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Differences in multihormonal responses to the dopamine agonist apomorphine between unipolar and bipolar depressed patients

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ABSTRACT

Background: A large number of studies suggest that dopaminergic function may be impaired in depressed patients, particularly in bipolar patients. The dopamine D2/D1 agonist apomorphine (APO) can be useful in the evaluation of dopaminergic function. However, most studies show conflicting results in APO test responses when evaluating unipolar and bipolar depressed patients. Thus, the objective of this study was to apply the APO test to assess whether hypothalamic-pituitary dopaminergic function is altered in unipolar and bipolar depression.
Methods: We evaluated multihormonal responses to APO test (0.75 mg subcutaneous) in 134 drug-free DSM-IV major depressed inpatients (54 with bipolar depression [BD] and 80 with unipolar depression [UD]), compared with 36 healthy controls (HCs). We also examined the cortisol response to the dexamethasone suppression test (DST, 1 mg orally) in all subjects.
Results: No significant differences in prolactin (PRL), cortisol, adrenocorticotropin (ACTH) or growth hormone (GH) baseline values were found across the three groups. ACTH/cortisol and GH responses to APO were also comparable. BD patients showed lower PRL suppression to APO than did UD patients and HCs (both $p < 0.00001$). Although responses to DST were comparable between UD and BD patients, the former exhibited higher post-DST cortisol levels than did HCs ($p < 0.05$).
Conclusions: Our results suggest that BD patients, unlike UD patients, have altered post-synaptic D2 receptor sensitivity at the pituitary level. This alteration does not seem secondary to hypercortisolemia. These findings, if confirmed by other studies with larger samples, may support the use of dopamine agents in BD patients treatment.

1. Introduction

Several studies suggest that dopamine function is altered in depressed patients, as based on evidence of alterations at the genetic level, transmission system and neuronal function. However, the role of dopamine in depression has been largely displaced in the research by the interest in the noradrenaline and serotonin containing circuits (Dunlop and Nemeroff, 2007).

On the other hand, the dopaminergic hypothesis has been raised in bipolar disorder. According to this model, a decreased central dopaminergic activity might underlie the depressive phase of the illness (Tissot, 1975). In fact, dopamine dysfunction has been more often described in bipolar than in unipolar patients (Linkowski et al., 1983; Mokrani et al., 1995; Berk et al., 2007; Cousins et al., 2009; Ashok et al., 2017).

In this line, pharmacological studies using two different dopaminergic agonists, bromocriptine and pramipexole, have shown that both compounds are able to improve symptoms in patients with bipolar depression. However, such results were not found in those with unipolar depression (Silverstone, 1984; Goldberg et al., 2004).

The neuroendocrine response to a subcutaneous (SC) injection of the dopamine (DA) agonist apomorphine (APO) can be useful in the evaluation of dopaminergic function in man (Lal, 1988), especially in psychiatric disorders (Meltzer et al., 1984). APO is a non-selective dopamine agonist which activates both DA D2-like (D2, D3, D4) and D1-like (D1, D5) receptors. APO has also affinity for serotonin receptors (5HT1A, 5HT2A, 5HT2B, and 5HT2C), and α-adrenergic receptors (α1B, α1D, α2A, α2B, and α2C) (Millan et al., 2002).

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It has been suggested that APO decreases prolactin (PRL) secretion via pituitary D2 receptors and stimulates growth hormone (GH) secretion via growth hormone-releasing hormone (GHRH) and adrenocorticotropic hormone (ACTH) secretion via corticotropin-releasing hormone (CRH), stimulating therefore cortisol secretion (Mokrani et al., 1995).

However, most studies to date evaluating hormonal responses to the APO test in bipolar depressed patients (BDs) and unipolar depressed patients (UDs) have reported discordant findings: normal (Casper et al., 1977; Jimerson et al., 1984) or increased (Wieck et al., 1991) GH responses in BDs and normal (Jimerson et al., 1984; McPherson et al., 2003) or blunted (Mokrani et al., 1995; Duval et al., 2000a; Monreal et al., 2005) PRL responses in BDs. So far, no studies have compared hormonal responses to APO in type I and type II BDs.

One reason that may explain these conflicting results may be that the dose of APO used was different in some studies (McPherson et al., 2003). Our group found a blunted PRL suppression using 0.75 mg of APO SC in small samples of BDs compared to UDs (Mokrani et al., 1995; Monreal et al., 2005).

The aim of this study was to assess central dopamine functionality by the hormonal response to the APO in bipolar depressed patients compared with unipolar depressed patients and control subjects. We also explored the hypothalamic-pituitary adrenal (HPA) axis activity with the dexamethasone suppression test (DST) since hypercotisolemia may inhibit PRL and GH secretion (Duval et al., 2006; Schatzberg, 2014; Duval, 2016). Our hypothesis was that the hormonal response to the APO would differ between UD and BD patients, but that HPA axis activity as measured by DST would be similar in both groups.

2. Methods

2.1. Subjects

Patients aged 25–59 years presenting a major depressive episode (DSM-IV) were consecutively recruited between 1998 and 2006, from the inpatient units of the Pôle 8/9, Psychiatric Hospital of Rouffach (France). Before being tested, the patients underwent washout supervised in the hospital to ensure that they were free of all drugs for a minimum of 2 weeks; this two-week period was respect to antidepressant and mood-stabilizing treatment, and a two months period was allowed to antipsychotic treatment. The patients were evaluated with at least two unstructured clinical interviews conducted by an experienced research psychiatrist (J.M-O. or F.D.), and a structured interview (Schedule for Affective Disorders and Schizophrenia-Lifetime Version; Spitzer and Endicott, 1975) conducted by a separate psychiatrist (S.F.). The final diagnoses were reached by consensus of two psychiatrists blind to endocrine results. Those who gave a history of clear-cut episode of mania or hypomania were categorized as bipolar depression, those without such as history as unipolar depression. Bipolar depressed patients were discriminated between type I or type II illness following DSM IV criteria. The severity of depression before testing was measured with the 17-item Hamilton rating scale for depression (HDRS; Hamilton, 1960). All had an initial score of 18 or more.

All patients were free of medical illness. Exclusion criteria were refusal to participate in the study, severe medical comorbidity, current depressive episode with psychotic symptoms or mixed symptoms, history of resistant depression, comorbid substance use, history of severe traumatic brain injury and intellectual disability.

All subjects in the control group were free of concomitant psychiatric and medical illnesses and none had a personal family history of major psychiatric illness.

The study was approved by the local ethics committee, and all subjects provided informed written consent after a complete description of the study. Routine blood tests and physical examination excluded subjects with medically relevant illnesses.

All patients and controls had normal basal hormone values (free thyroxine [FT4], free triiodothyronine [FT3], and TSH). We excluded all patients with a baseline of prolactin higher than 20 μg/L to confirm that the wash-out period defined was sufficient (Mokrani et al., 1995). All subjects included in the study were within 15% of ideal body weight and had received antidepressant treatment in the past. None of the patients had received fluoxetine, monoamine oxidase inhibitor antidepressants, lithium salts, long-acting neuroleptics or electroconvulsive therapy within 2 years prior to testing. Women taking oral contraceptives were excluded. Due to the transient increase in PRL and GH at ovulation (Leibenluft et al., 1994), all female subjects were tested outside the periovulatory phase of the menstrual cycle to minimize the influence of the menstrual phase on secretion of these hormones. All subjects were on a caffeine-restricted diet for at least 3 days before testing. In addition, to avoid a possible phase shift in nyctohemeral rhythm between patients and controls, their environment was synchronized, with diurnal activity from 0800 to 2300 h and nocturnal rest (sleep).

2.2. Procedures

On day 1, the DST was started at midnight, with oral ingestion of 1 mg of dexamethasone (Dectancyl, Laboratoires Roussel, Paris, France); blood samples were then collected for cortisol assay at 0800, 1600, and 2300 h the following day (Carroll et al., 1981).

On day 4, an APO test (SC injection of 0.75 mg Apokinon, Laboratoires Agettant, France) was carried out at 0900 h. The single dose of APO used was the same administered in the original test description in healthy volunteers and that was safe (Lal et al., 1972), and confirmed as a subemetic dose (Meltzer et al., 1984). After an overnight fast, subjects were awakened at 0700 h, and a cannula was inserted into a forearm vein and kept open with an isotonic saline infusion. Three baseline blood samples (at −30, −15 and 0 min) were drawn before APO administration, and further samples for assaying PRL, GH, ACTH, and cortisol were collected at 15, 30, 60, 90, 120 and 150 min (Mokrani et al., 1995). Throughout the test, the subjects remained in bed and did not smoke.

2.3. Assay procedures

Blood samples were immediately centrifuged at 3000 rpm and 4 °C; serum samples were then stored at −20 °C until used for assays. All hormone concentrations were determined by immunoassay techniques based on enhanced luminescence. The average intra-assay and inter-assay coefficients of variation were as follows: ACTH, 2.7–7.9%, sensitivity = 1 ng/L (Nichols Advantage® ACTH, Nichols Institute Diagnostics, San Juan Capistrano, CA, USA); GH, 3.9–7.5%, sensitivity = 0.1 μg/L (Nichols Advantage ® hGH, same supplier); PRL, 5.5–6%, sensitivity < 1.3 μg/L (Prolactin Assay, Amersham International plc, Amersham, UK); and cortisol, 6.2–8.9%, sensitivity < 3 nmol/L (Amerlite Cortisol Assay, same supplier), respectively.

2.4. Statistical analysis

The highest post-DST serum cortisol value in any blood sample obtained at 0800, 1600, and 2300 h on day 2 was used to evaluate the cortisol response to the DST.

Serum baseline PRL (PRLB), ACTH (ACTHB), and cortisol (cortisol B) values were defined as the level at time 0 (i.e., immediately before APO injection). This value was chosen rather than the mean of the three samples before APO administration because PRL, ACTH and cortisol concentrations exhibit a marked decrease in the morning due to the normal circadian rhythm (Mokrani et al., 1995; Duval et al., 2000b; Duval, 2003). Changes in ACTH and cortisol were expressed as the peak concentration after APO administration minus the baseline concentration value (Δ). The PRL response to APO was expressed as percentage of change from baseline according to the formula $PRL_S = (PRLS_{AUC}/PRLB_{AUC}) \times 100$ (Meltzer et al., 1984), where $PRLB_{AUC}$ is the basal PRL area under the curve (calculated as follows: PRLB x 150 min) and $PRLS_{AUC}$ is the PRL suppression area (defined as the difference between PRLAUC and PRLAUC after APO

administration). Serum baseline GH values were defined as the mean of the three samples (at −30, −15 and 0 min) before the APO test (GHB). The GH response to APO is expressed as the maximum increment above the baseline value (ΔGH). An inclusion criterion was GHB < 2 μg/L after washout and before APO (Mokrani et al., 1995).

All statistical analyses were computed using StatView (SAS Institute Inc, Cary NC, USA). Since the distribution of some data remained non-normal, we used nonparametric statistical methods. Differences between the three groups were examined by nonparametric analysis of variance (the Kruskal-Wallis H test). Differences between two groups were evaluated by the Mann-Whitney two-tailed test (*U* test), corrected with Bonferroni's method for multiple comparisons. Correlations between quantitative variables were estimated using the Spearman rank coefficient (ρ). Categorical data were analyzed by Fisher's exact test (two-tailed). Results were considered significant at $p \leq 0.05$. Post hoc power analysis was determined by OpenEpi statistical analyzing software (version 3.01).

3. Results

Characteristics of the 170 subjects are shown in Table 1. Seven patients declined to participate in the study, the main cause was their clinical status that did not allow for the washing period to be tolerated.

The control subjects (n = 36), and unipolar (n = 80) and bipolar (n = 54) patients were comparable with regard to age and sex. Similar HDRS scores were obtained for the depressed bipolar and unipolar patients. Table 2 shows the main data for the bipolar patients, discriminating them as having type I or type II illness.

3.1. Apomorphine test

No significant differences in cortisol, ACTH, PRL or GH baseline values were found among the 3 groups. ACTH/cortisol and GH responses to APO were comparable for the UD and BD patients and HCs. However, as illustrated in Fig. 1, the BD patients displayed significantly lower APO-induced PRL suppression (PRL_S) than did the HCs ($p < 0.00001$) and UD patients ($p < 0.00001$). PRL_S values were comparable in the type I and type II bipolar patients. Moreover, levels of hormones (PRL, GH, ACTH, and cortisol before and after APO) were not significantly influenced by age or sex in the overall population or in each group. GH and PRL responses to APO were unrelated to ACTH/cortisol responses. A post hoc power analysis showed that the study was sufficiently powered to detect a meaningful difference in PRL_S between BD patients and UD patients and HC respectively (100% power). The power analysis of this comparison between UD patients and HCs was lower (19, 4% power).

Table 1
Demographic characteristics and responses to the apomorphine test and dexamethasone suppression test in controls and in depressed patients.

	DEPRESSED PATIENTS		
	CONTROLS	Bipolar	Unipolar
AGE, years	35.6 ± 9.1	38.1 ± 6.3	39.1 ± 10.2
GENDER, M/F	21M/15F	33M/21F	43M/37F
HAMD	.....	25.5 ± 5.1	24.8 ± 4.7
PRL B (1)	10.6 ± 5.2	11.4 ± 5.8	11.2 ± 7.4
PRLs (2)	40.6 ± 10.4	21.1 ± 15.5 ****††††	38.4 ± 14.5
ACTHB	28.3 ± 19.0	31.4 ± 21.4	25.6 ± 13.1
ΔACTH (3)rowhead	58.5 ± 108.0	44.5 ± 73.2	35.8 ± 55.4
Cortisol B	326 ± 135	307 ± 124	331 ± 121
Δcortisol	168 ± 176	98 ± 124	105 ± 132
GHB (4)	0.5 ± 0.8	0.3 ± 0.9	0.7 ± 0.8
ΔGH	12.4 ± 9.4	12.6 ± 10.45	12.6 ± 9.0
DST Cortisol (5)	45 ± 31	93 ± 124	106 ± 108 §

The results are expressed as the mean ± SD. M/F male/female, HDRS Hamilton Rating Scale for Depression (17 item), (1) Baseline (B) prolactin (PRL) values at 8 AM (μg/L); (2) prolactin suppression (%); (3) maximum increment in serum corticotrophin level above (ΔACTH); (ng/L); (4) Δ growth hormone (μg/L); (5) highest pos DST values (nmol/L). Comparisons with Mann-Whitney two-tailed test (all p values are corrected with Bonferroni's method for 3 pairwise comparisons): ****p < 0.00001, bipolar patients vs. control subjects; ††††p < 0.00001, unipolar vs. bipolar patients; §p < 0.05, unipolar patients vs. control subjects.

Table 2
Demographic characteristics and PRL responses to the apomorphine test in type I bipolar patients (BD I) and type II bipolar patients (BD II).

	BD I	BD II
AGE, years	30.5 ± 11.4	38.9 ± 10.8
GENDER, M/F	23M/14 F	10M/7F
HAMD	25.6 ± 5.2	25.2 ± 4.9
PRLs (1)	19.8 ± 14.6	21.3 ± 15.4

Results are expressed as the mean ± SD. M/F male/female, HDRS Hamilton Rating Scale for Depression (17 item), (1), prolactin suppression (%).

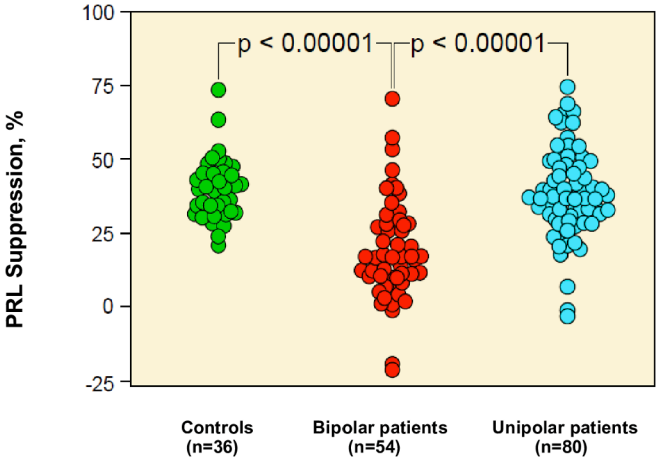

Fig. 1. Prolactin suppression in response to the apomorphine test in controls and patients. Bipolar patients had lower APO-induced PRL suppression than did controls and unipolar patients (both $p < 0.00001$).

3.2. Dexamethasone suppression test

Responses to DST were comparable between UD patients and BD patients, though the UD patients had higher post-DST cortisol levels than did the HCs ($p < 0.05$) (Fig. 2). When defining DST non-suppression as a plasma cortisol level in excess of 130 nmol/l in any of the three samples (0800 h, 1600 h, and 2300 h) (Carroll et al., 1981), the groups of BD and UD patients showed a comparable distribution of DST nonsuppressors (13 BDs and 27 UDs).

4. Discussion

According to a literature review, the populations evaluated in this study are the largest samples of unipolar and bipolar depressed patients assessed using the APO test.

4.1. PRL response to APO

It is generally admitted that the PRL response to APO evaluates the function of the pituitary post-synaptic D2 receptors since tuberoinfundibular DA neurons inhibit the release of PRL via D2 receptors (Meltzer et al., 1984; Lal, 1988; Mokrani et al., 1995; McPherson et al., 2003; Duval et al., 2006). The activity of this system is influenced by many factors (for a review, see Duval, 2016). In our population, we found no significant influence of sex or age on the PRL response to APO. Corticotropic axis activity may exert an inhibitory influence on PRL secretion. Although we found significant differences in DST results

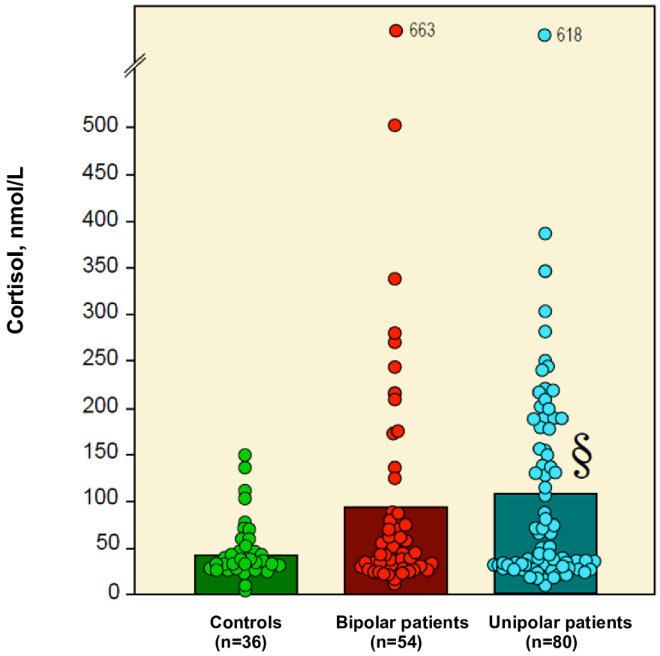

Fig. 2. Cortisol response to the dexamethasone suppression test (DST, 1 mg orally) in controls and patients (bipolar and unipolar depressed patients). Responses to DST were comparable between unipolar and bipolar patients, though unipolar patients had higher post-DST cortisol levels than did control subjects (§: $p < 0.05$).

between depressed patients and controls in our study, depressed bipolar patients and controls showed comparable post-DST cortisol responses. Finally, the two-week period of therapeutic withdrawal appears to be sufficient to avoid a residual effect of previous antidepressant therapies on the PRL response to APO (Pitchot et al., 1995). Therefore, alteration of the PRL response to APO cannot be considered to be an artifact of factors influencing PRL secretion in our study.

The findings suggest afunctional alteration of DA D2 pituitary receptor in BD patients, as reflected by the blunted response of PRL to the APO test. This alteration is not found in UD patients. This results in line with the hypothesis of the pathophysiology of bipolar disorder that suggests alteration in the homeostasis of post-synaptic DA receptors as well as the DA transporter. To date, there has been a lack of studies focusing on post-synaptic DA receptors in bipolar depression (Ashok et al., 2017).

Our current results replicate results previously published by our group (Monreal et al., 2005) with a more extensive population. In fact, only depressed type II bipolar patients were included in a previous study (Monreal et al., 2005), whereas we included bipolar type I and II patients in the current study and found comparable responses of PRL to APO in the two subgroups.

Nonetheless, our results do differ from previously published results. One reason for such differences is that few studies draw a distinction between unipolar and bipolar patients (for a review, see Lal, 1988). In a study that did involve this distinction, McPherson et al. (2003) found that the PRL response to the APO test was normal in both depressed bipolar and unipolar patients. However, the doses of APO used varied from 0.005 mg/kg to 0.008 mg/kg (as opposed to the 0.75 mg we used), and the results were presented in absolute values and not in relation to baseline, as in our study. These methodological differences may explain the divergent results between the McPherson et al. study and ours.

4.2. ACTH, cortisol and GH responses to APO

We found no significant differences between unipolar, bipolar and healthy subjects with regard to ACTH, cortisol and GH responses to APO, confirming some previously published results (Duval et al., 2000a; Lal, 1988; Meltzer et al., 1984; Mokrani et al., 1995; Monreal et al., 2005). However, the results differ from those of Ansseau et al. (1988) and Pitchot et al. (1992), who found decreased responses of GH with a lower dose of APO (0.5 mg SC) in depressed patients with a history of attempted suicide. These latter results are not comparable with the results from the present study because the dose of APO is a determining factor: 0.5 mg of apomorphine does not significantly stimulate ACTH and cortisol. Regardless, it is possible that the dose we used (0.75 mg SC APO) excessively stimulated GH, overriding hypofunctionality of the dopaminergic receptors involved in its regulation.

4.3. Limitations of the present study

Some shortcomings in our study require discussion. First, as in most studies using the APO test, plasma concentrations of APO were not measured. However, the fact that ACTH/cortisol and GH responses were comparable across bipolar, unipolar and control patients suggests that alteration of the response of PRL to APO was not due to pharmacokinetic differences between the three groups. Furthermore, the results of our study suggest that the decrease in PRL suppression in response to APO in depressed bipolar patients was not due to hyperactivity of the HPA axis. This decrease would therefore be explained by altered sensitivity of dopaminergic D2 post-synaptic receptors at the pituitary level.

Secondly, the DA system is complex, with regional and neuronal differences. The limitation of our work is that the APO test only evaluates dopaminergic function at the hypothalamic-pituitary level.

Another limitation of the study was that we did not analyze the prevalence of atypical features in the two groups of depressed patients. It is possible that the proportion of atypical cases of depression may vary between UD and BD patients as previous studies suggest that atypical features of depression are more prevalent in BD (Goodwin et al., 2008). However, responses to DST were comparable between UD and BD patients, and therefore the proportion of patients with atypical characteristics probably did not influence the results.

On the other hand, although we did not administer the Young Mania Rating Scale (YMRS) as some authors propose to assess the series of manic symptoms during depression (Fornaro et al., 2016), patients were evaluated by two different psychiatrists who excluded patients with mixed episodes according to DSM IV criteria. Nor did we analyze whether clinical aspects such as suicide history, number of episodes or age at onset of the disease could influence the results.

Finally, one factor that we did not consider in our study was to determine whether the differences in PRL responses to the APO test were due to functional alteration of lactotroph cells. However, this hypothesis was ruled out in a previous study (Monreal et al., 2005), in which we found a comparable PRL response to the protirelin (TRH) test between depressed unipolar patients and depressed bipolar patients and controls. In that previous study, we observed a blunted PRL response to APO in depressed bipolar patients, as in the current study. Moreover, given the complexity of the PRL regulation, we cannot rule out the involvement of additional hypothalamo-pituitary mechanisms in the blunted PRL response to APO in BD patients. Serotonin is also a PRL-releasing agent via stimulation of 5-HT1A and/or 5HT2A/2C receptors (for review see Lyon and Broberger, 2014). Since APO binds at 5HT2C/2A and 5HT1A receptors, the blunted PRL response to APO in BD patients could also reflect an increased activity of 5 HT receptors. Indeed, some previous studies reported that brain 5HT1A receptor binding measured by positron emission tomography is higher in unmedicated bipolar depressed patients (Lan et al., 2013).

In conclusion, the results of our study show that bipolar depressed patients have altered post-synaptic D2 receptor sensitivity at the tuberoinfundibular dopamine level, as determined by the PRL response to the APO test. This alteration is not present in unipolar depressed patients. These findings, if confirmed by other studies with larger samples,

may support the use of dopamine agents in the treatment of bipolar depressed patients.

Thus, in this line, the therapeutic efficacy in bipolar depression of atypical antipsychotics such as D2 partial agonists (namely, aripiprazole, brexpiprazole, and lurasidone) and all of those featuring fast post-synaptic D2 dissociation time, it could be explained by its modulating effect on the dopaminergic system (Kapur and Seeman, 2001).

On the other hand, some atypical antipsychotics with a differential mechanism such as cariprazine, are receiving attention as a possible treatment of bipolar depression: Cariprazine is a novel antipsychotic drug that exerts partial agonism of dopamine D2/D3 receptors with preferential binding to D3 receptor, antagonism of 5HT2B receptors and partial agonism of 5HT1A. According to is pharmacodynamic profile, cariprazine could be useful at lower doses for depression bipolar, to emphasize its agonist actions and potentially its uniquely D3 -preferring properties (De Berardis et al., 2016).

Conflicts of interest

No conflict of interest is declared.

Role of the funding source

Funding for this study was provided by inner hospital sources (Centre Hospitalier, Rouffach). No outside parties had any role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

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