11

A New Class of Antidepressant Drugs in the Treatment of Psychiatric Disorders: The Triple Reuptake Inhibitors

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1. Introduction

It is well established that many antidepressant compounds with proven clinical efficacy act on the serotonergic and noradrenergic pathways. The monoaminergic hypothesis of major depression (MD) stipulates that a deficit in brain monoaminergic neurotransmission in various brain areas including the frontal cortex, hippocampus, amygdala or hypothalamus would account for some of signs and symptoms of the pathology (Katz et al., 2010a). For instance, abnormalities in the serotonin (5-HT) transmission are associated with impulsivity, aggressive, and anxious behaviors (Handley et al., 1995), whereas alteration in noradrenergic transmission, with motor activity, attention, and arousal (Morilak and Frazer, 2004). The role of dopamine (DA) on the other hand, attracted less attention in the mechanisms of action underlying MD. However, the observations that reserpine, which depletes catecholamines, results in lowering mood (Schidkrautn 1965) or that an inhibition of tyrosine hydroxylase induces a worsening of depressive symptoms (Miller et al., 1996), strongly suggest that decreasing DA function may be of particular relevance. The fact that several symptoms observed in MD, including impaired motivation, concentration, and pleasure result from an attenuation of dopaminergic neurotransmission, strengthens the hypothesis that DA also regulates mood (Dunlop and Nemeroff, 2007).
Most antidepressants approved, such as the selective serotonin reuptake inhibitors (SSRIs), the norepinephrine (NE) reuptake inhibitor (NRIs) or the dual serotonin/norepinephrine reuptake inhibitors (SNRIs), act by enhancing brain 5-HT and/or NE levels. Despite their therapeutic action, residual symptoms remain and may explain the fact that approximately 50% of depressive individuals do not respond adequately to these agents (Berton and Nestler, 2006). The question can be asked as to whether these remaining symptoms are caused by the antidepressants or if they result from dysfunction in other neurotransmitters such as a blunted DA neurotransmission. In this context, a new generation of antidepressant drugs, the triple reuptake inhibitors (TRIs), has been developed with the hope to offer a clinically relevant advantage over single- or dual-acting agents (Guiard et al., 2009). Indeed, since TRIs simultaneously enhance extracellular levels of 5-HT, NE and DA neurotransmissions in various brain regions, this class of antidepressants could exert their therapeutic activity by treating more symptoms of MD and/or by attenuating some side

effects observed in response to traditional antidepressants. As an example, it is believed that the dopaminergic component of TRIs may prevent sexual dysfunctions induced by an increase in brain 5-HT.

The present review describes the serotonergic, noradrenergic and dopaminergic pathways in the brain and the specific symptoms of depression under their control. Then it focuses on the preclinical *in vitro* and *in vivo* properties of TRIs. Indeed, the knowledge of their pharmacological properties may help better understand their mechanism of action and anticipate their putative efficacy over SSRIs, NRIs and SNRIs in humans. Finally, since over 75% of depressed patients suffer from painful symptoms and that monoaminergic pathways control many of the psychological functions that are disturbed in depression and pain perception (Hache et al., 2011), this review addresses the possibility that TRIs may exert part of their antidepressant activity by preventing/reversing algesia in depressed patients.

2. Monoaminergic pathways in the brain and their reciprocal interactions

2.1 The serotonergic system

Serotonin (5-HT) is present in most brain regions in the central nervous system. In the brain, serotonergic neurons originate within the brain stem. This system is comprised of a relatively small number of neurons that are clustered in nine phylogenetically conserved nuclei grouped into caudal (B1–B5) and rostral (B6–B9) nuclei including the dorsal and median raphe (DR and MR; respectively), with the former projecting to areas of the deep cerebellar nuclei, cortex, and spinal cord, whereas the latter extends an axonal network throughout the forebrain and cortices (Dahlström and Fuxe, 1964). Of particular relevance to mechanisms of MD are projections to structural correlates of emotionality including the amygdala, prefrontal and cingulated cortices, hypothalamus, and thalamus (Hornung 2003). Recently, 5-HT neurons have been classified based on genetic lineages. Specifically, 5-HT neuronal progenitors can be subdivided into subpopulations, which are discriminated by differing genetic transcription factors such as Pet-1 (Kiyasova et al., 2011; Hendricks, 2003). Indeed, this factor is required for the acquisition of serotonergic identity in a majority of neurons in the raphe nuclei including the dorsal and median raphe nuclei. However residual 5-HT neurons outline a unique subpopulation of raphe neurons with highly selective anatomical targets particularly the brain areas involved in stress responses with dense innervation to the basolateral amygdala, the paraventricular nucleus of the hypothalamus, and the intralaminar thalamic nuclei. It has thus been proposed the existence of Pet1-dependent and Pet1-resistant 5-HT neurons targeting different brain centers that might delineate the anatomical basis for a dual serotonergic control on stress responses (Kiyasova et al., 2011).

2.2 The noradrenergic system

The central noradrenergic neurotransmitter system originates from two distinct groups of cells in the brainstem (Dell'Osso et al., 2010). The main noradrenergic brain circuits are located in the locus coeruleus (corresponding to A4+A6 cell groups), which send noradrenergic projections throughout the neuroaxis innervating areas such as the frontal cortex, hippocampus and amygdala as well as the cerebellum (Dahlström and Fuxe, 1965). This ascending projection system is also referred to as the dorsal noradrenergic bundle. 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 (Racagni and Brunello). Efferents from the lateral tegmentum (corresponding to A1, A2, A5 and A7 cell groups) have less extensive projections (Dahlström and Fuxe, 1965). They provide predominant innervation of the hypothalamus and also innervate areas of the septum and the extended amygdala nuclei including the bed nucleus of the stria terminalis (Moore and Card, 1984). Interestingly, noradrenergic and serotonergic systems overlap at several levels and are far away to be independent, both distributing to broad cortical areas (Brühl et al., 2010). Reciprocal projections between the major groups of 5-HT and NE cell bodies have been reported, creating ample opportunity for cross-modulation between these systems. For example, it is well established that NE stimulates the neuronal activity of 5-HT neurons in the DR (Mongeau et al., 1997). In a marked contrast, 5-HT projections from the DR nucleus to the locus coeruleus, impose a tonic inhibitory tone on the firing of NE neurons (Dremencov et al., 2009).

2.3 The dopaminergic system

Most DA-producing neurons in the brain are located in brainstem nuclei: the retro-rubro field (A8), the substantia nigra pars compacta (A9), and the ventral tegmental area (VTA) (A10) (Dunlop and Nemeroff, 2007). Projection pathways of the axons arising from these cell bodies follow specific pathways via the medial forebrain bundle to innervate specific cortical and subcortical structures, unlike the more diffuse innervation patterns of serotonergic and noradrenergic cells. The nigrostriatal pathway projects from the substantia nigra pars compacta to the dorsal striatum (caudate and putamen) and has a prominent role in the motor planning and execution of movement, although it clearly also plays an important role in non-motor functions, such as cognition (McClure et al., 2003). The mesocortical pathway arises from the VTA and projects to the frontal and temporal cortices, particularly the anterior cingulate, enthorinal, and prefrontal cortices. This pathway is believed to be important for concentration and executive functions such as working memory. The mesolimbic pathway also arises from the VTA but projects to the ventral striatum (including the nucleus accumbens), bed nucleus of the stria terminalis, hippocampus, amygdala, and septum. It is particularly important for motivation, the experience of pleasure and reward. The tuberoinfundibular pathway arises from the arcuate nucleus of the hypothalamus (A12) and projects to the median eminence of the hypothalamus, where DA released into the portal vessels acts to inhibit the secretion of prolactin from the anterior pituitary (Ben-Jonathan and Hnasko, 2001). The incertohypothalamic pathway originates from cell bodies in the medial portion of the zona incerta (A13) and innervates amygdaloid and hypothalamic nuclei involved in sexual behavior. Unlike the other dopaminergic pathways, the "thalamic dopamine system" arises from multiple sites, including the periaqueductal gray matter and may contribute to the control of nociception (Hache et al., 2011). Importantly, serotonergic and noradrenergic neurons also display a high degree of anatomical and functional connectivity with the dopaminergic system. For instance, in addition to its tonic inhibition of NE transmission, 5-HT is believed to inhibit the firing of DA neurons in the VTA (Guiard et al., 2008a; 2008b). The influence of NE on DA neurons is more complex since both excitatory and inhibitory impacts have been reported (Guiard et al., 2008a; 2008b; Linner et al., 2001). On the other and, growing evidence suggest that DA may modulate the activity of 5-HT and NE neurons. It is suspected that DA directly increases the neuronal activity of 5-HT neurons in the DR (Haj-Dahmane, 2001; Martin-Ruiz

et al., 2001), thereby enhancing local 5-HT outflow (Ferre et al., 1994; Ferre and Artigas, 1993; Martin-Ruiz et al., 2001). In contrast, multiple source of evidence demonstrates that DA inhibits the neuronal activity of NE neurons in the LC (Guiard et al., 2008a, 2008b; Deutch et al., 1986; Elam et al., 1986).

3. Depression: monoaminergic symptoms and disturbances

Based on the findings from studies of antidepressants, it may be possible to assign specific symptoms of depression to specific neurochemical mechanisms (Nutt, 2008a). Knowing which particular neurotransmitters are associated with particular symptoms of depression may help determine appropriate treatments that target specific mechanism that in turn target specific depression symptoms. 5-HT may be related to anxiety, compulsions and sleep disturbances; NE to alertness and energy as well as anxiety, attention, and interest in life; and DA to motivation, pleasure, and reward, as well as interest in life (Figure 1). Increasing any of these 3 neurotransmitters will elevate mood, but the other elements of depression may be particularly responsive to a certain neurotransmitter.

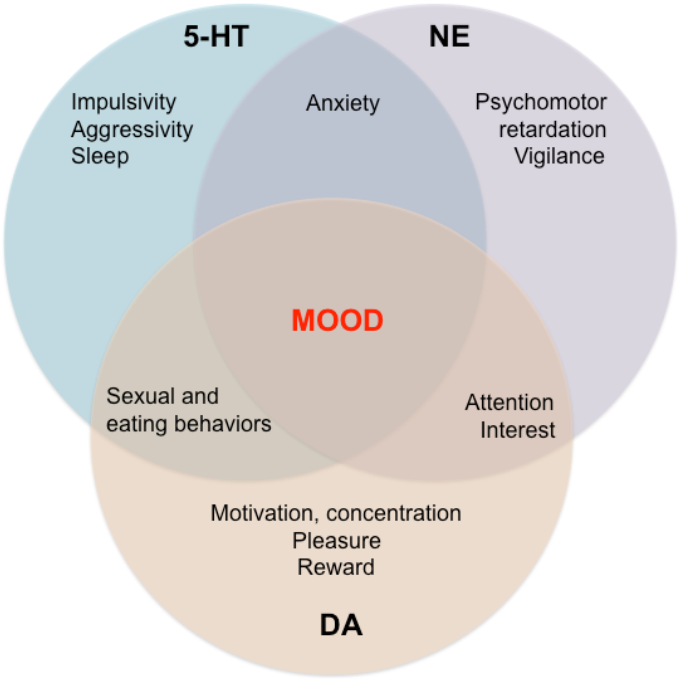

Fig. 1. Monoamine regulation of mood behavior (Adapted from Nutt, 2008).

3.1 Depressed mood and sadness

Neuroimaging studies have associated depressed mood and sadness with abnormal neuronal activity in the medial prefrontal cortex (Drevets, 1999). This brain region receives innervation from serotonergic (midbrain raphe), noradrenergic (locus coeruleus) and

dopaminergic (ventral tegmental area) pathways. Low levels of these monoamines may decrease mood whereas antidepressants that enhance levels of monoamines have been shown to improve depressed mood and sadness (Morilak and Frazer, 2004). Other symptoms and/or comorbidities such as sleep or appetite disturbances as well as nociception may be affected in patients with MD and should draw attention of physicians when choosing antidepressants therapy. Clearly, an improved treatment of MD should start with a good diagnosis, based on the symptoms patients encounter as disturbances in different neurotransmitter systems.

3.2 Diminished interest and pleasure

Reduced dopaminergic activity has been linked to decreased motivation (Salamone et al., 2003), anhedonia (loss of pleasure) and loss of interest (Willner, 1983), whereas increased dopaminergic transmission has been linked to positive affect (Depue and Collins, 1999). The mesocortical dopaminergic pathway, in particular the nucleus accumbens is a key regulator of pleasure. The prefrontal cortex is believed to be important in motivation (Drevets, 2001). A dysfunction of the mesocorticolimbic dopaminergic system innervating limbic structures including the nucleus accumbens, amygdala, ventral hippocampus and cortical areas may underlie the symptoms of loss of motivation, loss of interest and the inability to experience pleasure observed in MD. Antidepressants that enhance DA release including bupropion, may thus improve these symptoms (Dunlop and Nemeroff, 2007).

3.3 Fatigue and loss of energy

Brains areas controlling motor function such as the striatum innervated by DA and 5-HT neurons may be involved in physical fatigue, (Stahl et al., 2008). Mental fatigue and lack of mental energy may be related to other symptoms of depression, such as apathy (absence in feeling, emotion, interest) and lack of motivation. Cortical brain regions, especially the dorsolateral prefrontal cortex, are more likely to be involved in mental fatigue (MacHale et al., 2000). Consequently, antidepressants that increase DA and 5-HT, or both, may be preferable for patients with predominant symptoms of fatigue and loss of energy (Stahl et al., 2008).

3.4 Anxiety

The neuronal pathway of fears involved the amygdala, which receives NE and 5-HT innervation from the LC and DR, respectively. High levels of amygdala activation are associated with an increased prevalence of anxiety (Davidson et al., 2002) raising the possibility that antidepressants targeting both NE and 5-HT, may be more appropriate for treating depressed patients with comorbid anxiety disorders (Morilak and Frazer, 2004).

3.5 Sleep disturbance

There is a very strong association between sleep disturbance and major depression. Depressed patients usually complain of insomnia, notably of difficulties in falling asleep, frequent awakenings during the night, early waking up, and non-refreshing sleep (Benca et al., 1992). As well as distressing symptoms of sleep experienced by patients, changes in sleep architecture have been reported. Compared with normal controls, sleep continuity of depressed subjects is often impaired, with increased wakefulness (more frequent and

longer periods of wakefulness), and reduced sleep efficiency. Sleep onset latency is significantly increased and total sleep time reduced. Rapid eye movement (REM) latency is often shortened, and the duration of the first REM period is increased (Nutt et al., 2008b). The role of 5-HT in the regulation of sleep is well documented and studies indicate that the neuronal activity of 5-HT and its release is maximal during wakefulness (W), reduced during slow wave sleep (SWS), and minimal during rapid eye movement (REM) sleep (Adrien, 2002). Consequently, SSRIs, which increase 5-HT function increase REM latency, and reduce REM sleep (Wilson and Argyropoulos, 2005) may worsen sleep disturbance early in treatment (Hicks et al., 2002) and may leave residual sleep symptoms once mood is improved (Nelson et al., 2005). It is noteworthy that depressed patients may also display an excessive sleep and hypersomnia, particularly in atypical depression (Gold et al., 2002). This latter observation emphasizes the fact that a better diagnosis, based on the different subtypes of MD is a prerequisite to optimize and individualize antidepressant therapy.

3.6 Appetite and eating disorders

Eating disorders, the term now encompasses anorexia nervosa and bulimia nervosa (Jimerson et al., 1993), result from alteration, at least in part, in monoaminergic neurotransmission involved in the homeostatic control of appetite function. For example, positive correlations between mood disturbances and eating and weight concerns have been reported (Casper et al., 1998). Although, the background of eating disorders is complex, the involvement of impaired hypothalamic 5-HT function in these disorders is well documented (Wallin and Rissanen, 1994). In agreement with the observation that in this brain region, 5-HT contributes to post-ingestive satiety, several studies have shown that SSRIs, particularly fluoxetine, is effective in controlling bulimic episodes (Walsh, 1994). This is also the case for other serotoninergic drugs, among them fenfluramine, which was used in the treatment of obesity (Guy-Grand, 1992). There is growing notion that mesolimbic dopaminergic neurotransmission also contributes to the effect of DA on feeding behavior (Volkow and Wise, 2005). Sibutramine, in addition to its effect on 5-HT, inhibits the reuptake of other monoamines and has been shown to enhance postprandial satiety, reduce total calorie intake and to diminish the decline in energy expenditure usually associated with a diet-induced negative energy balance (Hansen et al., 1999). Consequently, combined blockade of NE and 5-HT reuptake by SNRIs results in reduced food intake and body weight that neither monoamine reuptake inhibitor could achieve on its own. Interestingly, bupropion the dual NE releaser and DAT inhibitor (Dong and Blier, 2001), cause weight loss by combined induction of hypophagia and thermogenesis (Billes and Cowley, 2007).

Recently there has been interest in investigating the use of SSRIs in the treatment of patients with anorexia nervosa. Although fluoxetine has been associated with weight loss, it was proposed that this medication, because of a favorable side effect profile, could have advantages for treating depressive symptoms in patients with anorexia (Gwirtsman et al., 1990).

3.7 Nociception

This is specifically illustrated in the fifth chapter of the present review.

4. Pharmacological properties of TRIs

As described in the precedent chapter some comorbid symptoms of depression such as anhedonia, loss of motivation and concentration are directly connected to a deficit in central dopaminergic transmission. Consequently, triple reuptake inhibitors (TRIs) that simultaneously inhibit the reuptake of the three monoamines 5-HT, NE, DA (Chen & Skolnick, 2007) may provide greater symptomatic relief than SSRIs, NRIs or SNRIs. The interest of TRIs may also rely on the excitatory effect of DA upon the serotonergic system (Haj-Dahmane, 2001; Martin-Ruiz et al., 2001), thus suggesting that an increase in dopaminergic neurotransmission would facilitate that of 5-HT. In accordance with this hypothesis, it was shown that combination of SSRIs with bupropion lead to a synergy on monoamine transmission (Ghanbari et al. 2010; Prica et al. 2008; Li et al. 2002), as well as producing a robust antidepressant effect especially in treatment-resistant depressed patients

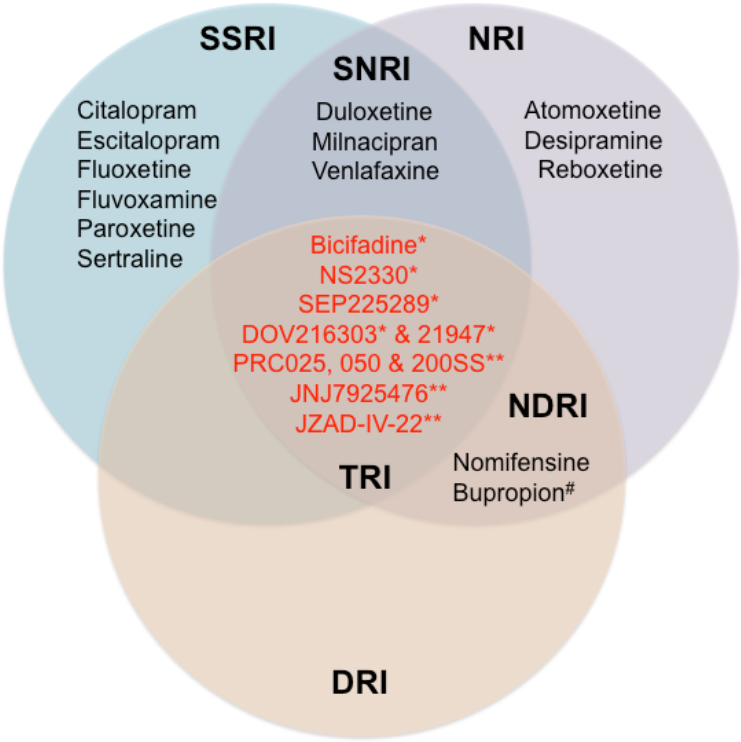

Fig. 2. Monoaminergic antidepressants blocking the serotonin, norepinephrine and/or dopamine transporter. These agents are in various clinical* or preclinical** phases of development in MD or comorbidities. Selective serotonin reuptake inhibitor (SSRI), norepinephrine reuptake inhibitor (NRI), dopamine reuptake inhibitor (DRI), serotonin/norepinephrine reuptake inhibitor (SNRI), norepinephrine/dopamine reuptake inhibitor (NDRI), triple reuptake inhibitor (TRI). #This agent is a dopamine reuptake inhibitor and a norepinephrine releaser (Dong and Blier, 2001).

(Leuchter et al. 2008; Zisook et al. 2006). A number of compounds with the ability to bind and block all three monoamine transporters have been developed. DOV Pharmaceutical, Inc. is the first company having provided *in vitro* and *in vivo* preclinical data with their triple reuptake inhibitors DOV216303 and DOV21947. New molecules have followed such as NS2330 (tesofensine, GlaxoSmith-Kline/NeuroSearch), SEP225289 (Sepracor Inc.), CNS-1 and CNS-2 (Albany Molecular Research Institute Inc), PRC-025, PRC-050, PRC-200SS (Mayo Foundation), JNJ7925476 (Johnson & Johnson Pharmaceutical Research & Development), WF-23 (Eli Lilly) and JZAD-IV-22 (PsychoGenics). Lundbeck laboratories develop their own compounds such as LuAA24530 but with the difference that they also antagonize monoaminergic receptors. Others compounds will undoubtedly emerge in a near future. Indeed, it is interesting to note that in 2010-2011, the pharmacological profiles of nine new compounds, studying the structure activity relationship (SAR), have been reported (Shao et al., 2011a; 2001b; 2011c; Caldarone et al., 2010; Carter et al., 2010; Lee et al., 2010; Lucas et al., 2010; Micheli et al., 2010a, 2010b; Schoedel et al., 2010). Despite the emergence of these compounds, older molecules with the abilities to inhibit all three monoamines transporters were already available such as the tryciclic agent nefopam approved in Europe (Heel et al., 1980), bicifadine in phase III (Basile et al., 2007) or indatraline (Lengyel et al., 2008) (Figure 2).

4.1 Preclinical in vitro properties

4.1.1 Binding properties

Many studies provide Kd values for their compounds, or Ki values, which are sometimes used interchangeably. These values for the SERT, NET and DAT are provided in Table 1. It can be noticed that some TRIs such as the PRC series preferentially bind to the SERT and NET while displaying a lower affinity for the DA transporter (DAT). This is, however, not the case for the other compounds which display a similar or higher affinity for the DAT than for the SERT or the NET. Interestingly, the affinity of most of these new compounds for monoamines transporters is lower than that of SSRIs and NRIs at binding SERT and NET, respectively (Hache et al., 2011). Therefore, the analysis of the binding properties and functional activity of the TRIs indicates that the novelty of these pharmacological agents lies in their relative balanced binding profile rather than in their potency at blocking monoamines transporters (Hache et al., 2011).

TRIs	In vitro binding (Ki or Kd in nM)			References
	SERT	NET	DAT	
Bicifadine[a]	2400	5000	5200	Basile et al., 2007
Indatraline[a]	0.6	2	4	Lengyel et al., 2008
DOV216303[a]	190	380	190	Chen and Skolnick, 2007
DOV21947[a]	110	260	210	Skolnick et al., 2003
JNJ7925476[a]	0.9	16	5	Aluisio et al., 2008
PRC025[b]	6	10	53	Shaw et al., 2007
PRC050[b]	12	1.2	43	Shaw et al., 2007
PRC200-SS[b]	2.1	1.5	61	Liang et al., 2008

Table 1. In vitro binding affinities of triple reuptake inhibitors (TRIs). [a]Ki values are expressed in nM (Ki for inhibition of radioligand binding). [b]Kd values are expressed in nM and represent the equilibrium dissociation constant. The smaller the Kd values, the higher affinity of a drug is for the corresponding monoaminergic transporter.

4.1.2 Functional activity: Synaptosomes

Inhibition of [^{3}H]-5-HT or [^{3}H]-NE reuptake in synaptosomes, is one of the most widespread method to assess the *in vitro* potency of reuptake inhibitors (Sanchez and Hytell, 1999) and to predict indirectly, their selectivity on biogenic amines transporters. In addition, it is noteworthy that the binding properties of triple reuptake inhibitors do not necessarily correspond to their *in vitro* functional activity assessed from rat brain synaptosomes (Tables 1 and 2). For example, although *in vitro* studies with PRC compounds (PRC025, PRC050 and PRC200SS: *1S,2S*-isomer of racemic PRC050), revealed a perfect correlation between binding affinity and functional activity towards monaminergic transporters (i.e. the rank of potency is NET>SERT>DAT), DOV216303 which preferentially binds to SERT and DAT, mainly inhibits the uptake of [^{3}H]5-HT and [^{3}H]NE (Chen and Skolnick, 2007; Skolnick et al., 2003). Such a discrepancy could be explained by the fact that the uptake of [^{3}H]NE from synaptosomal fractions involved the DAT. Indeed, unselective reuptake mechanisms have been previously reported with monoaminergic systems. In particular, it is well established that the clearance of DA from the extracellular space can occur through the NET in various brain regions including the hippocampus, the FC and the NAcc (Carboni et al., 2004; Bymaster et al., 2002; Moron et al., 2002). More recent evidence shows that DA may also be taken up by the SERT (Larsen et al., 2011).

4.2 Preclinical in vivo properties

In vivo strategies for characterizing the selectivity and potency of monoamines reuptake inhibitors examine the electrophysiological and neurochemical effects of these compounds, generally in rat or mouse brain. At presynaptic level, when the 5-HT or NE transporters are blocked on the serotonergic or noradrenergic cell bodies, respectively, there results an accumulation of 5-HT or NE in the vicinity of somatodendritic 5-HT1A or α2 autoreceptors in the dorsal raphe (DR) or locus coeruleus (LC). This lead to an attenuating firing of DR 5-HT or LC NE neurons in a dose-dependent manner due to the activation of these neuronal elements exerting a negative feedback influence (Tremblay and Blier 2006). This parameter can be used to characterize the pharmacological profile of reuptake inhibitors. At nerve terminals, an accumulation of 5-HT or NE also occurs in response to the inactivation of the 5-HT or the NE transporter by SSRIs or NRIs, and the enhancement of extracellular levels of monoamines can be probed by microdialysis in various brain regions (Guiard et al., 2009). This approach constitutes a second parameter to study the functional activity of reuptake inhibitors. Nevertheless, since microdialysis methodology may vary between laboratories, the electrophysiological approach seems to be more appropriate to establish relevant comparisons between compounds.

4.2.1 Functional activity: Electrophysiology

Electrophysiological recordings with TRIs (in comparison with single- or dual-acting agents) on monoamines neuronal activities have yet to be determined. Nevertheless, an initial study reported, that relative high intravenous doses of the TRIs SEP225289 and DOV216303 were required to inhibit the electrical activities of DR 5-HT, LC NE and VTA DA neurons. Although this may result from a lower affinity for the monoaminergic transporters than selective reupake inhibitors or from a poor brain penetration, 5 mg/kg; iv of DOV216303, produced an inhibition of 80% of LC NE neuronal activity but only of 30% and 40% of DR 5-HT and VTA DA neurons; respectively (Guiard et al., 2011). The observation that both TRIs

exerted a predominant effect in the LC, while producing only a partial decrease in DR 5-HT firing activity was puzzling given the equal *in vitro* affinity and potency of the former drugs for all three transporters. The reciprocal interactions between monoaminergic neurons might have thus contributed to alter the functional *in vivo* activity of TRIs because the majority of SSRIs, NRIs and SNRIs produce a complete suppression of DR 5-HT neurons firing (Hache et al., 2011). The possibility has been raised that the lesser than expected effect of SEP225289 or DOV216303 on the firing activity of 5-HT neurons resulted, at least in part, from the accumulation of DA and NE in the DR, which are supposed, as abovementioned to be excitatory on the neuronal activity of 5-HT neurons (Katz et al., 2010b).

4.2.2 Functional activity: Intracerebral microdialysis

With respect to microdialysis data, as expected all TRIs increase extracellular monoamines levels with distinct intensities, depending on their pharmacological properties, on the brain regions studied and their relative equipment in monoamines transporters and, on the model used "naïve" *vs* depressed animal (Table 2). In a recent study performed in control rats, PRC200-SS was shown to increase the extracellular levels of the three monoamines in the medial prefrontal cortex cortex (mPFC) and the Nucleus accumbens (NAcc) (Liang et al., 2008). In the mPFC, in agreement with its *in vitro* pharmacological profile, PRC200-SS (5 and 10 mg/kg; ip) significantly increased extracellular levels of NE and 5-HT with a more pronounced effect for NE. Nevertheless, in this brain region PRC200-SS failed to modify the extracellular levels of DA. This result is somewhat surprising given the dense dopaminergic innervation and the high expression of DAT in the frontal cortex (Kuikka et al., 1995). The lack of increase in cortical DA extracellular levels may be explained by its heterologous reuptake from the NET (Moron et al., 2002; Giros et al., 1994). However the observations that catecholamine uptake blockers such as nomifensine, desipramine or GBR12909 increase DA levels (Devoto et al., 2004; Valentini et al., 2004; Gresh et al., 1995) could emphasize the importance of the reciprocal interactions between the DA and NE or 5-HT system at nerve terminal. Indeed if NE and/or 5-HT exert an inhibitory influence on cortical dopaminergic projections, as describe in the VTA (Guiard et al., 2008a), this might have produced counter-productive effects. However, in the core of the NAcc, where the density of DAT is relatively high, PRC200-SS (10 mg/kg; ip) increased DA and, to a lower extent, 5-HT outflow without affecting NE, probably because of the absence of noradrenergic innervation in this brain area (Carboni et al., 2006). Using microdialysis in the cortex of freely moving rats, confirmation of the blocking activity of JNJ7925476 on the SERT, NET and DAT has also been provided. A robust and dose-dependent increase in all three monoamines, lasting for several hours, was detected with a maximal effect for DA compared to 5-HT and NE at the highest dose tested (10 mg/kg; sc) (Aluisio et al., 2008). These results strongly contrast with *in vitro* data showing that JNJ7925476 displayed a better *in vitro* binding affinity and blocking activity for SERT than for DAT (Aluisio et al., 2008). Differences in transporter occupancy cannot explain these findings since this parameter followed the same trend observed with cortical extracellular monoamines levels. It has therefore been proposed that the high cortical levels of DA might have resulted from the blockade of the NET by this drug, which displays a high affinity for the DAT (Moron et al., 2002; Giros et al., 1994). Another possibility would be that JNJ7925476 acted by stimulating the release of DA but this property has not been demonstrated yet. Indirect effects might have also involved functional interaction between monoaminergic neurons leading to high extracellular levels of cortical DA. Together, these findings illustrate the fact that the *in vivo* activity of TRIs does

not necessarily reflect their *in vitro* functional activity, probably due, at least in part, to functional interactions between monoaminergic neurons. Another interesting example of unexpected results comes from neurochemical studies with bicifadine. Indeed, microdialysis studies in normal waking rats indicated that bicifadine preferentially increase DA and 5-HT than NE extracellular levels in the nucleus accumbens at the highest dose tested (60 mg/kg; i.p.) despite the higher potency of this TRI at binding and inhibiting the SERT and NET (Nicholson et al., 2009; Basile et al., 2007). Although the selectivity of this compound at the dose tested can be questioned, it is possible that the combined elevation in 5-HT and DA produce robust inhibitory effect on the noradrenergic system.

In olfactory bulbectomized rats, a model of depression (Song et al., 2005), it has been shown that the removal of olfactory bulbs results in a significant decreased in DA, but not 5-HT and NE, cortical extracellular levels when compared to sham operated. Interestingly, although after acute administration, DOV216303 increased DA, 5-HT and NE outflow in sham and bulbectomized rats, chronic administration resulted in a blunted rise in neurotransmitter (Prins et al., 2011; Prins et al., 2010). In the hippocampus, no changes in monoamines levels were observed in bulbectomized rats, DOV216303 increase DA, 5-HT and NE in both sham and bulbectomized rats either after acute or chronic treatment (Prins et al., 2011). This raises the possibility that monamines homeostasis in response to TRIs is regulated in a region-dependant manner. In the search for new drugs, adaptations in receptor and transporter density pre- and post-synaptically after chronic drug administration should be investigated as well.

TRI	In vitro uptake (Kd or IC50 in nM)			In vivo uptake			References
	SERT	NET	DAT	5-HT	NE	DA	
Bicifadine[a]	117	55	910	+++	++	+++	Nicholson et al., 2009 ; Basile et al., 2007
DOV216303[a]	30	45	80	+++	++	++	Caldarone et al., 2010 ; Prins et al., 2010
DOV21947[a]	12	23	96	ND	ND	ND	Skolnick et al., 2003
JNJ7925476[a]	1	1	2.5	+++	+++	+++	Aluisio et al., 2008
JZAD-IV-22[a]	15	84	120	++	+++	+++	Caldarone et al., 2010
PRC025[b]	6	19	100	ND	ND	ND	Shaw et al., 2007
PRC050[b]	6	0.4	120	ND	ND	ND	Shaw et al., 2007
PRC200-SS[b]	2	0.6	18	+	+++	++	Liang et al., 2008
SEP225289[a]	14	4	2	ND	ND	ND	Guiard et al., 2011

Table 2. In vitro and in vivo functional activity of triple reuptake inhibitors (TRIs) from synaptosomes and intracerebral microdialysis; respectively. [a]Values are expressed in IC50. [b]Values are Kd expressed in nM and represent the equilibrium dissociation constant. The smaller the Kd values, the higher inhibitory effect of a drug is for the corresponding monoaminergic transporter. In microdialysis experiments, signs "+" reflects the relative increase in 5-HT, NE and DA obtained with the highest acute dose used. ND: not determined.

4.3 Antidepressant-like activity

In humans, it is accepted that antidepressant and more particularly SSRIs, typically inhibit 80% of the SERT binding sites at minimally effective doses (Blier, 2008). It is, however, not known how much inhibition or occupancy for each transporter is required for antidepressant action. Correlation between *in vitro* binding profile towards monoamines transporters and *in vivo* behavioral studies may help shed light on some important and often debated issues.

4.3.1 In test predictive of antidepressant-like activity

The most frequently paradigms used to screen the antidepressant-like activity of pharmacological agents are the forced swimming and the tail suspension tests (FST and TST, respectively). Interestingly in the FST a further distinction can be made in swimming and climbing behaviors. Swimming is a parameter that reflects the activation of the brain serotonergic system in rodents (Cryan and Lucki, 2000; Reneric and Lucki, 1998; Detke et al., 1995). Such an association comes from the observation that pretreatment with the tryptophan hydroxylase inhibitor parachlorophenylalanine, prevents SSRIs-induced increase in swimming behavior (Page et al., 1999). On the other hand, climbing behavior has been shown to reflect the activation of noradrenergic system, particularly the subpopulation of neurons arising from the lateral tegmentum (Cryan et al., 2002). Surprisingly, none of the studies evaluating the antidepressant-like activity of TRIs has examined the climbing response, to compare for example, their *in vivo* potency at stimulating brain serotonergic and noradrenergic neurotransmissions. It is also important to mention that only one test in animals cannot cover all the complex depressive aspects. Ideally, novel compounds should be tested in several behavioral paradigms and animal models in order to address their putative antidepressant-like activity on a wide variety of symptoms of MD. In this prospect, Guilloux et al., (2011) have recently developed a score integrating measures from different tests to provide a robust characterization of the underlying "emotionality" of individual mouse, similarly as mood and related syndromes are defined in humans through various related symptoms over time.

Behavioral data currently available, have clearly demonstrated the antidepressant-like effect of triple reuptake inhibitors that act by increasing the time of mobility and/or by reducing the time of immobility in the FST or the TST (Aluisio et al., 2008; Liang et al., 2008; Shaw et al., 2007; Skolnick et al., 2003) (Table 3). Among the TRIs tested, PRC200-SS and JNJ7925476 produced the most robust antidepressant-like effects in these tests. For example, JNJ7925476 (0.3 mg/kg; sc) or PRC200-SS (10mg/kg; ip) produced a greater increase in the time of mobility in the mouse TST than that observed with PRC025, PRC050 (Aluisio et al., 2008; Bannwart et al., 2008; Liang et al., 2008; Shaw et al., 2007; Skolnick et al., 2003). In the rat FST, PRC200-SS is also the compound exhibiting the best performance since at the dose of 10 mg/kg; ip, it produced a more pronounced increase in the time of immobility than that observed with the corresponding doses of DOV21947, PRC025 and PRC050. Interestingly, both compounds (i.e. JNJ7925476 and PRC0200-SS) display a higher affinity for the SERT and the NET compared to the others compounds, suggesting that this double action is an important prerequisite to produce maximal effects. Since DA is known to enhance locomotor activity, the possibility cannot be excluded that triple reuptake inhibitors increased the time of immobility in these various studies, through a psychostimulant effect. In various studies, however, TRIs did not modify locomotor activity at doses that produce

antidepressant-like effects (Aluisio et al., 2008; Liang et al., 2008; Shaw et al., 2007; Skolnick et al., 2003), thus suggesting that the antidepressant-like activity of TRIs does not appear to be from "false-positive" results.

4.3.2 In animal models of depression

An important drawback in the development of antidepressants is the fact that the new compounds are tested after acute administration in "naïve" non-depressed animals. Their chronic use in animal models is likely more relevant and would provide more informative results to determine whether or not a new pharmacological agents worth being tested in clinical trials. A recent study in bulbectomized rats has provided some interesting results. In this model, a 14-day regimen of DOV216303 (20 mg/kg/day; po), normalized bulbectomy-induced hyperactivity in the open field, similar to the effect of imipramine at the same dose (Breuer et al., 2008). Further studies in these animal models are required to precise the potential of TRIs and dissect their mechanism of action in pathological conditions.

TRIs	Doses, routes	Tests	Mobility (% of baseline increase)	Immobility (% of baseline decrease)	References
DOV 216,303	10 mg/kg; po 15 mg/kg; po 20 mg/kg; po	FST (mice)	ND ND ND	-20% (*) -20% (*) -40% (*)	Skolnick et al., 2003
DOV 21,947	5 mg/kg; po 10 mg/kg; po 15 mg/kg; po 20 mg/kg; po 5 mg/kg; po 10 mg/kg; po 15 mg/kg; po 20 mg/kg; po	TST (mice) FST (rats)	ND ND ND ND ND ND ND ND	-25% (***) -40% (***) -40% (***) -55% (***) -20% (*) -25% (***) -30% (***) -40% (***)	Skolnick et al., 2003
JNJ-7925476	0.3 mg/kg; po	TST (mice)	115%	ND	Aluisio et al., 2008
PRC025	5 mg/kg; ip 10 mg/kg; ip 5 mg/kg; ip 10 mg/kg; ip	TST (mice) FST (rats)	+60% (*) +60% (*) +145% (*) +100% (*)	-40% (*) -40% (*) -40% (*) -30% (*)	Shaw et al., 2007
PRC200-SS (active enantiomere of PRC050)	5 mg/kg; ip 10 mg/kg; ip 5 mg/kg; ip 10 mg/kg; ip	TST (mice) FST (rats)	+80% (*) +70% (*) +110% (*) +165% (*)	-40% (*) -80% (*) -30% (*) -55% (*)	Shaw et al., 2007

TRIs	Doses, routes	Tests	Mobility (% of baseline increase)	Immobility (% of baseline decrease)	References
PRC200-SS (active enantiomere of PRC050)	0.5 mg/kg; ip 1 mg/kg; ip 10 mg/kg; ip 1 mg/kg; ip 5 mg/kg; ip 10 mg/kg; ip	TST (mice) FST (rats)	+40% (*) +95% (**) +95% (**) +130% (*) +246% (*) +226% (*)	-40% (*) -90% (**) -90% (**) -45% (*) -85% (*) -75% (*)	Liang et al., 2008
JZAD-IV-22	15 mg/kg; ip 30 mg/kg; ip 60 mg/kg; ip 15 mg/kg; ip 30 mg/kg; ip 60 mg/kg; ip	TST (mice) FST (mice)	ND ND ND ND ND ND	-15% (ns) -30% (*) -35% (*) -20% (ns) -40% (*) -70% (*)	Caldarone et al., 2010
6-(3,4-dichlorophenyl)-1-[(methyloxy) methyl]-3-azabicyclo[4.1.0] heptane	3 mg/kg; ip 10 mg/kg; ip 30 mg/kg; ip	FST (mice)	ND ND ND	-30% (**) -70% (**) -90% (**)	Micheli et al., 2010a
1-(Aryl)-6-[alkoxyalkyl]-3-azabicyclo[3.1.0] hexanes and 6-(aryl)-6-[alkoxyalkyl]-3-azabicyclo[3.1.0] hexanes	1 mg/kg; ip 3 mg/kg; ip 10 mg/kg; ip	FST (mice)	ND ND ND	-20% (ns) -40% (*) -90% (**)	Micheli et al., 2010b
3-aryl-3-azolylpropan-1-amines	3 mg/kg; po 10 mg/kg; po	TST (mice) FST (mice)	ND ND	-60% (*) -15% (*)	Lee et al., 2010

TRIs	Doses, routes	Tests	Mobility (% of baseline increase)	Immobility (% of baseline decrease)	References
4-(3,4-dichlorophenyl)-N-methyl-1,2,3,4-tetrahydronaphthalenyl amines (compound#10)	3 mg/kg; ip 10 mg/kg; ip 30 mg/kg; ip	TST (mice)	ND	-15% -20% (*) -50% (*)	Shao et al., 2011a
N-methyl-1-(1-phenylcyclohexyl) methanamine (compound #1)	3 mg/kg; ip 10 mg/kg; ip 30 mg/kg; ip	TST (mice)	ND	-5% -10% -25% (*)	Shao et al., 2011b
N-methyl-1-(1-phenylcyclohexyl) methanamine (compound #31)	3 mg/kg; ip 10 mg/kg; ip 30 mg/kg; ip	TST (mice)	ND	-10% -14% (*) -30% (*)	Shao et al., 2011c

Table 3. Antidepressant-like activity of triple reuptake inhibitors (TRIs) in rodents assessed in the forced swimming test (FST) or the tail suspension test (TST). Po: per os; ip: intraperitoneal; ND: not determined. *p<0.05, **p<0.01 and p<0.001: significantly different from vehicle-treated group.

4.4 Clinical properties of TRIs

On the basis of preclinical data, TRIs are in process of development (Millan, 2009) and most are now in Phase II clinical trials (Table 4). A small citalopram-controlled trial of DOV216303 in severely depressed patients yielded significant improvements in Hamilton Depression Rating Scale (HAM-D) scores in both groups at both one-week and two week time points (Skolnick et al., 2006). Since the optimal selectivity of TRIs at the three transporter sites remains undetermined, it is plausible that different potency ratios may result in different clinical effects. It can be envisaged to adapt the treatment to the nature of depressive symptoms. Drugs with high affinities for the 5-HT and NE transporters could be prescribed to patients displaying anxious symptoms, whereas compounds with a high affinity for the DAT could be more beneficial to patients having a loss of motivation and/or anhedonia. Despite these encouraging data, further investigations failed to demonstrate the beneficial therapeutic effect of NS2359 resulting in discontinued development. Of particular importance, a concern with drugs that block DA transporters is their potential reinforcing property and abuse liability. This comes from the fact that drugs that block DAT do not necessarily lead to dependence. Indeed, Volkow and collaborators showed that DA-transporter-blocking drugs must induce more than 50% DAT blockade to produce reinforcing effects (Volkow et al., 2005). Hence, DA reuptake inhibitors have been classified into two groups: type 1 blockers, which produce addiction and euphoria, and type 2 blockers, which do not (Rothman, 1990). It is thus possible that the capacity of DA reuptake blockers to produce dependence may involve other mechanisms that should carefully be

considered with multi-targets agents such as TRIs. Nevertheless, although rigorous clinical feedback is yet to come, it can be hoped that TRIs will prove to have acceptable abuse and dependence potential and will offer improved efficacy in the management of depression. Accordingly a recent study involving comparing tesofensine vs. placebo, D-amphetamine and bupropion, in recreational stimulant users shows that although the effects of D-amphetamine were significantly greater than those of placebo on all primary and secondary subjective measures, tesofensine were not significantly different from those of placebo and lower than those of D-amphetamine and bupropion suggesting that the abuse potential for tesofensine is no greater than that of bupropion (Schoedel et al., 2010). Similar conclusions were reported with bicifadine, which display a low abuse potential (Nicholson et al., 2009). With respect to MD and eating disorders, weight loss has also been observed as an adverse event in studies with tesofensine (Hauser et al., 2007; Hansen et al., 2010), prompting further research for the indication of obesity. This effect is believed to result from appetite suppression (Axel et al., 2010; Sjodin et al., 2010). Recently published data from the first randomized, double-blind, Pl-controlled phase-II trial in primarily healthy, obese subjects showed that tesofensine was able to produce a greater weight loss after 24 weeks about twice that of currently approved drugs (Astrup et al., 2008a, 2008b). Appetite was significantly suppressed after an overnight fast after treatment with tesofensine in this study (Astrup et al., 2008a, 2008b).

5. Pain relief by TRIs, an example of symptom of depression

Acute and chronic pains may result from reduced levels of endogenous 5-HT, NE and DA activities, at both the spinal and supraspinal levels (Ren and Dubner, 2002). Indeed, pain is a bi-directional process of ascending and descending neuronal pathways involving monoaminergic systems whose activation may have an inhibitory influence on nociception. Despite the complexity of pharmacological interactions between monoaminergic neurons, that sometimes may attenuate monoaminergic neurotransmission, one would expect a better efficacy of dual-or triple-acting agents over selective 5-HT or NE reuptake inhibitors in analgesia (Hache et al., 2011). Indeed, since all three monoamines are involved in antinociception, the recruitment of more than one system may produce additional effects. Selected antidepressants suppress pain by diverse mechanisms and are now considered as an essential component of the therapeutic strategy for treatment of many types of persistent pain (Sawnyok et al., 2001). Their main mechanism of action involves reinforcement of the descending inhibitory pathways by increasing the amount of 5-HT and NE, but also DA in the synaptic cleft at both supraspinal and spinal levels (Hache et al., 2011). Several open-label randomized controlled clinical trials, meta-analyses, and systematic reviews have confirmed the clinical efficacy of selected antidepressants in persistent pain conditions (Dharmshaktu et al., 2011). Precedent for the use of TRIs in the treatment of clinical pain exists with nefopam, a tricyclic agent with non-narcotic analgesic (Heel et al., 1980). It was reported that DA played a critical role in nefopam analgesia as indicated by the observation that rats with selective loss of DA neurons, have a marked reduction in nefopam-induced analgesia. In a marked contrast, the lesion of the serotonergic or noradrenergic systems induced by 5,7-duhydroxytryptamine (5,7-DHT) or DSP4, respectively, failed to affect nefopam-induced analgesia in rats (Esposito et al., 1986; Girard et al., 2006; Girard et al., 2011). The potential interest of TRIs in the relief of pain has been corroborated by a recent publication characterizing the antinociceptive effects of the TRI bicifadine in acute,

persistent and chronic models of pain (Basile et al., 2007). In this study, bicifadine potently suppressed pain responses in two models of acute inflammatory pain in both rats and mice. It also normalized the nociceptive threshold in the complete Freund's adjuvant model of persistent inflammatory pain and suppressed mechanical and thermal hyperalgesia and mechanical allodynia in the spinal nerve ligation model of chronic neuropathic pain. Mechanical hyperalgesia was also reduced by bicifadine in the STZ model of neuropathic pain (Basile et al., 2007). Clinical (phase II/III) studies have demonstrated that bicifadine is an effective analgesic in the treatment of postoperative pain (Krieter et al., 2008). The impact of bicifadine on 5-HT, NE and DA neurotransmissions was confirmed by *in vitro* binding assays and intracerebral *in vivo* microdialysis study in freely moving rats. In a second study, another TRI, NS7051, has shown comparable antinociceptive properties to tramadol confirming the interest of these antidepressants in the relief of pain (Munro et al., 2008). The molecule has undergone several Phase II and III trials for the treatment of pain, including acute postsurgical pain and chronic low back pain, and is being evaluated for painful diabetic neuropathy (clinical trial.gov). However, bicifadine has failed to meet endpoints in a number of trials such as diabetic neuropathy (clinical trial.gov) suggesting that TRIs may be used in specific pain. Other TRIs currently under development for depression should draw attention for future investigations in the field of pain and confirm whether or not they display any activity in diabetic neuropathy.

6. Conclusion

Numerous arguments support the contention that multi-target mechanisms may be more effective and better tolerated than their highly selective counterparts in the management of MD (Millan, 2009). Hence, drugs in preclinical and clinical studies (Table 4) include, but are not limited to TRIs, which simultaneously increase brain 5-HT, NE and DA neurotransmissions. Several lines of evidence specifically substantiate interest in dual-and triple-acting antidepressants. First there is no single cause of major depression. A vast array

TRIs	Comparator(s)	Phases	Conditions
Tesofensine	placebo	I	Obesity
Tesofensine	placebo	II	Obesity
DOV21947	placebo	II	Major Depressive Disorder
SEP225289	placebo venlafaxine	II	Major Depressive Disorder
Bicifadine	placebo standard analgesic treatment	III	Chronic low back pain
Nefopam	dexmedetomidine fentanyl	IV	Post operative analgesia

Table 4. Clinical studies with triple reuptake inhibitors (TRIs) in major depressive disorder or related morbidities. Details of these studies can be found on http://www.clinicaltrials.gov using the Boolean research for the following keywords: "Triple reuptake inhibitors".

of interacting genes, epigenetic influences, developmental events, and environmental factors collectively compromise mood. Second, agents that have complementary components of action may have a greater chance of controlling both the mood deficits of depression and other residual symptoms such as sleep disturbances, eating, sexual disorders or pain. This review particularly focuses on nocicpetion since over 75% of depressed patients suffer from painful symptoms (Hache et al., 2011), predicting a greater severity and a less favorable outcome of depression. In addition, imaging, anatomical and functional studies have demonstrated the existence of common brain structures, neuronal pathways and neurotransmitters in depression and pain raising the possibility that managing pain in depressed patients may help them recover more rapidly and efficiently. This is an example illustrating the fact that MD does not rely on only one impaired system and that an improved antidepressant therapy requires a diagnosis taking into considerations symptom profiles.

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