta), most of them using an adenylcyclase second messenger system, particularly in the central nervous system (CNS). Normally, Noradrenaline is degraded to Normetanephrine, 3,4-Dihydroxymandelic acid, 3-Methoxy-4-hydroxymandelic acid, 3-Methoxy-4-hydroxyphenylethylene glycol, and Epinephrine [21,22].

Behavioral Correlates of Noradrenergic Systems

As previously mentioned, noradrenergic transmission seems to be particularly correlated with attention, arousal, motor, and cognitive activity [15,17]. Noradrenergic pathways are involved in different emotional functions and mediate stress response to fearful stimuli. For instance, melancholic symptoms and pervasive anxiety during atypical depressive episodes have been related to the noradrenergic system [23]. On one hand, converging evidence indicates that an increase of noradrenergic transmission may ameliorate poor concentration, apathy, and depressive symptoms [24]. On the other hand, an increase of noradrenergic levels might lead to a behavioral state of arousal, increased vigilance, cognition, learning, and sleep dysregulation [25]. Connections to the endocrine and cardiovascular systems, via the hypothalamus, might be involved in the pathogenesis of anxiety, mediated by parasympathetic activation [26–27]. Anxiety symptoms through specific noradrenergic pathways might initiate or exacerbate depressive symptomatology [28]. Many studies have shown that the noradrenergic transmission is significantly increased when novel stimuli are presented and, thus, noradrenaline appears to play an important role in controlling the disturbances of vegetative functions associated with affective, anxiety, and cognitive disorders [28]. Noradrenaline deficiency, particularly in those pathways connecting the locus coeruleus with the limbic system, may reduce concentration, affect working memory, and cause psychomotor retardation, resulting in apathy and depression [25].

Taken as a whole, behavioral correlates of noradrenergic transmission are particularly related to motor activity, attention, arousal, and cognitive processes. Impairment in these behaviors, due to altered noradrenergic transmission, are not specific of MD and they can be found also in anxiety disorders, impulse control disorders, attention deficit and hyperactivity disorder (ADHD), etc.

Antidepressants and Other Psychotropic Compounds Acting on Noradrenergic Systems

Different classes of compounds can enhance noradrenergic activity, basically acting on the inhibition of the reuptake transporters (Tables 1 and 2). These include some tricyclic antidepressants (TCAs) such as Desipramine and Nortryptiline, or relatively pure noradrenaline reuptake inhibitors (NRIs) like Reboxetine and Atomoxetine. In addition, serotonin and noradrenaline reuptake inhibitors (SNRIs), noradrenaline and dopamine reuptake inhibitors (NDRIs), noradrenergic and specific serotonergic antidepressants (NaSSAs) and, more recently, the novel class of triple reuptake inhibitors (TRIs), under development to selectively inhibit the reuptake of the three main monoamines, can boost the noradrenergic transmission. Finally, monoaminoxidase inhibitors (MAO-Is) still represent a therapeutic option in MD, acting on the three main biogenic amines though with a reduced pattern of selectivity accounting for major adverse effects. Even some atypical antipsychotics, such as Quetiapine, and its metabolite Norquetiapine in particular, act on the noradrenergic system binding the NAT. Other compounds are able to inhibit enzymes inactivating noradrenaline in the synaptic cleft such as Tropolone, a catechol-O-methyl transferase (COMT) blocker [29]. Phentolamine, a compound used for hypertensive emergencies, is known to be an alpha receptor blocker, while Clonidine, used to treat migraine, hypertension, and tachycardia, can stimulate the same sites of the receptor. Finally, amphetamines are involved in the release of noradrenaline at nerve terminals [30].

Aim of the Study

The present article is aimed to provide a comprehensive and updated overview in relation to the noradrenergic action of currently available antidepressants, focusing on main pharmacological

Table 1 Dose range, clinical indications, and main side effects of psychotropic compounds with noradrenergic action

Molecule	Standard dosage (mg/day)	Common clinical uses	Major side effects
Tricyclics with prevalent noradrenergic action			
Desipramine Nortriptyline Amitriptyline	100–200 50–150 75–150	Major depressive disorder particularly with neurovegetative symptoms, generalized anxiety disorder, posttraumatic stress disorder	Inhibition of myocardial excitability, arterial hypotension, and central and peripheral anticholinergic side effects
Mono amine oxidase inhibitors (MAO-I)			
Moclobemide	300–600	Agoraphobia or social anxiety, Parkinson's disease, clinical and resistant depression, and anxiety	Drowsiness, dizziness, increased sun sensitivity, or blurred vision. Stomach upset, loss of appetite, tremors, irritability, sleeplessness, flushing, severe headache, rapid or irregular heart rate, skin rash, fever, yellowing of the eyes or skin
Noradrenergic reuptake inhibitors (NRIs)			
Reboxetine	8–12	Major depressive disorder, seasonal depression, attention-deficit/hyperactivity disorder, anxiety disorders (generalized anxiety disorder), bulimia, sexual dysfunction (ipoactive sexual disorder), and schizophrenia	Mainly due to anticholinergic properties: dry mouth, constipation, headache, drowsiness, dizziness, excessive sweating, urinary retention, and insomnia
Atomoxetine	40–100	Attention-deficit/hyperactivity disorder	Abdominal pain, loss of appetite, nausea, and vomiting
Serotonin-noradrenaline reuptake inhibitors (SNRIs)			
Venlafaxine Desvenlafaxine	75–375 50–100	Major depressive disorder and anxiety disorders (social anxiety disorder, generalized anxiety disorder, posttraumatic stress disorder, panic disorder, and obsessive-compulsive disorder)	Nausea, diarrhea, dry mouth, dizziness, somnolence, fatigue, insomnia, sexual dysfunction
Duloxetine	60–120	Major depressive disorder, generalized anxiety disorder (plus nonpsychiatric indications as peripheral diabetic neuropathic pain and female stress urinary incontinence)	Nausea, dry mouth, headache, constipation, dizziness, and fatigue
Milnacipran	100–200	Major depressive disorder and anxiety disorders; nonpsychiatric indications such as fibromyalgia	Nervousness, nausea, constipation, sweating, dizziness
Noradrenaline-dopamine reuptake inhibitors (NDRIs)			
Bupropion	150–300	Major depressive disorder with melancholic features or hypersomnia and fatigue, seasonal depression and augmentation strategies; smoking cessation	Seizure, hypertension, insomnia, sweating, anxiety, liver toxicity
Noradrenergic and specific serotonergic antidepressants (NaSSA)			
Mirtazapine	15–45	Major depressive disorders particularly for patients at midlife and older, anxiety disorders (obsessive-compulsive disorder) undifferentiated somatoform disorder	Drowsiness, sedation, increased appetite, weight gain
Mianserine	30–90	Depression associated with anxiety and agitation, particularly in cases where sedation is requested	Somnolence, fatigue
Triple reuptake inhibitors			
Brasofensine, Dichloropane, Diclofensine, Indatraline, Tesofensine	on study	Major depression, on study for neurological condition such as Parkinson disease, Alzheimer disease, chronic pain, obesity, alcoholism, and cocaine addiction	On study
Atypical Antipsychotics			
Quetiapine	300–800	Bipolar disorder, Schizophrenia, and off label: obsessive-compulsive disorder, post-traumatic stress disorder, restless legs syndrome, autism, alcoholism, Tourette' syndrome, sleep disorders	Sedation, tachycardia, tardive dyskinesia, neuroleptic malignant syndrome

Table 2 Affinity for noradrenalin transporter (NET) for some pronoradrenergic compounds

Compounds	Affinity for NET
Atomoxetine (NRI)	++++
Nortriptiline (TCA)	++++
Duloxetine (SNRI)	+++
Amitriptiline (TCA)	+++
Norquetiapine (Metabolite of Quetiapine)	+++
Venlafaxine (SNRI)	++
Quetiapine (Atypical Antipsychotic)	-

TCA, tricyclic antidepressant; SNRI, serotonin noradrenaline reuptake inhibitor; NRI, noradrenalin reuptake inhibitor.

mechanisms of action, pharmacodynamic and pharmacokinetic properties, and clinical indications.

Material and Methods

Articles for inclusion were identified conducting a literature search in PubMed referring, in particular, to the last 10 years (from January 2000 to June 2010). The following terms were searched by two independent reviewers: "noradrenaline," "noradrenaline reuptake inhibitors" (NRIs), "noradrenergic antidepressants," "dual action antidepressants," "serotonin noradrenaline reuptake inhibitors" (SNRIs), "noradrenaline dopamine reuptake inhibitors" (NDRIs), and "TRIs.". Only papers published in English were taken into account. For the purpose of the study, the attention was focused particularly on *meta*-analyses, placebo-controlled studies, systematic reviews, and international treatment guidelines.

Results

More than 150 articles were identified and the following classes of antidepressants and related compounds were carefully examined: tricyclics with prominent noradrenergic activity (i.e., Nortryptiline and Desipramine), MAO-Is, NRIs (Reboxetine and Atomoxetine), SNRIs (Venlafaxine and Desmetylvenlafaxine, Duloxetine and Milnacipran), NDRI (Bupropion), NASSAs (Mirtazapine and Mianserin), and TRIs. The atypical antipsychotic Quetiapine was also briefly reviewed. Herein, each specific class with related compounds is examined summarizing its main pharmacological features and clinical activity.

Tricyclics with Prevalent Noradrenergic Activity

Desipramine and Nortriptyline are the TCAs with prevalent activity on the noradrenergic system.

When Amitriptyline undergoes oxidative metabolism in the side chain, the secondary amine Nortriptyline is produced [31]. Nortriptyline has 100 times higher affinity for the NAT than for the serotonin transporter [32]. While Amitriptyline is one of the most anticholinergic antidepressants, Desipramine, an active metabolite of Imipramine, is the least anticholinergic tricyclic [33].

Both Nortriptyline and Desipramine have been widely used in patients with depression and anxiety disorders, with different efficacy. In an interesting study analyzing the profile of action of Desipramine versus the SSRI Paroxetine in hospitalized veterans, Desipramine was more effective in reducing motor retardation and hostility whereas Paroxetine initially improved anxiety and hostility [34]. More recently, in a multicenter trial (the Genome Based Therapeutic Drugs for Depression study), 811 adults with moderate-to-severe unipolar depression were treated with flexible doses of Escitalopram or Nortriptyline for 12 weeks. Results showed no difference between the two compounds in terms of efficacy. However, mood and cognitive symptoms improved more with Escitalopram than with Nortriptyline, while neurovegetative symptoms improved more with Nortriptyline [32].

On the basis of several small trials in the acute treatment of bipolar depression, Imipramine and Desipramine resulted similarly or less efficacious than irreversible nonselective MAO-Is, SSRIs (i.e., Fluoxetine and Paroxetine), and Bupropion [35]. However, the use of tricyclics in bipolar disorder has been associated with a higher risk of antidepressant-induced mania [36]. When used in patients with generalized anxiety disorder (GAD) and poststroke depression, Nortriptyline showed a greater effect than placebo [37]. With regard to the treatment of obsessive compulsive disorder (OCD), compounds with predominant noradrenergic activity were found to be less effective than drugs with proserotonergic action, being the serotonin reuptake inhibition an essential requirement for drugs effective in OCD [38]. Tricyclics have demonstrated high levels of efficacy in the treatment of mood disorders, being certainly not less effective than second-generation antidepressants [33]. In particular, among the tricyclics, the secondary amines like Desipramine and Nortriptyline have fewer side effects compared to the tertiary amines (e.g., Amitriptyline, Imipramine) [35]. Nevertheless, the potential toxicity of tricyclic compounds is well established and consists of the inhibition of myocardial excitability, arterial hypotension, and central and peripheral anticholinergic effects. Being the second-generation antidepressants potentially less toxic and better tolerated than tricyclics, they are preferred as first-choice treatment in both anxiety and depressive disorders [39].

Monoamine Oxidase Inhibitors

The monoamine oxidase inhibitors (MAOIs) act by inhibiting the activity of the enzyme monoamine oxidase, thus preventing the breakdown of monoamine neurotransmitters and increasing their available stores. Two distinct isoforms of monoamine oxidase exist: MAO-A and MAO-B. The former preferentially deaminates serotonin, melatonin, epinephrine, and noradrenaline, whereas the latter preferentially deaminates phenylethylamine and trace amines. Dopamine is equally deaminated by both types. MAOIs differ by their selectivity to the MAO receptor. In terms of clinical efficacy, metanalyses with intent-to-treat samples revealed overall comparable effects for MAOIs like Phenelzine, Isocarboxazid, and Tranylcypromine. In addition, both Phenelzine and Tranylcypromine appeared to be more effective than tricyclics in depressed outpatients with atypical features. MAOIs are also effective treatments for outpatients who have failed to respond to TCAs [40]. Despite their efficacy in MD and some anxiety disorders (e.g.,

social anxiety disorder) [41], tolerability issues may be troublesome. MAOIs, in fact, react with certain foods, alcoholic beverages, and some medications, to produce a severe reaction which often does not appear for several hours after taking the medication and may include a dangerous increase in blood pressure, as well as headache, nausea, vomiting, tachycardia, seizures, stroke, and coma.

Noradrenenaline Reuptake Inhibitors

Reboxetine

Reboxetine acts binding the NAT and blocking the reuptake of extracellular noradrenaline into terminals, with low affinity for other transporters or receptors [42]. Actually, Reboxetine is a mixture compound of two out of four possible stereoisomers of the same molecule with therapeutic action. It is mostly bioavailable (around 95%) with a half-life of 13 h [43]. Reboxetine' metabolism is mainly hepatic and involves CYP3A4: its main metabolites are excreted with urine [44]. Both hepatic and renal failures usually tend to vary Reboxetine' half-life and blood levels should be considered while deciding the starting dose [43]. To date, studies, on Reboxetine plasma levels are not available but could be of interest in assessing a safe therapeutic range. The World Federation of Societies of Biological Psychiatry (WFSBP) provides guidelines about dosage, recommending a starting dose between 4–8 mg per day in older adults, and 8–12 mg per day at the standard dose. With respect to the antidepressant action of the molecule in unipolar depression, a recent *meta*-analysis found Reboxetine less effective than other new-generation antidepressants [45]. Nevertheless, Reboxetine has been effectively used for the treatment of different psychiatric disorders besides MD such as seasonal depression, ADHD, GAD, bulimia, hypoactive sexual disorder, and even schizophrenia [46]. Additionally, as off-label, clinical studies with Reboxetine have been performed for the treatment of fibromialgia and neuropathic pain [47].

With respect to seasonal affective disorder, a recent study comparing Escitalopram to Reboxetine found that response and remission rates were not significantly different in the two treatment groups. Time of onset, however, was shorter with Reboxetine, whereas Escitalopram showed less side effects [48]. Reboxetine might also be useful for augmentation strategies to SSRIs and, in this perspective, its efficacy might be compared to SNRIs [49]. Common side effects of Reboxetine are consistent with its anticholinergic properties and include dry mouth, constipation, headache, drowsiness, dizziness, excessive sweating, and insomnia [50]. However, as most third-generation antidepressants, Reboxetine is usually well tolerated or anyway better tollerated than MAO-Is and tricyclics, with lower rate of discontinuation [51]. Few data are available on safety in overdose.

Atomoxetine

Atomoxetine is a selective NRI with only a slight affinity for other neurotransmitter transporters and receptors [52]. Atomoxetine acts on the presynaptic membrane by blocking the noradrenaline reuptake pump: in this way, the availability of intrasynaptic noradrenaline results increased [53]. Atomoxetine is not labeled as a stimulant and its main indication is the treatment of ADHD [54].

Atomoxetine is metabolized by the cytochrome P450 2D6 and the clearance of other drugs metabolized by CYP enzymes is not influenced by Atomoxetine [55]. It has been investigated in the treatment of depression. However, the lack of a significant effect compared to placebo did not allow the molecule to be approved for the treatment of MD. Nevertheless, there is some recent evidence that Atomoxetine may be effective in treating ADHD with comorbid depression in adolescents [56] and be a possible augmentation strategy for treatment-resistant patients [57]. In terms of tolerability, abdominal pain, loss of appetite, nausea, and vomiting are the most frequent side effects reported by patients with ADHD on Atomoxetine [58]. Even though not approved for mood disorders, the use of Atomoxetine in ADHD, a condition characterized by impaired executive functions, hyperactivity, inattentive and impulsive behaviors, may help to understand how the action on the noradrenergic system can affect cognitive and motor skills.

Serotonin Noradrenaline Reuptake Inhibitors

SNRIs increase the levels of both serotonin and noradrenaline within the CNS by selectively inhibiting their reuptake in the synaptic clefts. Venlafaxine and its active metabolite Desmetylvenlafaxine, Duloxetine, and Milnacipran are currently included in the class of the SNRIs.

Venlafaxine and Desmetylvenlafaxine

Venlafaxine blocks the synaptic reuptake of serotonin at lower doses, the noradrenaline reuptake at higher doses and the dopamine reuptake at the highest dosages [59]. Venlafaxine is a 2-phenyl-2-(1-hydroxycycloalkyl) ethylamine derivative. The major metabolite of Venlafaxine is O-desmethylvenlafaxine, which is similar to Venlafaxine in potency for inhibiting 5HT and NE uptake and in affinity for the 5HT and NE transporters. The starting dose of Venlafaxine is generally 75 mg/day and its recommended maximum dose is 375 mg/day.

Several randomized controlled trials demonstrated the efficacy and safety of Venlafaxine in the treatment of anxiety disorders including social anxiety disorder, GAD, posttraumatic stress disorder, panic disorder, and OCD [60]. Generally, Venlafaxine is well tolerated and its side effects usually decline with continued treatment [61]. Main reported side effects pertain the digestive (e.g., nausea, dry mouth), nervous (e.g., dizziness, somnolence, insomnia), and urogenital (delayed ejaculation) systems [62]. Sweating is a frequently reported dose-dependant side effect. Discontinuation rates are not higher than those reported with other antidepressant like Fluoxetine or Paroxetine [63].

Des-metil-venlafaxine succinate has been approved by the Food and Drug Administration (FDA) in February 2008 for the treatment of adult patients with major depressive disorder (MDD) and it is the third SNRI with FDA approval for this condition [64], though not approved for MD by the European Medicines Agency (EMEA). Under a pharmacokinetic point of view,

Des-metil-venlafaxine differs from its parent drug particularly in terms of metabolism: Venlafaxine is metabolized primarily by CYP2D6, whereas Des-metil-venlafaxine is conjugated via uridine diphosphate glucuronyl transferase. For this reason, potential drug interactions may be higher for Venlafaxine than for Desvenlafaxine during concomitant administration with other medications that affect the CYP 2D6 pathway [65].

Clinical studies investigating the efficacy of Des-metil-venlafaxine for the treatment of MD found the dose of 50 mg/day more effective than placebo in the reduction of depressive symptoms [66]. The 50–100 mg/day dose range is considered the therapeutic one, with no additional benefit at higher dosages and a significantly higher risk of side effects [67]. Main side effects include nausea, insomnia, decreased appetite, fatigue, somnolence, and constipation [68].

Duloxetine

Duloxetine is a potent inhibitor of serotonin and noradrenaline reuptake, with weak effects on dopamine reuptake. It has a low affinity for other receptors. Duloxetine is a dual action antidepressant with approved oral dosage range of 40–60 mg/day [69]. Duloxetine is currently approved for MD, peripheral diabetic neuropathic pain, female stress urinary incontinence, and GAD [70]. When Venlafaxine and Duloxetine were compared in the treatment of GAD, both resulted superior to placebo and equally effective [71].

Duloxetine is generally well tolerated and the most commonly observed side effects are nausea, dry mouth, headache, constipation, dizziness, and fatigue. With respect to cardiovascular risks, Duloxetine does not seem to be associated with significant risks including sustained blood pressure elevations, QTc-interval prolongation, or other electrocardiographic changes [72].

Milnacipran

Milnacipran is a SNRI with minor effects on any presynaptic or postsynaptic receptors [73].

With respect to its pharmacokinetic and pharmacodynamic profile, Milnacipran clearly differs from the other SNRIs. It has an equipotent serotonin and noradrenaline reuptake inhibition and a linear dose-concentration trend at therapeutic doses. As its interaction with the cytochrome P-450 system is very limited, Milnacipran has a low risk of drug interaction. On the other hand, it is eliminated by renal excretion, therefore, particular attention should be paid to those patients with any renal failure. Its half-life is approximately 8–12 h. Milnacipran has been approved in some Asian countries for the treatment of MD and it is also effective in the treatment of fibromyalgia, fatigue, and anxiety symptoms. The overall effectiveness and tolerability of Milnacipran versus other antidepressants do not seem to differ in the acute treatment of MD; both are superior to those of TCAs and comparable to those of SSRIs.

Taken as a whole, SNRIs represent a valid alternative to SSRIs and they are increasingly used in patients with anxiety disorders. In the treatment of MD, SNRIs may combine a shorter latency of onset with higher rates of overall remission compared to SSRIs, and may be of particular value in patients with comorbid somatic symptoms [60].

Noradrenaline Dopamine Reuptake Inhibitor

Several molecules share a relatively selective action on noradrenaline and dopamine transporters, enhancing their levels in the synaptic cleft, such as Amineptine, Methylphenidate, Pipradol, and Nomifensine [74]. However, many of these compounds have shown major side effects due to their structure and action, which are actually similar to psychostimulant drugs. Even two phytochemical compounds, derived from St. John's Wort (Hypericum perforatum)—Hyperforin and Adhyperforin—were found to positively act on a transient receptor potential ion channel causing an inhibition of monoamine reuptake while interfering with the entry of sodium and calcium into the cell [75]. The most widely used compound in this class is represented by Bupropion.

Bupropion

Bupropion' molecular structure is a monocyclic aminoketon, somehow similar to amphetamines. They both act on monoamines reuptake, amphetamines by enhancing their release, Bupropion by blocking not permanently their reuptake. In 1974, Bupropion was initially termed "amfebutamone" and only later the WHO changed the name of the molecule into the current one. Bupropion acts as a quite selective dopamine reuptake inhibitor [76–78], anyway its affinity *in vitro* is weaker than many drugs or even some SSRIs, such as Sertraline. Despite the lack of affinity, Bupropion increases the expression of dopamine transporter mRNA, rising dopamine concentration [79–81]. However, Bupropion's main antidepressant properties are due to the noradrenaline reuptake, even though its affinity for the noradrenaline reuptake is even weaker than dopamine, because the massive noradrenaline reuptake is due to hydroxybupropion, a metabolite increasing the progenitor compound by 6-fold. This increase of noradrenaline further inactivates dopamine [82]. Finally, Bupropion works indirectly on serotonin metabolism and possibly inhibits alpha3beta4 nicotinic receptors [83].

Bupropion has hepatic metabolism due to CYP2B6 and, secondarily to CYP1A2, 2A6, 2C9, 3A4, and 2E1. Hydroxybupropion is its main metabolite (Radafaxine), but it also has many other metabolites eliminated through renal excretion. Maximum concentration is reached in 2–3 h and the steady state in 5–8 days. Half-life and effective dose show a wide range due to its variable metabolism.

Therapeutic indications are broadly MD with melancholic features and seasonal depression, but its first use was for smoking cessation with reduced urge of smoking rate [83]. Further proposed treatment perspectives include the management of sexual dysfunction induced by serotonergic antidepressants, chemotherapy, and even those of primary origin as well as ADHD [84–86]. As an antidepressant, Bupropion showed a higher remission rate while compared to placebo, but a slightly minor effect when compared to SSRI or SNRI [87,88]. However, this result is controversial

as a higher rate of remission than Venlafaxine has been reported as well [89].

Bupropion has been also used in augmentation to SSRIs, showing a favorable profile of tolerability [90]. Bupropion is not indicated for patients with a clinical history of seizure and, as all antidepressants, should be used with caution in bipolar depression due to the risk of mania induction. Seizure was the main adverse effect that provoked the revocation from the market for most NDRIs. Initially, in fact, even Bupropion was revoked, as it lowered significantly the seizure threshold when given at the dose of 450–600 mg/day. This effect, however, was found to be strictly dose dependent and uncommon with the currently approved dose of 150–300 mg/day [91]. Nonetheless, this potential risk needs to be taken into account when the compound is prescribed in patients with brain tumors, substance or alcohol discontinuation, and with anorexia or bulimia nervosa. Concerning metabolism, patients with liver or kidney failure should receive a lower dosage of Bupropion. Most commonly reported side effects include nausea, insomnia, sweating, and anxiety. Hypertension without effect on heart frequency rate has been reported as well [92].

Noradrenergic and Specific Serotonergic Antidepressants

Mianserin

Mianserin is a tetracyclic antidepressant drug administered as racemate of R (–) and S (+) mianserin hydrochloride in a dose of 30–90 mg/day [93]. Some of its metabolites are supposed to play a role both in therapeutic and toxic effects [94]. Mianserin was originally designed as an antiallergic drug. It has sedative properties and the most frequently reported side effect is drowsiness, which often diminishes within the first week of treatment. As observed in clinical trials, peripheral anticholinergic effects are less frequent than with tricyclics. Of note, the lack of cardiovascular side effects such as increased heart rate and hypotension is a further important advantage of Mianserin [95,96]. Mianserin is indicated for the treatment of depression associated with anxiety and agitation and, like Mirtazapine, it is particularly indicated for patients experimenting insomnia [97].

Mirtazapine

Mirtazapine is a potent antagonist of central $\alpha(2)$-adrenergic autoreceptors and heteroreceptors. The blockade of presynaptic autoreceptors ultimately enhances the noradrenaline release. On the other hand, the blockade of heteroreceptors on serotonergic neurons increases serotonin release. The blockade of the 5-HT2 and 5-HT3 receptors enhances serotonin release, resulting in an increase in 5-HT1-mediated neurotransmission. Mirtazapine has low affinity for muscarinic, cholinergic, and dopaminergic receptors, but its high affinity for H1-histaminic receptors determines its main antihistaminergic effects (e.g., drowsiness, weight gain, and sedation), which predominate at lower doses, while noradrenergic neurotransmission increases with higher doses, counteracting some of the antihistaminergic effects. Unlike Venlafaxine, Mirtazapine has minimum effects on monoamine reuptake. Along with Amineptine, Bupropion, and Moclobemide, Mirtazapine is one of the antidepressants with the lowest risk of sexual dysfunction [98,99]. Mirtazapine may be particularly suitable for selected subgroups of patients like severely depressed ones, especially those at midlife and older. Its side effect profile is still somewhat more favorable than that of tricyclics [100]. Mirtazapine has also shown some degree of effectiveness in the treatment of anxiety disorders (including posttraumatic stress disorder, panic disorder, social anxiety disorder, and OCD) and undifferentiated somatoform disorder [101].

Triple Reuptake Inhibitors

Serotonin-noradrenaline-dopamine reuptake inhibitors, better known as TRIs are a class of antidepressants under development in order to selectively inhibit the serotonin, noradrenaline, and dopamine transporters. Over the last 3 years, several compounds have been studied: DOV 216, 303, DOV 21,947, PCR200-SS, NS-2359, and SEP-225289. Each of these compounds is characterized by a peculiar affinity for the different transporters [102]. To date, most studied compounds are Brasofensine (NS-2214), Dichloropane (RTI-111, O-401), Diclofensine (Ro-8–4650), Indatraline (Lu-19–005), and Tesofensine (NS-2330). Each of these molecules has active metabolites which, in turn, may have antidepressant effects. A faster onset of action is a main expectation for TRIs [103]. Furthermore, network analyses of the brain and its dysfunction suggest that agents with multiple and complementary modes of action are more likely to show broad-based efficacy against core and comorbid symptoms of depression [104]. Ultimately, the major aim of TRIs would be to achieve greater efficacy in terms of response and remission rates while maintaining a favorable profile of tolerability due to the selective action on the monoamine transporters.

At present time no TRI is in the market, while most of them are undergoing preclinical trials.

Atypical Antipsychotics

Quetiapine

Quetiapine, an atypical antipsychotic traditionally used for the treatment of Schizophrenia, has been successfully used over the last years in the treatment of depression, bipolar depression in particular [104]. As of December 2009, the FDA has approved Quetiapine XR for the adjunct treatment of MD. More recently, Quetiapine' efficacy has also been demonstrated in the treatment of bipolar depression. Suppes and colleagues performed an 8-week placebo-controlled, randomized double blind trial on bipolar depressed patients, showing a significant degree of efficacy and remission [105]. Quetiapine' antidepressant action effects on 5-HT(2A), 5-HT(1A), dopamine and glutamate receptors, and NAT [106,107]. Norquetiapine (the main metabolite of Quietiapine), in particular, has a strong affinity for NET and potently inhibit it, while Quetiapine itself does not even bind to the NET (Norquietiapine:Ki = 34.8 mMol; Quetiapine: Ki>10000) (Table 2).

Discussion

Converging evidence that compounds acting on the noradrenergic neurotransmission are more effective than those with pure serotonergic action exists. Bauer and colleagues in a *meta*-analysis of all available trials with Venlafaxine in the treatment of MD, including treatment-resistant depression and long-term relapse prevention, found that Venlafaxine was associated with greater response and remission rates compared to SSRIs with similar drop-out rates. Compared to tricyclics, response to Venlafaxine was estimated to be greater but not to a statistically significant extent. No difference in remission rates was observed. Tricyclics were less tolerated with overall higher drop-out rates. Authors concluded that Venlafaxine appears more effective than SSRIs, and at least as effective as TCAs, in the treatment of MDD [108,109].

Anderson and Tomenson, in their *meta*-analysis assessing the efficacy of SSRIs and TCAs, observed that the latter were more effective than SSRIs in inpatients with severe depression [110]. These data might suggest that antidepressants with a noradrenergic action are more effective in the treatment of severe depression than those with an exclusive serotonergic component. Besides, in the cited study, those antidepressants with a greater degree of noradrenergic inhibition or dual action (i.e., Mirtazapine, Venlafaxine, and Milnacipran), showed greater efficacy than the SSRIs. The superior efficacy of these antidepressants may be related to their noradrenergic component [111].

As a matter of fact, in the largest *meta*-analysis conducted to date, comparing the efficacy of SSRIs versus serotoninergic and noradrenergic antidepressants (including Venlafaxine, Duloxetine, Milnacipran, Mirtazapine, Mianserin, and Moclobemide), a modest advantage was found in favor of the latter compounds [112].

In terms of efficacy and tolerability, a recent *meta*- analysis, comparing Reboxetine with SSRIs in the treatment of MD, found a lower rate of discontinuation due to intolerance to the SSRIs and an overall efficacy [112]. Comparable results were found considering Mirtazapine versus SSRIs [113]. With respect to the treatment of SSRI-resistant depression, switching to a non-SSRI class seems to produce a modest, but statistically significant, advantage than switching to a different SSRI [115]. On the other hand, different studies indicate that SSRIs (i.e., Escitalopram) are as effective as Venlafaxine or Duloxetine, and better tolerated [114]. Finally, some *meta*-analyses indicate Escitalopram to be superior to other SSRIs and SNRIs [115].

It would be of great clinical interest not only to compare the efficacy and tolerability of noradrenergic and mixed antidepressants among themselves and in comparison to the SSRIs in affective disorders, but also to assess how the noradrenergic action translates in terms of symptom improvement. For instance, when this was done in previous studies [13], important correlations emerged in terms of specific antidepressant action and initial symptom improvement (e.g., Desipramine worked better on motor retardation and depressed mood while Paroxetine on hostility and anxiety). Further studies in this perspective would be therefore highly appreciated in order to rationally develop new drugs and better understand the effect of the current ones.

In conclusion, despite the striking advances in the pathophisiology of affective disorders of the last decade, the noradrenergic system still has a pivotal role in the clinical psychopharmacology of antidepressants. Though pure pronoradrenergic compounds may not be as effective as SSRIs in the treatment of MD, when the two actions are combined—as it occurs in many mixed-action antidepressants—a synergic effect is obtained. Pharmacogenomic and pharmacogenetic studies in the next future should help clinicians to understand which patients are supposed to better respond to a specific antidepressant rather than to another one.

Conflict of Interest

The authors have no conflict of interest.

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