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A new strategy for antidepressant prescription

Francis Lavergne*[1] *and Thérèse M. Jay*[1,2]

[1] *Physiopathologie des Maladies Psychiatriques, Centre de Psychiatrie et Neurosciences,INSERM U894, Centre Hospitalier Sainte-Anne, Paris, France*
[2] *Université Paris Descartes, Paris, France*

Edited by:
Xiao-Ming Ou, University of Mississippi Medical Center, USA

Reviewed by:
Xiao-Ming Ou, University of Mississippi Medical Center, USA
Michael F. O'Neil, Eolas Biosciences Ltd, UK

***Correspondence:**
Thérèse M Jay, Centre de Psychiatrie et de Neurosciences, INSERM U894, 2ter rue d'Alésia, 75014 Paris, France.
e-mail: therese.jay@inserm.fr

From our research and literature search we propose an understanding of the mechanism of action of antidepressants treatments (ADTs) that should lead to increase efficacy and tolerance. We understand that ADTs promote synaptic plasticity and neurogenesis. This promotion is linked with stimulation of dopaminergic receptors. Previous evidence shows that all ADTs (chemical, electroconvulsive therapy, repetitive transcranial magnetic stimulation, sleep deprivation) increase at least one monoamine neurotransmitter serotonin (5-HT), noradrenaline (NA) or dopamine (DA); this article focuses on DA release or turn-over in the frontal cortex. DA increased dopaminergic activation promotes synaptic plasticity with an inverted U shape dose–response curve. Specific interaction between DA and glutamate is mediated by D1 receptor subtypes and Glutamate (NMDA) receptors with neurotrophic factors likely to play a modulatory role. With the understanding that all ADTs have a common, final, DA-ergic stimulation that promotes synaptic plasticity we can predict that (1) AD efficiency is related to the compound strength for inducing DA-ergic stimulation. (2) ADT efficiency presents a therapeutic window that coincides with the inverted U shape DA response curve. (3) ADT delay of action is related to a "synaptogenesis and neurogenesis delay of action." (4) The minimum efficient dose can be found by starting at a low dosage and increasing up to the patient response. (5) An increased tolerance requires a concomitant prescription of a few ADTs, with different or opposite adverse effects, at a very low dose. (6) ADTs could improve all diseases with cognitive impairments and synaptic depression by increasing synaptic plasticity and neurogenesis.

Keywords: antidepressant, dopamine, prefrontal cortex, major depression, synaptic plasticity

INTRODUCTION

Original antidepressants treatments (ADTs) were discovered by serendipity and their mechanism of action is still unclear. There is a delay of action between chronic ADT administration and patient's response. Side effects differ between ADTs but not with efficiency. All chemical ADTs increase at least one monoamine neuromodulator (serotonin, noradrenaline (NA), DA). Assessment of depression intensity shows that all items of depression scales are strongly inter-correlated. The response does not differ with different ADTs or with different clinical profiles.

Depression involves emotion, cognition, and physical symptoms. Clinical depression is characterized in the DSM-IV-R (APA, 2004) by low mood (sadness, loss of motivation, worthlessness/guilt, and suicidal ideas), reduced cognition (low psychomotor activity, fatigue, concentration/attention deficit), and body symptoms like retardation, appetite, and sleep changes. Depression is characterized by a reduction of confidence in one-self, the world, and the future. Depression is often preceded by a period of acute or chronic stress.

Animal models of depression induce low mood (*e.g., anhedonia can be expressed by reduction in sucrose preference*) and psychomotor retardation (e.g., reduced reactivity can be expressed by immobility in the Porsolt test or escape deficit in the learned helplessness model). To induce depression-like behavior, animals are submitted to intense stress (unavoidable electric shocks), or chronic mild stress (2 weeks of unpredictable changes in the environment). Moreover, stress induces DA release in the prefrontal cortex (Del Arco and Mora, 2001).

In our working hypothesis, depression is a state of synaptic depression brought by a low rate of dopaminergic transmission with D1 receptor up-regulation that can be reversed by an increase in DA transmission. *We propose* that D1 receptors regulate mood. *We see depression in a temporal dimension*: in stressful situations, the organism releases DA in the brain as a way to adapt to stressful situations and cortisol release contributes to this adaptation. *If this fighting phase is successful the person will heal from his stress.* In depression this "fighting phase" persists and ends in a "loosing phase" in which DA cannot be released anymore and D1 receptors are up-regulated. We choose to study our hypothesis at the level of the prefrontal cortex since this brain area is at the intersection of mood and cognition and is an essential component for personality integration. The prefrontal cortex, receives the projections from the limbic system, may serve to integrate the cognitive and emotional information. This area is modulated by NA, serotonin, and DA neurotransmission.

DEPRESSION AS A HYPODOPAMINERGIC STATE

At the pharmacological level, depression is a state involving low levels of DA transmission resulting in D1 receptor up-regulation. In the rat model of depression, a 4 weeks stress session induces a depressive state and reduces DA concentration in the prefrontal cortex for 3 months (Mizoguchi et al., 2008b). Moreover, adrenalectomy induces a depressive state with impaired working memory (Mizoguchi et al., 2004) and a hypodopaminergic state

with a D1 receptor up-regulation (Mizoguchi et al., 2004). This hypodopaminergic function can be reversed by (1) D1 agonists, (2) DA release, and (3) ADT administration.

(1) Infusion of a D1 agonist, SKF81297, in the rat prefrontal cortex, reverses the working memory impairment due to adrenalectomy (Mizoguchi et al., 2004), and the rotarod impairment due to both chronic stress (Mizoguchi et al., 2002) and adrenalectomy (Mizoguchi et al., 2008a). Furthermore, working memory is enhanced in naïve, non-depressed rats, 12 h after learning (Floresco and Phillips, 2001). Other specific D1 receptor agonists A68930 (D'Aquila et al., 1994), and the partial agonist SKF38393 (D'Aquila et al., 1994; Gambarana et al., 1995; Takamori et al., 2001), reverse, after the first administration, the escape deficit induced by the learned helplessness model of depression. SKF38393 also reduces the spontaneous escape deficit of rats not exposed to the inescapable shocks (Gambarana et al., 1995). When given repeatedly this D1 agonist produces tolerance to its own protective effect. Indeed, long term administration of this selective D1 agonist is known to down-regulate D1 receptors number in the prefrontal cortex (Gambarana et al., 1995). The specific D1 receptor antagonist SCH23390 reverses the effects of SKF 38393, (Takamori et al., 2001) and completely antagonized the effect of a chronic-2-weeks-imipramine treatment in the learned helplessness model of depression (D'Aquila et al., 1994). *It is of interest to see that ADT is suppressed by D1 antagonist.*

(2) DA challenge, with 30 mg of D-amphetamine induces a larger mood elevating effect, in unmedicated depressed patients when compared to controls. *Controls are healthy volunteers without history of axis I disorders in DSM-IV-R* (Tremblay et al., 2005). This mood enhancing DA challenge could indicate that D1 receptors *are up-regulated* during depression and more sensitive to DA increase.

(3) Chronic ADT treatment with imipramine reverses the escape deficit induced by the learned helplessness model of depression (D'Aquila et al., 1994; Gambarana et al., 1995) and down regulates D1 receptor number in the prefrontal cortex (Gambarana et al., 1995).

At the cellular level depression may be a state of depressed synaptic plasticity that can be reversed by (1) D1 agonist administration, (2) DA release, and (3) AD treatments.

(1) The selective D1 receptor agonist, SKF81297 at an optimal dose facilitates long term potentiation (LTP) in the hippocampal–prefrontal cortex pathway whereas the D1 antagonist SCH23390 caused a dose-related impairment of its induction (Gurden et al., 2000).

(2) DA released from DArgic axon terminals in the prefrontal cortex facilitates synaptic plasticity whereas a depletion of cortical DA levels generates a dramatic decrease in this LTP (Gurden et al., 1999). Magnitude of this prefrontal LTP is also enhanced by clozapine and this effect is reversed by the D1 receptor antagonist SCH23390 (Matsumoto et al., 2008).

(3) Administration of ADTs, tianeptine and to a lesser extent fluoxetine, reverses the long lasting inhibition of *in vivo* LTP induced by stress in rats (Rocher et al., 2004). In contrast, the selective D1 antagonist SKF83566 combined with high-frequency stimulation by electrode implanted in the corpus callosum prevented prefrontal cortex LTP and resulted in long term depression (Coppa-Hopman et al., 2009). Together these data indicates that D1 receptor activation is necessary for the induction of medial prefrontal cortex glutamate-based LTP (Gurden et al., 2000; Coppa-Hopman et al., 2009).

ALL ANTIDEPRESSANTS INCREASE DOPAMINE LEVELS

We performed a literature search, retrieving the articles that measure DA release in the prefrontal cortex using chemical and non-chemical antidepressant treatments. The studies show that, in rat, mouse, monkey, and man electroconvulsive therapy (Glue et al., 1990; Yoshida et al., 1998; Inoue et al., 2003), repetitive transcranial magnetic stimulation (Lisanby and Belmaker, 2000; Ohnishi et al., 2004), sleep deprivation (Lara-Lemus et al., 1998; Gillin et al., 2001; Wu et al., 2001), and all classes of chemical antidepressants, increase DA release in the prefrontal cortex (see **Table 1**). Administration of ADTs was either through ip, po, or intra-cortical route. Assessments of DA levels were mostly done through *in vivo* microdialysis.

The following ADTs induce DA release in PFC:

- From the "tricyclic" class: imipramine (Jordan et al., 1994; Tanda et al., 1994; Valentini et al., 2005), clomipramine (Tanda et al., 1994; Owen and Whitton, 2006), desipramine (Carboni et al., 1990; Tanda et al., 1994; Gresch et al., 1995; Carlson et al., 1996; Shoblock et al., 2004; Valentini et al., 2004; Bongiovanni et al., 2005), amoxapine (Kobayashi et al., 1992), amitriptiline (Kihara and Ikeda, 1995), nortryptiline (Carlson et al., 1996), maproptyline (Kihara and Ikeda, 1995).
- From the "Noradrenalin Serotonin Reuptake Inhibitor" class: duloxetine (Carlson et al., 1996; Gobert et al., 1997a,c), milnacipran (Muneoka et al., 2009), venlafaxine (Weikop et al., 2004).
- From the "specific serotonin reuptake inhibitor" (SSRI) class: fluoxetine (Jordan et al., 1994; Tanda et al., 1994; Gobert et al., 1997a,b,c, 1999; Pozzi et al., 1999; Millan et al., 2000; Sakaue et al., 2000; Bymaster et al., 2002; Koch et al., 2002), citalopram (Pozzi et al., 1999; Valentini et al., 2005), paroxetine (Carlson et al., 1996; Owen and Whitton, 2006), fluvoxamine (Jordan et al., 1994).
- From the "MonoAmine Oxidase Inhibitor" class: deprenyl (Lakshmana et al., 1998), moclobemide (Kan et al., 1987), IMAO-A (Inoue et al., 2003).
- From "Other ADs" class: mianserine (Tanda et al., 1996a; Valentini et al., 2004), mirtazapine (Devoto et al., 2004; Nakayama et al., 2004), tianeptine (Louilot et al., 1990; Sacchetti et al., 1993), amineptine (Invernizzi et al., 1992; Garattini, 1997), agomelatine (Millan et al., 2003), bupropion (Li et al., 2002; Inoue et al., 2003), reboxetine (Invernizzi et al., 2001; Linner et al., 2001; Page and Lucki, 2002; Kitaichi et al., 2004; Valentini et al., 2004; Carboni et al., 2006; Owen and Whitton, 2006).

Table 1 | Prefrontal dopamine release from antidepressant treatment.

Reference	Antidepressant dosage/administration	Prefrontal dopamine increase (I) from antidepressant
ELECTROCONVULSIVE THERAPY (ECT)		
Inoue et al. (2003)	ECT	I
Yoshida et al. (1998)	1–8 ECS	I from first ECT
Glue et al. (1990)	1–8 ECS	I from first ECT
REPETITIVE TRANSMAGNETIC STIMULATION (rTMS)		
Ohnishi et al. (2004)	rTMS in right primary motor cortex, 5 Hz	I in the mesolimbic pathway
Lisanby and Belmaker (2000)	rTMS chronic	I dopamine content and turn over rate
SLEEP DEPRIVATION		
Lara-lemus et al. (1998)	REM sleep deprivation 48 h	I: +33%
Gillin et al. (2001)	Total sleep deprivation in men (eight papers)	I endogenous release of dopamine
Wu et al. (2001)	Total Sleep Deprivation in men, one night (seven papers)	dopamine release was associated with AD
CHEMICAL ADs		
Tricyclic		
Valentini et al. (2005)	Imipramine	I
Jordan et al. (1994)	Imipramine	I
Tanda et al. (1994)	Imipramine 10 mg/kg	I
Tanda et al. (1994)	Clomipramine 10 mg/kg	I
Owen and Whitton (2006)	Clomipramine (1–7 days)	I after day 7
Bongiovanni et al. (2005)	Desipramine 10–20 mg	I
Tanda et al. (1994)	Desipramine 10 mg	I
Gresch et al. (1995)	Desipramine 1 µM ic	I: +149%
Gresch et al. (1995)	Desipramine + tail shock	I: +584%
Valentini et al. (2004)	Desipramine	I dose dependently
Carlson et al. (1996)	Desipramine 10 mg, 21 days	I
Carboni et al. (1990)	Desipramine	I
Shoblock et al. (2004)	Desipramine	I
Tanda et al. (1996)	Desipramine 10 mg 1 day (and chronic 14 days)	I: +300% I: +300%
Kobayashi et al. (1992)	Amoxapine Acute, chronic	I (same level during acute and chronic treatment)
Kihara and Ikeda (1995)	Amitriptyline 6–25 mg per os	I
Carlson et al. (1996)	Nortryptiline 10 mg	I
Kihara and Ikeda (1995)	Maproptyline	I
IRSN		
Gobert et al. (1997b)	Duloxetine 5 mg	I: +115%
Gobert et al. (1997a)	Duloxetine 5 mg	I: +65%
Kihara and Ikeda (1995)	Duloxetine 3–12 mg	I
Muneoka et al. (2009)	Milnacipran	I
Weikop et al. (2004)	Venlafaxine 10 mg	I: +200%
SSRI		
Gobert et al. (1997b)	Fluoxetine	I: +55%
Pozzi et al. (1999)	Fluoxetine 10 or 25 mg	I: +167% or +205%
Pozzi et al. (1999)	Fluoxetine 25 mg + PCPA	I: +202% (same level with and without PCPA)
Sakaue et al. (2000)	Fluoxetine	I
Koch et al. (2002)	R-fuo	I
Bymaster et al. (2002)	Fluoxetine acute	I
Bymaster et al. (2002)	Citalopram, Fluvoxamine, Paroxetine, Sertraline acute	No I for the four ADs at the dosage used
Gobert et al. (1997a)	Fluoxetine 10 mg	I: +60%
Gobert et al. (1997a)	Fluoxetine + Buspirone	I: +240%
Gobert et al. (1997c)	Fluoxetine10 mg	I: +200%
Jordan et al. (1994)	Fluoxetine ip	I
	Fluoxetine ic	I

(Continued)

Table 1 | ***Continued***

Reference	Antidepressant dosage/administration	Prefrontal dopamine increase (I) from antidepressant
Tanda et al. (1994)	Fluoxetine	I
Gobert and Millan (1999)	Fluoxetine 10 mg	I: +55%
	Fluoxetine + buspirone	I: +300%
	Fluoxetine + raclopride	I: +90%
Millan et al. (2000)	Fluoxetine	I
Tanda et al. (1996)	Fluoxetine 5 mg acute	I: +200%
	Fluoxetine 10 mg, 14 days)	I: +200%
Pozzi et al. (1999)	Citalopram 25 mg/kg	I: +216%
Pozzi et al. (1999)	Citalopram 25 mg/kg + PCPA	I: 211% same level without (+191%) PCPA
Valentini et al. (2005)	Citalopram	No I
Valentini et al. (2005)	Paroxetine 10 mg	I
Nakayama (2002)	Paroxetine	I
Nakayama (2002)	Paroxetine + granisetron	Granisetron (5HT3–) inhibit paroxetine effect
Carlson et al. (1996)	Paroxetine 10 mg, 21 days	I
Owen and Whitton (2006)	Paroxetine 10 mg	I
Jordan et al. (1994)	Fluvoxamine ic	I
MAOI		
Inoue et al. (2003)	IMAO	I
Lakshmana et al. (1998)	Deprenyl 0.25 mg 8 days	I: +87%
Lakshmana et al. (1998)	Deprenyl + clorgyline 1 mg	I: +245%
Kan et al. (1987)	Moclobemide	I dose-dependent
Others		
Valentini et al. (2004)	Mianserine	I
Tanda et al. (1996)	Mianserine 1–10 mg	I: +600%
Nakayama et al. (2004)	Mirtazapine 4–16 mg	I
Devoto et al. (2004)	Mirtazapine 5–10 mg	I, DOPAC
Devoto et al. (2004)	Mirtazapine + ic desipramine)	I Additional increase dopamine and DOPAC
Millan et al. (2000)	Mirtazapine acute and chronic	I
Sacchetti et al. (1993)	Tianeptine 10	I
Louilot et al. (1990)	Tianeptine 10–20 mg acute	I
	Tianeptine chronic	I in DOPAC less pronounced after 15 days
Millan et al. (2003)	Agomelatine	I
Invernizzi et al. (1992)	Amineptine 5–20 mg/kg	I at 10–20 mg, no I at 5 mg
Garattini (1997)	Amineptine	I
Li et al. (2002)	Bupropion 10 mg/kg	I +260%
Li et al. (2002)	Bupropion + fluoxetine 10 mg	I: +357%
Inoue et al. (2003)	Bupropion	I
Kitaichi et al. (2004)	Reboxetine acute 0, 3–20 mg	I
Kitaichi et al. (2004)	Reboxetine + Sub Li	I
Carboni et al. (2006)	Reboxetine	I
Invernizzi et al. (2001)	Reboxetine 10 mg, 2–14 days	I: +257% at day 2 and I: +342% at day 14
Page and Lucki (2002)	Reboxetine 20 mg	I (no I at 10 mg)
Page and Lucki (2002)	Reboxetine + tailpinch stress	I with reboxetine not in saline
Linner et al. (2001)	Reboxetine 15–13, 5 mg ip	I
	Reboxetine 333 μM ic	I
Valentini et al. (2004)	Reboxetine	I
Owen and Whitton (2006)	Reboxetine 10 mg acute	I
Owen and Whitton (2006)	Reboxetine chronic 4–21 days	I (gradual increase up to day 7)
Owen and Whitton (2006)	Reboxetine + amantadine	I (Amantadine increases speed and intensity)

Table 1 indicates that all ADTs, irrespective of their mechanism of action, (electroconvulsive therapy, repetitive transcranial magnetic stimulation, sleep deprivation, and all chemical class of antidepressants), induce DA release in the prefrontal cortex. They also increase DA in other brain areas like the limbic system, the nucleus accumbens, the striatum, and other cortical regions, but the

increase was not as systematic as in the frontal cortex. DA increases with the first ADT administration and is kept at this increased level during chronic treatment. Acute ADT treatment releases DA in the same range as a 2–3 weeks chronic treatment (Tanda et al., 1996b; Page and Lucki, 2002). DA release is increased by 50–600%, depending on the type of ADT and on the dosage of ADT that is administered. From these data, *we could predict the "strength" of an ADT (speed/efficacy) on its capacity to increase DA levels in the prefrontal cortex*. In some studies using SSRI, it was found that a low ADT dosage does not produce the expected increase in DA, while higher dosages of ADTs do induce the increase in DA (Invernizzi et al., 1992; Pozzi et al., 1999; Valentini et al., 2005). As mentioned above, the increase in DA could be a direct pharmacological effect (e.g., imipramine is an inhibitor of DA reuptake) or could result from an indirect mechanism. For example, sleep deprivation increases the release of thyroid and estrogen hormones (Baumgartner et al., 1993), which in turn can enhance DA release, and SSRI can release DA through 5HT3 receptors activation in prefrontal cortex (Tanda et al., 1995).

Some receptors are specifically implicated in this DA increase. Pharmacological experiments show that DA release can be attributed to specific receptor activation or deactivation. **Table 2** shows, in animals, that alpha 2, 5HT3, 5HT1A, 5HT2C, D2 receptors can mediate the release of DA. DA increases when blocking Alpha 2, 5HT2C, and D2 receptors at a low dose. DA is also increased when activating the 5HT1A, and maybe the 5HT3 receptors. In contrast agonists of Alpha 2, 5HT2C, and D2 receptors and antagonists of 5HT1A and 5HT3 receptors reduce DA release.

Table 2 indicates:

- Antagonists of the Alpha 2 receptor, idazoxan (Gresch et al., 1995; Weikop et al., 2004), yohimbine (Tanda et al., 1996a; Millan et al., 2000), fluparoxan (Millan et al., 2000), atipemazole (Gobert et al., 1997c), 1-(2-pyrimidinyl)piperazine (Gobert et al., 1997c, 1999), RX821002 (Gobert et al., 1998), BRL44408 (Gobert et al., 1998) increase prefrontal DA release. Conversely, receptor agonists: clonidine (Gresch et al., 1995; Tanda et al., 1996a; Devoto et al., 2004), demedetomidine (Gobert et al., 1998), guanabenz (Gobert et al., 1998), S18616 (Gobert et al., 1997c) reduce prefrontal DA release.
- Antagonist of the 5HT2C receptor, SB206553 (Gobert et al., 2000), SB242084 (Millan et al., 1998; Gobert et al., 2000) increase prefrontal DA, while 5HT2C receptor agonists decrease prefrontal DA (Millan et al., 1998; Gobert et al., 2000).
- Selective or mixed receptors antagonists of the D2 receptor increase prefrontal DA: raclopride (Gobert et al., 1998, 1999) haloperidol (Carboni et al., 1990). *The atypical antipsychotic drug risperidone, a multireceptor antagonist, which lacks 5-HT6 receptor antagonist properties, at doses of 0.1, 0.3, and 1.0 mg/kg, produces a bell-shaped dose response effect on DA efflux in the prefrontal* (Li et al., 2007). Conversely, the selective D2/3 agonist CGS 15855A decreases DA by 50% (Gobert et al., 1998). Interestingly, neuroleptic augmentation of ADT treatment has been used in severely depressed patients with good results. The explanation might be that neuroleptic (D2 antagonists) increase DA release and *therefore are likely to augment ADT response*. Indeed the studies show that sulpiride (Ago et al., 2005) and haloperidol (Carboni et al., 1990; Ago et al., 2005) enhance fluvoxamine-induced DA release. In addition, haloperidol (Carboni et al., 1990) enhances desmethylimipramine and oxaproptiline-induced DA release. All antipsychotics that share a common D2 and 5HT2C receptor antagonism should increase DA release. Indeed, zotepine (Nakamura et al., 2005), risperidone (Huang et al., 2006), and clozapine (Zhang et al., 2000) enhance prefrontal DA concentration. Risperidone (Huang et al., 2006) and olanzapine (Zhang et al., 2000) enhance AD-induced DA release. The olanzapine + fluoxetine combination (Zhang et al., 2000) increases prefrontal DA by 360% compared to baseline. This combination was significantly greater than either drug alone.
- Selective or mixed agonists of the 5HT1A receptor increase prefrontal DA release: pindolol (Gobert and Millan, 1999), buspirone (Tanda et al., 1994; Gobert et al., 1997a; Sakaue et al., 2000), 8-OH-DPAT (Gobert et al., 1998, 1999; Hughes et al., 2005), flibanserin (Invernizzi et al., 2003). In contrast, specific 5HT1A antagonists WAY100635, decreases prefrontal DA that was previously increased either by imipramine (Valentini et al., 2005), mirtazapine (Nakayama et al., 2004), or by the association of sulpiride and fluvoxamine (Ago et al., 2005).
- Direct perfusion of the 5-HT3 agonist, *N*-methylquipazine, in the anterior medial prefrontal cortex produces a concentration-dependent increase in extracellular DA level (Kurata et al., 1996). A recent review (Rajkumar and Mahesh, 2010) proposed that 5-HT3 receptor could mediate the SSRI effect. 5HT3 antagonist, ICS205930, prevents the DA increase due to fluoxetine or desipramine when infused in the prefrontal cortex or when administered systemically (Tanda et al., 1995) and Granisetron reduces the DA increase due to paroxetine (Nakayama, 2002). The 5HT3 antagonist, BRL4647OA, produces a dose dependent decrease of DA when infused in the anterior medial prefrontal cortex (Kurata et al., 1996).

Drugs known to increase the speed or efficiency of AD response also increase DA in the prefrontal cortex: lithium (Morissette and Paolo, 1996; Kitaichi et al., 2005), pindolol (Gobert and Millan, 1999; Millan and Gobert, 1999), idazoxan (Gresch et al., 1995; Weikop et al., 2004), buspirone (Tanda et al., 1994; Gobert et al., 1997a; Sakaue et al., 2000), yohimbine (Tanda et al., 1996a; Millan et al., 2000). Those drugs, also potentiate the DA increases due to ADs: chronic lithium increases milnacipran-induced DA release (Kitaichi et al., 2005), pindolol potentiates fluoxetine- and duloxetine-induced DA release (Gobert and Millan, 1999), yohimbine increases fluoxetine-induced DA release (Millan et al., 2000). Buspirone augments duloxetine-induced DA up to 550% (Gobert et al., 1997a) and fluoxetine-induced DA up to 300% (Gobert et al., 1997a; Gobert et al., 1999). Idazoxan with venlafaxine increases DA up to 200% (Weikop et al., 2004). These compounds also act to block their respective 5HT and NE autoreceptors.

Other drugs or hormones increase DA in the prefrontal cortex and present AD efficiency. This is the case for cortisol (Imperato et al., 1989; Mizoguchi et al., 2004, 2008a), estrogen, (Dazzi et al., 2007) thyroid hormones (Watanabe, 1999), substance *P* (Cador et al., 1989), and nicotine. Nicotine (Shearman et al., 2005; Tsukada

Table 2 | Prefrontal dopamine release from compounds.

Reference	Receptor activation	Compound alone	Dopamine increase (I) or decrease (D)	Compound with drug:increase (I) or decrease (D) compared to drug alone
Weikop et al. (2004)	Alpha2–	Idazoxan 1, 5 mg	I	I: venlafaxine + 200%
Gresch et al. (1995)		Idazoxan ic 0, 1–5 nM	I	
Gobert and Millan (1999)		1-PP	I: +90%	I: fluoxetine + 200%
Tanda et al. (1996a)		Yohimbine	I	
Millan et al. (2000)		Yohimbine	I	I: fluoxetine
Millan et al. (2000)		Fluparoxan	I	I: fluoxetine
Gobert et al. (1997b)		Atipamezole	I: +180%	I: duloxetine + 370% I fluoxetine + 170%
Gobert et al. (1997b)		1-PP 2, 5 mg	I: +90%	I: duloxetine + 600%
Gobert et al. (1998)		RX821,002	I: +73%	
Gobert et al. (1998)		BRL44408	I: +85%	
Gresch et al. (1995)	Alpha 2+	Clonidine 0, 2 mg	D	D: fluoxetine/buspirone
Tanda et al. (1996a)		Clonidine	D	
Devoto et al. (2004)		Clonidine 0, 15 mg ip		D: mirtazapine
Gobert et al. (1997b)		S 18616	D: –51%	
Gobert et al. (1998)		Dexmedetomidine	D: –45%	
Gobert et al. (1998)		Guanabenz	D: –50%	
Gobert and Millan (1999)		S18616		D: fluoxetine/buspirone
Tanda et al. (1996a)	5HT2–	Ritanserine 1 mg	No I	I: yohimbine
Gobert et al. (2000)		5HT2A MDL100907	No I	
Gobertet al. (2000)		5HT2C/B SB206553	I	
Gobert et al. (2000)		5HT2C SB 242084	I	
Gobert et al. (2000)		5HT2B SB204741	No I	
Millan (1998)		5HT2C– SB 242084	I	
Millan (1998)	5HT2+	5HT2C+ Ro600175	D	
Gobert et al. (2000)		5HT2C+ Ro600175	D	
Gobert and Millan (1999)	5HT1a+	Pindolol	I	I: fluoxetine I: duloxetine
Millan and Gobert (1999)		Pindolol	I	
Gobert et al. (1997a)		Buspirone 2, 5 mg	I: 100%	I: duloxetine + 550% I: Fluoxetine + 240%
Tanda et al. (1994)		Buspirone 1 mg	I	
Sakaue et al. (2000)		Buspirone	I	
Gobert et al. (1997b)		Buspirone	I: +100%	I: fluoxetine + 300%
Gobert et al. (1997b)		8-OH-DPAT	I: +135%	I: fluoxetine
Hughes et al. (2005)		8-OH-DPAT 0, 3 mg	I	I: paroxetine + 400%
Sakaue et al. (2000)		MKC242: 0, 3–1 mg	I	
Invernizzi et al. (2003)		Flibanserin 10 mg	I: +63%	
Gobert et al. (1998)		8-OH-DPAT	I: +100%	
Ago et al. (2005)	5HT1a–	WAY100635		D: sulpiride/fluvoxamine
Valentini et al. (2005)		WAY100635		D: imipramine
Invernizzi et al. (2003)		WAY100635		D: flibanserin 10 mg
Nakayama et al. (2004)		WAY 100635		D: mirtazapine

(Continued)

Table 2 | ***Continued***

Reference	Receptor activation	Compound alone	Dopamine increase (I) or decrease (D)	Compound with drug:increase (I) or decrease (D) compared to drug alone
Gobert et al. (1998)	5HT1b+	GR46611	No I	
Gobert et al. (1998)	5HT1b–	GR127,935	No I	
Kurata et al. (1996)	5HT3+	*N*-methylquipazine ic	I: dose dependent	
Nakayama (2002)	5HT3–	Granisetron		D: paroxetine
Tanda et al. (1995)		ICS 205930 ic and ip		D: fluoxetine
Kurata et al. (1996)		BRL46470A ic	D: dose dependent	
Rivet et al. (1998)	5HT	PCPA 20 mg		Despite PCPA, ADs induce DA increase: fluoxetine + 85%, duloxetine + 350%, desipramine + 290% mirtazapine + 300% fluoxetine + 202% citalopram + 211%
Gobert et al. (1998)	D2+	CGS15855A	D:–50%	
Gobert and Millan (1999)	D2–	Raclopride 16 mg/kg	I: +60%	
Gobert et al. (1998)		Raclopride	I:+60%	
Ago et al. (2005)		Sulpiride 10 mg	No I	I: fluvoxamine 10 mg
Ago et al. (2005)		Haloperidol 1 mg		I: fluvoxamine 10 mg
Carboni et al. (1990)		Haloperidol	I	I: desmethylimipramine I: oxaproptiline
Nakamura et al. (2005)	Atypical Antipsychotique D2– and 5HT2–	Zotepine 10 mg	I	
Huang et al. (2006)		Risperidone 1 mg	I	I: citalopram 10 mg
Zhang et al. (2000)		Olanzapine		I: fluoxetine +360% I: sertraline
Valentini et al. (2004)		Clozapine	+DOPA	
Owen and Whitton (2006)	NMDA antagonist	Amantadine 40 mg/kg	No I	I: reboxetine I: clomipramine I: paroxetine
Toide (1990)		Amantadine 40 mg/kg	I: +16%	
Owen and Whitton (2006)		Budipine 10 mg/kg	No I	I: reboxetine I: clomipramine I: paroxetine
Spanagel (1994)		Memantine 5–20 mg	I: +50%	
Hesselink (1999)		Memantine	No I	
Shearman et al. (2006)		Memantine	I	
Kitaichi et al. (2005)	Li	Lithium (7 days)		I: milnacipran
Morissette and Paolo (1996)		LiCl 10 mEq	I	
Watanabe (1999)	Hormones	Thyroid hormone T3		I: desipramine
Dazzi et al. (2007)		Estrogen: estrous cycle	I: Estrus D: Proestrus	
Morissette and Paolo (1996)		Estrogen E2	No I	I: Li
Mizoguchi et al. (2008)		Adrenalectomy	D	
Mizoguchi et al. (2004)		Adrenalectomy	D	
		Cortisol Replacement	I	
Imperato et al. (1989)		Corticoïd	I	

et al., 2005) and anticholinesterase drugs such as galantamine (Noda et al., 2010; Schilstrom et al., 2007) and donepezil (Shearman et al., 2006), enhance extracellular levels of DA in the medial prefrontal cortex. In addition, anticholinesterase treatment presents AD properties (Tanaka et al., 2004; Rozzini et al., 2007; Cummings et al., 2008) and anticholinesterase augmentation of AD treatment improves the response in depressed patients (Pelton et al., 2008) and the release of DA in the prefrontal cortex (Wang et al., 2007a). The pro-cognitive effect of anticholinesterase drugs could rely on the synaptic potentiation of the D1/NMDA activation, since the

D1 antagonist, SCH23390, and not the muscarinic acetylcholine receptor antagonist, scopolamine, reverses the cognitive improvement due to galantamine in an animal model of Alzheimer's disease (Wang et al., 2007b). The D1 antagonist, SCH23390 also abolishes the pro-cognitive effect of the galantamine–risperidone association in a chronic phencyclidine model of cognitive deficit (Wang et al., 2007a).

DOPAMINE MODULATION OF NEUROPLASTICITY IN DEPRESSION

Pharmacological evidence for a role of D1 receptors in the bidirectional modulation of synaptic plasticity in the prefrontal cortex has been demonstrated in the past few years by different groups including ours. DA through D1 receptors increases NMDA currents and this synergism which occurs at the postsynaptic level appears to be mediated through both a PKA and Ca^{2+}-dependent mechanisms (Jay et al., 1998; Gurden et al., 1999, 2000; Jay, 2003; Kruse et al., 2009). In addition, DA through D1 receptors appears to control the rate of phosphorylation/dephosphorylation of NMDA and AMPA receptor subunits which is required for a functional NMDA receptor (Sun et al., 2005; Gao and Wolf, 2008). D1 receptors may facilitate LTP by increasing the AMPA receptor pool available for synaptic insertion. Conversely, stimulation of D2 receptors decreased surface and synaptic GluR1 expression. Abnormal engagement of such mechanism could account for the maladaptive plasticity of prefrontal cortex, an area that we identified to be a target for intervention in stress-relates disorders like depression (Rocher et al., 2004; Cerqueira et al., 2007; Caudal et al., 2010). Emerging findings reveal that ADT treatment enhance membrane expression of AMPA receptors and phosphorylation of GluR1 subunit in the prefrontal cortex and hippocampus (Martinez-Turrillas et al., 2002, 2007; Qi et al., 2009). The mechanisms involved in the synaptic targeting of AMPA receptors by desipramine and paroxetine, ADs which differentially affect monoamine reuptake (NA and 5-HT), are similar but not identical. The mechanisms activated by these ADs could lead to an enhanced neuronal plasticity probably underlying, at least in part, the clinical efficacy of ADs treatment. A coordinated activation of DA D1 and NMDA systems is also an important feature of adaptive behavior. The processing of working memory in the mPFC involves DA D1 receptors that depend, at least in part, of NMDA receptors activity in this cortical area.

In our understanding of the AD-induced DA changes, the DA enhancement provides an AD effect through its interaction with NMDA receptors. The direct action on the NMDA receptors could bypass the DA increase and induce a strong AD response (Pacher et al., 2001; Skolnick et al., 2009; aan het Rot et al., 2010). On the other hand, the DArgic-antidepressant mechanism could provide a regulation that may be protective for the neuron: the DA inverted U dose–response curve of NMDA effects could bring some regulation and prevent toxic response.

WORKING HYPOTHESIS: DEPRESSION AS A SYNAPTIC LONG TERM DEPRESSION STATE

As we have seen in the prefrontal cortex, DA-induced activation of NMDA receptors could be the final common pathway for AD treatments (Lavergne and Jay, 2009). LTP is facilitated, in naïve rats, when DA is released (Jay et al., 2004) or when D1 agonist is infused in the prefrontal cortex (Gurden et al., 2000; Matsumoto et al., 2008). Conversely D1 antagonist reverses the D1 agonist effect on LTP (Gurden et al., 2000; Matsumoto et al., 2008; Coppa-Hopman et al., 2009). D1/NMDA activation is required for synaptic plasticity. Our working hypothesis proposes that depression is a state of synaptic depression and that AD induces synaptic potentiation. Both emotional and cognitive aspects of depression rely on synaptic plasticity. The hypothesis predicts several characteristics for AD activity: the AD response should (1) be non-specific (same efficacy for all types of depressions), (2) be global (all items of the depression scales should improve together), (3) be regulated inside a physiological range, (changes in synaptic plasticity are kept under strict homeostatic regulation), (4) needs time to archive the changes in synaptic plasticity (delay of action of AD), and (5) depends on a correct dosage (too little or too much AD should be ineffective, they should be a therapeutic window). All those five points are demonstrated in the literature.

(1) Non-specific
   (a) All characterized types of depression respond the same way to an AD treatment (Lavergne et al., 2005). ADs improve identically the different forms of clinically characterized depression (melancholy, atypical depression, recurrent depression, post partum depression, seasonal depression, previous suicide attempts, bipolar spectrum), only severe depression with psychotic symptoms responded less to 30 mg/day of mirtazapine and possibly did not reach the synaptic potentiation state. (b) The healing process in depression is identical under AD treatment compared to placebo. Patients, with and without AD treatment, present the same response profile when healing. With placebo only the less depressed patients respond (Rabkin et al., 1987). ADs increase the speed of response and allows response in severely depressed patients.

(2) Global
   Clinicians know that mood and psychomotor retardation improve together when the patient respond. The global AD effect is demonstrated by the fact that all ADs, despite different lateral effects, induce a parallel decrease of all depression scale items in clinical trials. Before and during treatment all depression items are strongly inter-related.

(3) Regulated inside a physiological range
   The range goes from synaptic depression to synaptic potentiation. The outside of the D1/NMDA inversed U curve corresponds to a state of synaptic depression; the inside of the curve corresponds to a state of synaptic potentiation. An argument to believe that AD efficacy is limited inside a physiological range is the limitation of the AD response. At the end of a 6 weeks-AD treatment (mirtazapine), the remission rate (stable response with > 50% MADRS score decrease) is only 30.9% (Lavergne et al., 2005). The benefit of treatment is to facilitate a state of synaptic potentiation. ADs cannot modulate mood higher. The state of synaptic potentiation is, with time, reduced by D1 receptors down-regulation. The slowdown in improvement observed after

the first 2 weeks of treatment presumably results from homeostatic counter-regulation. In fact most of the AD response occurs before the counter-regulation. All the ADs studied in the mirtazapine French regulatory "dossier de transparence" were pooled in a meta-analysis. At 2-week the score decrease was 60% of the end-point score decrease (Lavergne and De Mouzon, 2000), indicating that most of the score decrease occurs before the second week of treatment. The AD activity is limited by the D1/NMDA inversed U curve and by the D1 receptors down-regulation. Subsequent improvement relies on the new positive life experiences that are now possible in a state of synaptic potentiation.

Another argument to believe that AD activity is kept within homeostatic regulation is the lack of perception of an AD effect. Patients and healthy volunteers perceive the AD effect like a global positive mood change "more good days than usual" and do not perceives a "high" like with alcohol, cocaine…

(4) Time needed to archive synaptic potentiation

Changes, from synaptic depression to synaptic potentiation, takes time, and likely more time when the patient is in a profound state of synaptic depression. This would explain the AD delay of action. Animals and healthy volunteers respond to ADs within 3 h, while it takes longer for depressed patients to respond to ADs. In animal models of depression, the behavioral effects can be measured 20 min after AD administration and the increased synaptogenesis and neurogenesis can be measured after 2–3 h. Behavioral changes, in healthy volunteers, are noticed 3 h after administration of the ADs (Harmer et al., 2003a,b; Tse and Bond, 2003). In all clinical trials with ADs, the depression scales' score decrease is larger in the first half of treatment compared to the second half. The speed of improvement, measured as the score change per day, is maximal in the first week of treatment (2.65%/day, on the Montgomery Asberg Depression Rating Scale). The improvement period (rate of improvement > 2%/day) lasted only 2 weeks. Subsequent improvement was much slower (<0.5%/day). The AD activity is not delayed but is time-limited (Berlin and Lavergne, 1998). In clinical trials the AD improvement is observed after 4 days. In the Zurich meta-analysis, Angst and coworkers (Stassen et al., 1993, 1996) found that the score decrease in the AD group differs from the placebo group starting on the fourth day of treatment. After 1 week clinicians can usually observe the patient's improvement. In a mirtazapine study, 50% of the 4771 depressed patients present, a "little improvement" after 1-week treatment (one point increase or more with the Clinical Global Impression Scale) and a 18.5% score decrease with the Montgomery Asberg Depression Rating Scale. Another argument that points toward early AD effect is that an improvement predicts the final response. A "one point increase or more" on the Clinical Global Impression-Improvement scale was found to allow correct classification of responders in 71.6% of the patients when the response was defined as a "50% score reduction in the Montgomery Asberg Depression Rating Scale" (Lavergne et al., 2005).

(5) Therapeutic window

The D1/NMDA inversed U response curve implies a minimum and a maximum therapeutic dose. It predicts a therapeutic window for the AD response. It is intuitive that too low dosage would be inefficacious and less intuitive and that high dosage could be detrimental on efficacy. Too low dosage could be archived by interrupting the monoamine pathway. Catecholamine and tyrosine depletion induce a depressive relapse, within a few hours, in recently remitted depressed patients (Heninger et al., 1996; Delgado et al., 2002). We speculate that an interruption of transmission in the monoamine pathways or administration of a D1 antagonism could treat a manic episode. Tyrosine depletion decreases the release of DA produced by amphetamine (McTavish et al., 2001). The same amino acid mixture lacking tyrosine and its precursor phenylalanine lowers both subjective and objective measures of the psychostimulant effect of methamphetamine (McTavish et al., 2001) and impairs spatial recognition memory and spatial working memory in volunteers (Harmer et al., 2001). It also reduces mania ratings in bipolar patients (McTavish et al., 2001). High AD dosage or high blood concentration of AD in patients with low drug metabolism, may compromise the response. High blood concentration of amitriptyline compromises the therapeutic effect in depressed patients. The data support the existence of a therapeutic window (70–220 ng/ml) for amitriptyline serum level (Ulrich et al., 2001). Moreover high blood concentration of paroxetine and desipramine compromises the benefit of treatment in patients with panic disorder (Watanabe et al., 2007) and the analgesia in chronic back pain (Atkinson et al., 2007). Future research is needed to more precisely test the hypothesis that high dosage of D1 agonist compromises AD activity in an animal model of depression.

NEW PRESCRIPTION STRATEGY FOR ANTIDEPRESSANT TREATMENT

The D1/NMDA inversed U dose–response curve predicts a therapeutic window. To reach the therapeutic window we recommend to start the prescription at a low dosage (from 1/10 to 1/3 of the usually recommended dosage) and to increase the dosage, every 4–7 days, until the patient presents a qualitative positive change in his mood and functioning. This progressively incremental dosage will find the "minimal individual effective dosage." The progressive increase will likely reduce the adverse effects intensity and might reduce the speed of the D1 receptors down-regulation, providing a longer D1/NMDA activation. In our practice we expect a small improvement after 3–7 days of treatment in mildly depressed young patients and expect the improvement to take longer in severely older depressed patients. However, the AD dosage should start at a higher level in severely depressed patients compared to less depressed patients.

One can take advantages of the fact that different monoamines pathways can increase DA release. A new strategy for AD treatment is to mix low doses of AD to augment efficiency and tolerance. This strategy can increase efficacy if the mixed ADs have synergetic effects on DA release and increases tolerance

if the ADs have opposite side effects. *Efficacy*: AD of different mechanisms of action, and drugs known to enhance speed and efficacy of AD response, have synergistic effects on DA release. See **Table 2**. For example, monoamine reuptake inhibitors could be co-prescribed with one or two AD with other mechanism of action (monoamine-oxidase inhibitor, 5-HT2C antagonist, alpha 2 antagonist, 5-HT1A agonist), to promote DA increase. The benefit of AD association has been tested. Mianserine augmentation of fluoxetine treatment increases response in depressed patients, previously not responding to fluoxetine alone (Ferreri et al., 2001). *Tolerance*: Increasing tolerance requires concomitant prescription of several ADs, with different or opposite side effects. The prescribed ADs should have different – and ideally opposite – types of side effect. For example, three ADs each given at a third of the recommended dosage should reduce the adverse effects intensity and possibly increase the type of adverse effects. The strategy becomes interesting when ADs have opposite side effects. For example, sedative antidepressants can be co-prescribed with stimulating ADs, nausea inducing ADs can be prescribed with appetite increasing ADs, libido decreasing ADs can be prescribed with libido increasing ADs. The new strategy predicts that mixing different ADs increases efficacy and tolerance.

CONCLUSION

Our research and literature search indicate that (1) D1 receptors activation (D1 stimulation, DA availability in the prefrontal cortex), is the common denominator of all AD treatments (2) depression appears as a state of D1 receptor deactivation (D1 up-regulation with little DA availability). In our working hypothesis depression is a state of synaptic depression that can be reversed by AD treatment. Indeed ADs promote synaptic potentiation. All ADs enhance DA release in the prefrontal cortex. Activation of D1 receptors induces NMDA activation and an enhancement of synaptic potentiation through an inverted U dose–response curve that could represent a form of mood regulation. The mood improvement, with ADs, has to be in a physiological range, being maximal at the start of treatment and reduced thereafter because of D1 receptors down-regulation.

Based on this understanding, we propose a new strategy for prescribing Ads which consists on a progressive escalating dosage of an association of ADs. Mixing ADs with opposite side effects should increase tolerance. Mixing ADs with synergistic mechanism on DA release should increase efficacy. The strength of an AD can be assessed by the DA release in the prefrontal cortex. The benefit of AD treatment can be valuable in all states of cognitive deficits, even in non-depressed patients.

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