Current Neuropharmacology, 2017, *15*, 315-323

REVIEW ARTICLE

Psychotic Symptoms Associated with the use of Dopaminergic Drugs, in Patients with Cocaine Dependence or Abuse

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ARTICLE HISTORY

Received: September 23, 2015
Revised: December 29, 2015
Accepted: March 10, 2016

DOI: 10.2174/1570159X14666160324144912

Abstract: ***Background*:** In the field of dual diagnosis, physicians are frequently presented with pharmacological questions. Questions about the risk of developing psychotic symptoms in cocaine users who need treatment with dopaminergic drugs could lead to an undertreatment.

***Objective*:** Review the presence of psychotic symptoms in patients with cocaine abuse/dependence, in treatment with dopaminergic drugs.

***Methods*:** Systematic PubMed searches were conducted including December 2014, using the keywords: "cocaine", dopaminergic drug ("disulfuram-methylphenidate-bupropion-bromocriptine-sibutramine-apomorphine-caffeine") and ("psychosis-psychotic symptoms-delusional-paranoia"). Articles in English, Spanish, Portuguese, French, and Italian were included. Articles in which there was no history of cocaine abuse/dependence, absence of psychotic symptoms, systematic reviews, and animal studies, were excluded.

***Results*:** 313 papers were reviewed. 7 articles fulfilled the inclusion-exclusion criteria. There is a clinical trial including 8 cocaine-dependent patients using disulfiram in which 3 of them presented psychotic symptoms and 6 case-reports: disulfuram (1), methylphenidate (1), disulfiram with methylphenidate (2), and bupropion (2), reporting psychotic symptoms, especially delusions of reference and persecutory ideation.

***Conclusion*:** Few cases have been described, which suggests that the appearance of these symptoms is infrequent. The synergy of dopaminergic effects or the dopaminergic sensitization in chronic consumption are the explanatory theories proposed by the authors. In these cases, a relationship was found between taking these drugs and the appearance of psychotic symptoms. Given the low number of studies found, further research is required. The risk of psychotic symptoms seems to be acceptable if we compare it with the benefits for the patients but a closer monitoring seems to be advisable.

Keywords: Bupropion, cocaine, disulfiram, dopaminergic drugs, methylphenidate, psychotic symptoms.

INTRODUCTION

Dopamine (DA) is a neurotransmitter which participates in various cognitive functions, such as attention and concentration [1]. Additionally, its involvement in facilitating learning mediated by the reward system, in memory [2], in craving, and in substance dependence [3], has been demonstrated. Furthermore, an increase of DA in the mesolimbic system is linked with emotional conduct and positive psychotic symptoms, and in the mesocortical system with negative symptoms [4].

There are different substances which act *via* different pathways, as direct and indirect dopamine agonists, such as inhibition of reuptake through blockage of the presynaptic membrane transporter (cocaine) [5], inhibition of the metabolization of dopamine in the neuronal synapses (disulfiram) [6], or as agonists of the post-synaptic dopamine receptors (bromocriptine) [7].

Cocaine (benzoylmethylecgonine) is a tropane crystal alkaloid which is extracted from the leaves of the coca plant. It is a serotonin (5-HT), DA and noradrenaline (NA) reuptake inhibitor [8], which facilitates dopaminergic transmission in the cerebral cortex [9] and prefrontal cortex [10]. The principal functional and addictive properties of cocaine appear to be produced by actions on dopaminergic neurotransmission systems, particularly in mesostriatal areas [11-14]. The increase in DA has been associated with the

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1875-6190/17 $58.00+.00

presence of psychotic symptoms [12]. According to studies, between 29 and 75% of patients (or possibly more) with cocaine dependence experience psychotic symptomatology during their life-time [15, 16]. The psychotic symptoms most frequently associated with cocaine consumption are ideation and delusions of reference, persecutory ideation, and auditory/verbal hallucinations [16].

On the other hand, various drugs and substances have a direct or indirect dopaminergic effect and have even been trialed as treatment for cocaine dependence [8]. Among the most frequently used are:

- Disulfiram blocks the metabolism of alcohol through the inhibition of aldehyde dehydrogenase (ALDH), for which is has been used as an interceptor in patients with alcohol dependence [17]. In addition, it acts as an inhibitor of the enzyme dopamine beta-hydroxylase (DBH) blocking conversion of DA to NA, for which it has been used in the treatment of patients with cocaine dependence [18].
- Methylphenidate is a potent DA and NA reuptake inhibitor. At the presynaptic level it produces liberation of DA and NA (indirect agonist), while at a postsynaptic level it acts as a direct agonist. In this manner, it significantly increases the concentration of these neurotransmitters in neuronal synapses. Methylphenidate is used in the treatment of Attention Deficit Hyper-activity Disorder (ADHD) [19], as a stimulator in depressive disorders which include psychomotor inhibition, in narcolepsy, and in some eating disorders [20]. In patients with cocaine dependence, it has been used to treat ADHD [21, 22] comorbidity, leading some authors to conclude that its use during childhood may reduce substance use in adolescence and adulthood [23].
- Bupropion is derived from diethylpropion (appetite-suppressant amphetamine) which acts as a selective reuptake inhibitor of DA, and to a lesser degree, NA. Its efficiency has been demonstrated in reducing the symptoms associated with nicotine-withdrawal syndrome, detoxification of cocaine dependence in patients undergoing methadone treatment [8], and for treatment of depression in patients who have not responded adequately to other antidepressants [24].
- Bromocriptine is an ergot derivative with D2 receptor dopaminergic agonist effects, which is used for the treatment of pituitary disorders and Parkinson's Disease [25]. Due to the dopaminergic effects, it has been proposed as a pharmaceutical option in treatment for cocaine dependence and detoxification [26].
- Sibutramine is a 5-HT, NA and DA reuptake inhibitor. It has been used in treatment of obesity, due to its appetite-suppressant effects. However, it is currently withdrawn from the market on account of its addictive properties, and psychiatric and organic side effects, most notably cardiovascular [27].
- Apomorphine is a dopaminergic agonist of D1 and D2 cerebral receptors. At low doses it behaves like an agonist of the presynaptic dopaminergic receptors, producing inhibition of the liberation and synthesis of DA, and as such acts like an antagonist. At higher doses it behaves like a dopaminergic agonist of postsynaptic receptors [28]. Among its immediate action highlights the induction of yawning, erection and vomiting. It has been used in clinical practice in the treatment of erectile dysfunction and Parkinson's Disease. In addicted patients, apomorphine has been used as a biomarker to diagnose early relapses in consumption [29].
- Caffeine is a methylxanthine of vegetable origin with stimulant properties that are similar to those of cocaine and amphetamine [30]. The psychostimulant effects of caffeine and other methylxanthines include a dopaminergic component. The functional antagonistic interaction between adenosinergic and dopaminergic transmission makes up the currently accepted hypothesis about the prodopaminergic effects of methylxanthines, even though a direct dopaminergic effect cannot be excluded [31]. Methylxanthines have been used with relative efficacy in the treatment of ADHD [32], Parkinson's Disease [33], extrapyramidal side effects resulting from long-term neuroleptic treatment [34], essential tremor [35], and has been proposed as a medical treatment of cocaine detoxification [36].

Given the use of these dopaminergic drugs in cocaine users and given that they are prescribed for treating other comorbidities (as, for example, ADHD or alcoholism) and given that there are some hopeful results that encourage further research with some of these drugs for treatment cocaine dependence [8], all the side effects related to the interactions between cocaine and the dopaminergic drugs should be studied in depth. There is a special interest in clinically relevant symptoms, such as the psychotic symptoms (frequently described in cocaine users) [15, 16], as well as in the fact that, hypothetically, these symptoms could be related with the increased levels of dopamine produced by dopaminergic agents [5-11].

The objective of this article is to revise current existing data about the relation between the appearance of psychotic symptomatology and the use of drugs with dopaminergic effects, in patients with cocaine abuse or dependence and the concern about the risk of psychotic symptoms which can lead to an undertreatment.

MATERIAL AND METHODS

A systematic PubMed search of articles published up and including December 2014 was performed, with the keywords “cocaine”, dopaminergic drugs (“disulfiram”, “methylphenidate”, “bupropion”, “bromocriptine”, “sibutramine”, “apomorphine” and “caffeine”) and “side effects” (psychosis / psychotic symptoms / delusional / paranoia). Articles written in English, Spanish, Portuguese, French, and Italian were included, but articles in which patients did not present a history of current or previous cocaine dependence or abuse, articles in which no psychotic symptoms were reported, systematic reviews and animal studies, were excluded. The large volume of studies found was due to the inclusion of the keyword “side effects”, since both psychiatric and somatic side effects are included in this term (Table **1**).

Table 1. Selection of articles.

Methylphenidate 83 papers	Bupropion 29 papers	Disulfiram 32 papers	Bromocriptine 33 papers	Caffeine 90 papers	Apomorphine 45 papers	Sibutramine 1 paper	TOTAL 313 papers
			→ Repeated articles: 32				↓
71	25	23	33	87	41	1	281
			→ Articles in other languages:14				↓
69	25	22	32	78	40	1	267
			→ Reviews: 68				↓
50	23	19	23	48	35	1	199
			→ Animal studies: 40				↓
41	21	18	20	42	16	1	159
			→ No cocaine abuse/dependence and/or no psychotic symptoms or other unrelated articles: 152				↓
3*	2	2*	0	0	0	0	**7 selected**

*Two papers include both methylphenidate and disulfiram. These papers have been included only in the methylphenidate column to avoid duplications.

RESULTS

On completion of the search process, seven articles described the appearance of psychotic symptomatology in patients with prior or current cocaine dependence or abuse, who were treated with dopaminergic drugs, and fulfilled the specified criteria. Two articles in relation to disulfiram, one article in relation to methylphenidate, two in relation to the interaction between methylphenidate and disulfiram, and two referring to bupropion. In two of the articles, both disulfiram and methylphenidate were used, and as such they appeared repeatedly in each search. Finally, they were included in the section of methylphenidate, since the psychotic symptoms are seen to appear when the dose of methylphenidate, maintaining the dose of disulfiram constant (Table **2**).

Disulfiram

In a clinical trial, Haamedi *et al*. (1995) proposed that disulfiram, when used in patients with cocaine dependence, interferes directly with the euphoric effects of cocaine. They studied six men and two women, during nine days in an in-patient unit. Four subjects received disulfiram (250mg) on days one and two and placebos on days eight and nine, and the remaining four subjects completed the reverse process. Additionally, 2mg/kg of cocaine was administered intranasally one hour after administering the drug. During the administration period, three subjects presented psychotic symptomatology. One female subject presented mutism, hypervigilance, and ideas of reference. One male subject, with a previous history of cocaine-induced paranoia, presented persecutory ideation towards the investigators. Finally, another male subject presented suspiciousness and persecutory ideation (poisoning) towards the staff. The authors suggested a dose dependent theory of the effects of cocaine and dopaminergic drugs, to justify the observed psychotic symptomatology [37].

Mutschler *et al*. (2009), described the case of a 31-year-old male with an eight-year history of intranasal cocaine dependence, without a history of psychotic symptoms induced by cocaine, in whom disulfiram (250mg) was used as medical prevention of relapse of cocaine abuse. The medication was introduced during admission for detoxification, and was later maintained during out-patient follow-up. After eight months of abstinence, the patient suffered a relapse of cocaine consumption, on the day that treatment was omitted. On the third day the patient attended an assessment unit, with a presenting complaint of sensory hyperesthesia (light and sound sensitivity), after consuming 1g of cocaine intranasally. Later, the patient consumed a further 1g of cocaine intranasally, presenting an hour later with delusions of reference, delusional ideation, illusions, kinesthetic hallucinations, increased anxiety and insomnia. The authors attributed the psychotic symptoms to the theory of additive interaction between dopaminergic drugs and cocaine [38].

Table 2. Results.

Study & Year	Drug	Sex	Age Years	Psychiatric History	Other Active Treatments	Substance Abuse or Dependence	Psychotic Symptoms	Resolution of Symptoms
Haamedi *et al*. 1995	Disulfiram 250 mg	1 F 2 M	NS	No	No	Cocaine dependence (active). Alcohol abuse (not active).	Delusions of reference and persecutory ideation. (One patient had a history of psychotic symptoms only during cocaine consumptions)	Cocaine and disulfiram cessation
Mustler *et al*. 2009	Disulfiram 250 mg	1 M	31	No	No	Cocaine dependence (active).	Delusions of reference, persecutory ideation, and kinaesthetic hallucinations.	Cocaine and disulfiram cessation
Caci and Baylé. 2007	Disulfiram 400 mg and MPH 36 mg	1 M	33	ADHD	No	Cocaine abuse (not active).	Visual hallucinations.	Symptoms only appear when disulfiram and MPH are prescribed at the same time.
Grau-López *et al*. 2012	MPH slow release (increasing dose to 54 mg) and Disulfiram 250 mg	1 M	31	BPD, ADHD, PPD	No	Cocaine dependence (not active).	Delusions of reference, persecutory ideation and auditory hallucinations.	Olanzapine 10mg, MPH cessation but not disulfiram
Delavenne *et al*. 2012	MPH slow release 30 mg	1 M	43	ADHD	No	Cocaine dependence (active). Cannabis dependence (not active)	Delusions of reference, persecutory ideation, visual and auditory hallucinations. (The patient had a history of psychotic symptoms only during cocaine consumptions but never hallucinations)	Cocaine cessation, Olanzapine 20mg and MPH cessation.
Farooque *et al*. 2010	Bupropion 100 mg/12h	1 F	47	PTSD, MDD	Escitalopram 20mg, Trazodone 100mg.	Cocaine abuse (not active).	Delusions of reference, persecutory ideation, visual hallucinations.	Bupropion cessation and Paliperidone 3mg
Hahn *et al*. 2007	Bupropion 150 mg	1 M	41	MDD	Methadone 80mg	Cocaine abuse (not active). Opioid analgesic dependence (not active)	Persecutory ideation, magic capabilities. (The patient had a history of psychotic symptoms only during cocaine consumptions)	Bupropion cessation and quetiapine 25mg

M= male; F= female; NS=not specified; MPH= methylphenidate; ADHD= Attention Deficit/Hyperactivity Disorder; BPD= Borderline Personality Disorder; PPD: Paranoid Personality Disorder; PTSD: Posttraumatic Stress Disorder; MDD= Major Depressive Disorder.

Methylphenidate

Caci H. and Bayle F. (2007) described the case of a 33-year-old male, with a history of cocaine dependence, who was admitted to an intensive care unit upon presentation of a seizure, and was diagnosed during his admission with alcohol abuse. After a one-month admission period, he was transferred to another unit, where treatment with disulfiram 400mg/day was initiated, without suffering any side effects. During the admission he was diagnosed with ADHD. On discharge he began treatment with methylphenidate for the first time, at 36mg a day. After the first dose, visual hallucinations were reported which lasted until the evening of the same day, and were reported by the patient as being subjectively similar to those induced by acute cocaine intoxication. Following this episode, treatment with methylphenidate was withdrawn, but disulfiram was maintained. Two months later the diagnosis of ADHD was confrimed during an out-patient appointment; the absence of any psychotic symptoms was reported at that time. Three months later disulfiram was withdrawn, and methylphenidate was reintroduced at a dose of 36mg/day, increasing to 54mg/day during the following three months, without any recurrence of the psychotic symptoms [39].

Grau-López *et al*. (2012), reported a case of 31-year-old male with a history of dependence on alcohol (60-100g/day) and cocaine (2g/week), mixed borderline-paranoid personality

disorder and ADHD, who was admitted to a hospital unit for detoxification of both substances. During the out-patient follow-up, treatment with disulfiram 250mg/day and methylphenidate slow release at an increasing dose, were initiated, without cocaine relapse. Upon reaching 54mg/day of methylphenidate, the patient presented psychotic symptoms, consisting of delusions of reference, suspiciousness, persecutory delusions, auditory and other hallucinations, and thought block. Methylphenidate was withdrawn, while disulfiram was maintained and olanzapine 10mg/day was introduced, with a complete remission of the symptoms within two weeks. The authors made reference to the dose-dependent theory of the dopaminergic effects of the drugs used [40].

Delavenne *et al*. (2012) reported a case of a 43-year-old male with crack cocaine and cannabis dependence, who began out-patient follow-up with complete abstinence from first contact with the services. In the personal history, episodes of psychotic symptoms during intoxication were described. During the first month of abstinence, the patient was diagnosed with ADHD after a meticulous assessment. After two months of abstinence methylphenidate sustained release was introduced (30mg/day), with an improvement in symptoms. However after ten days of treatment, and having consumed cocaine in the two previous days, the patient was hospitalized with auditory and visual hallucinations, delusions of reference, and persecutory delusions. Treatment with methylphenidate was withdrawn, and olanzapine was initiated at a dose of 20mg and continued for a period of two months, after which the patient did not suffer any further psychotic episodes. In the discussion, the dose-dependent hypothesis of dopaminergic substances was postulated [41].

Bupropion

Farooque *et al*. (2010), described the case of a 47-year-old African American woman with mild recurrent major depressive disorder, posttraumatic stress disorder, and cocaine use (in early full remission). Due to complaints of low energy levels in the context of a depressive episode, she was started on bupropion at 100mg twice a day. After four months of treatment, psychotic symptoms of delusions of reference, paranoid ideation, social isolation and visual hallucinations of shadows, were observed. Bupropion was withdrawn and paliperidone 3mg was introduced, with subsequent remission of the symptoms. The authors explained the appearance of the symptoms using the theory of sensitization of the dopaminergic system [42].

Hahn *et al*. (2007), presented the case of a 41-year-old male with a history of multiple substance abuse (including cocaine, from 19 to 27 years of age, which was discontinued on presentation of psychotic symptoms) and major depressive disorder. On suffering a new episode of depression, the patient had a relapse of cocaine consumption and twelve weeks later presented in the Emergency Department. He was using cocaine for five weeks, after which he recommenced treatment with bupropion, which he had used as treatment in the past. He reported that in the one to two hours *a posteriori* to administration of bupropion 150mg, he presented a feeling of being "under a spell", he felt afraid, suffered persecutory delusions and had a sensation of being able to predict the future. These symptoms would last approximately two hours and afterwards receded spontaneously. Whenever the patient missed a dose of bupropion, these episodes did not occur. On withdrawal of treatment with bupropion and introduction of quetiapine 25mg/day, the symptoms did not recur. The authors proposed the dose-dependent effect of dopaminergic drugs as an explanation for these symptoms [43].

DISCUSSION

Despite the breadth of the search, which included seven dopaminergic drugs, only seven articles were found. There is a clinical trial including eight cocaine dependent patients using disulfiram in which three of them presented psychotic symptoms and six case-reports (one for disulfuram, two for methylphenidate, one with both disulfiram and methylphenidate, and two for bupropion) reporting psychotic symptoms, specially delusions of reference and persecutory ideation.

Given that the distribution of cocaine consumption in the general population is approximately three men for each woman [44], this proportion is congruent with the prevalence of patients with cocaine abuse or dependence.

The number of cases of psychotic symptoms detected in patients with cocaine abuse or dependence in which dopaminergic drugs are prescribed is minimal despite their broad range of use in psychiatric pathology. As such, a higher frequency of the appearance of psychotic symptoms would be expected, than was found in this literature review.

Methylphenidate is one of the treatments of choice for ADHD, which is a disorder with a prevalence of 15-25% of patients with abuse or dependence of cocaine [45, 46]. Disulfiram is used in patients with alcohol and cocaine dependence [47]. Meanwhile, given that depressive disorders are very prevalent in patients with cocaine dependence [48], bupropion is a drug that is frequently used [24].

The low detection rate of psychotic symptoms associated with dopaminergic drugs may be explained by several theories. The appearance of cocaine-induced psychosis (CIP) is very frequent (up to 86.5%) in cocaine users [16, 49]; as such, psychotic symptoms may be attributed to consumption and not to the concomitant administration of dopaminergic drugs. On the other hand, it is possible that subthreshold symptoms exist that are not detected. Finally, it may be hypothesized that the association is infrequent, given that to produce this type of symptom, prior damage at the level of the dopaminergic system produced by chronic cocaine consumption is necessary, but also a certain genetic vulnerability also appears to be necessary [50, 51]. In all of the reported cases, the psychotic symptoms were of acute onset, enabling the establishment of a temporal relation with the administration of the dopaminergic drug, in most cases. In all of the patients, an early remission of the symptoms was produced on withdrawal of the dopaminergic drug.

Various questions remain. It is difficult to establish, given the paucity of reported cases and the variety of drugs included, whether or not the appearance of these symptoms may be dose-dependent, despite the fact that a previous study

has reported this relation in reference to methylphenidate [40]. The wide range of self-administered doses is also relevant.

On one hand, many of the dopaminergic drugs studied may also be responsible for producing psychotic symptoms [52-58] and these types of symptoms appear frequently in individuals who consume cocaine [15]. In some of the studied cases psychotic symptoms appeared when a dopaminergic drug and cocaine were taken concomitantly [38, 41, 43], and in others, when two dopaminergic drugs were combined [39, 40]. In only one case was there a reported history of CIP without exposure to dopaminergic drugs. This data supports the hypothesis of a dose-dependent effect of the two substances, with an effect on the production of psychotic symptoms by the dopaminergic system [37-41, 43]. The mechanism of action of some of these drugs also supports this theory; for example, disulfiram acts by inhibiting dopamine beta-hydroxylase (DBH) thus increasing the levels of dopamine centrally [59, 60], which explains why the combination of this drug with another dopaminergic substance, such as cocaine, could provoke psychotic symptoms.

On the other hand, the hypothesis of sensitization may be supported by the fact that in one case psychotic symptoms appeared in the absence of concomitant use of dopaminergic substances. Chronic consumption of cocaine can produce damage to dopaminergic neurons [42], and consequently provoke an adaptation of that system [61]. Through sensitization of the D2 receptors in the mesocorticolimbic pathways, dopaminergic hyperactivity may be produced, facilitating the appearance of psychotic symptoms when dopaminergic drugs are administered [62].

The evidence that DBH may be implicated in the pathogenesis of CIP in cocaine users has been supported by some genetic studies [50, 51], in which it has been reported that individuals with low activity of DBH are more susceptible to paranoia induced by cocaine than those who have higher activity of this enzyme; in function of the genotype of DBH present, individuals respond better or worse to disulfiram as treatment of cocaine addiction [50]. These findings support the existence of a genetic susceptibility with regards to the appearance of psychotic symptoms when substances that increase central dopamine levels are administered. However, there are other aspects which ought to be considered, such as the effect of using other drugs; multiple substance use is frequent, for example, cocaine and cannabis [63], and cannabis has been reported to produce CIP in those with cocaine dependence [16, 64].

Finally, as a limitation of this study, it should be pointed out that other stimulants have been proposed for the treatment of cocaine-dependent patients and there are some hopeful results that encourage further research with these drugs, mainly with dextro-amphetamine [8, 65]. Recent clinical trials carried out with extended release amphetamines in cocaine abusers [66] or cocaine-dependent patients [67] should be mentioned.

Previously, in human laboratory studies using dextro-amphetamine in cocaine-dependent participants, no unexpected or serious adverse events were reported [68]. Recently, in cocaine users with ADHD, dextro-amphetamines showed improvement in ADHD symptoms and cocaine abstinence as well as these drugs were well tolerated [66]. In the same way, in another clinical trial those cocaine-dependent patients receiving lisdexamphetamine reported significantly less craving for cocaine than participants receiving placebo [67]. No psychotic symptoms were described in these studies.

To conclude, in the reported cases there appears to be a relationship between the onset of psychotic symptoms and the use of dopaminergic drugs in cocaine users. Although there is not full knowledge on the relationship between cocaine and the dopaminergic system [69], there are currently two principal theories that are used to explain the production of psychotic symptoms. The theory of the additive effect of cocaine and dopaminergic drugs, and the theory that chronic consumption of cocaine produces damage to and subsequent adaptation of the dopaminergic system, facilitating the appearance of psychotic symptoms on administration of these drugs. These theories are not mutually exclusive, and it is probable that other factors influence the appearance of these types of symptoms, such as the use of other substances, or the activity of DBH, which suggests a genetic vulnerability to suffer these symptoms.

Given the low number of reported cases, at this moment it is not possible to establish a causal association between the use of these types of drugs and the appearance of psychotic symptoms in patients with cocaine abuse or dependence. However, given the existence of such cases in the literature, this possibility must be considered on prescription of this type of drug in these patients. We recommend that the physician must be cautious when dopaminergic drugs are prescribed to these patients and these side effects should be evaluated. However, assessing the benefit to these patients, the use of these drugs seems an acceptable risk, being necessary an exhaustive review of prior psychiatric history and a close monitoring, especially during the first weeks of treatment or if two or more dopaminergic medications are simultaneously used, and also during relapses in cocaine consumption.

Given how widely used these drugs are, it is of great importance to complete other systematic studies to elucidate to what degree and in which specific conditions, these drugs could facilitate the appearance of psychotic symptoms in cocaine users. Observational cohort studies with a wide sample of patients with cocaine addiction (distinguishing if there is an active consumption of cocaine or not) who are prescribed dopaminergic agents, could help in this way.

CONFLICTS OF INTEREST AND SOURCE OF FUNDING

No conflicts of interest declared. We received a grant from the Instituto Carlos III: FIS PI13/1911 “Alucinaciones cenestésicas: factor pronóstico en dependientes de cocaína” (Kinaesthetic hallucinations: a prognostic factor in cocaine dependence) and a grant from the Delegación del Gobierno para el Plan Nacional sobre Drogas 2013I044: “Complicaciones clínicas y accidentabilidad asociadas a la presencia de síntomas psicóticos en consumidores de cocaína” (Clinical

Complications and Accident Rate Associated with the Presence of Psychotic Symptoms in Consumers of Cocaine).

ACKNOWLEDGEMENTS

We are grateful for the grant received from the Subdirecció General de Drogodependències (Department of Health, Generalitat de Catalunya) which has enabled us to study cocaine dependence, the grant from the Instituto Carlos III: FIS PI13/1911 "Alucinaciones cenestésicas: factor pronóstico en dependientes de cocaína" (Kinaesthetic hallucinations: a prognostic factor in cocaine dependence), and the grant from the Delegación del Gobierno para el Plan Nacional sobre Drogas 2013I044: "Complicaciones clínicas y accidentabilidad asociadas a la presencia de síntomas psicóticos en consumidores de cocaína" (Clinical Complications and Accident Rate Associated with the Presence of Psychotic Symptoms in Consumers of Cocaine).

We would like to thank Rebecca Oglesby, MD for assisting with the editing of the manuscript and the reviewing English grammar and spelling. We are also grateful to our research team on cocaine dependence for their support, particularly Drs. Begoña Gonzalvo, Joan Alvarós, Ángel Egido, Jesus Pérez-Pazos (Psychiatrist), Constanza Daigre, Laia Rodriguez-Cintas, Nuria Tarifa, Nina Vela and Alejandra Herrero (Psychologists).

REFERENCES

[1] Stahl, S.M.; Pradko, J.F.; Haight, B.R.; Modell, J.G.; Rockett, C.B.; Learned-Coughlin, S. A Review of the Neuropharmacology of Bupropion, a Dual Norepinephrine and Dopamine Reuptake Inhibitor. *Prim. Care Companion J. Clin. Psychiatry,* **2004**, *6*(4), 159-166. [http://dx.doi.org/10.4088/PCC.v06n0403] [PMID: 15361919]

[2] Corominas, M.; Roncero, C.; Casas, M. Corticotropin releasing factor and neuroplasticity in cocaine addiction. *Life Sci.,* **2010**, *86*(1-2), 1-9. [http://dx.doi.org/10.1016/j.lfs.2009.11.005] [PMID: 19914260]

[3] Song, X.G.; Lü, H.; Cai, X.H. Survey of studies on drug abstinence with acupuncture in recent 10 years. *Zhongguo Zhenjiu,* **2012**, *32*(7), 669-672.

[4] Masana, M.; Bortolozzi, A.; Artigas, F. Selective enhancement of mesocortical dopaminergic transmission by noradrenergic drugs: therapeutic opportunities in schizophrenia. *Int. J. Neuropsychopharmacol.,* **2011**, *14*(1), 53-68. [http://dx.doi.org/10.1017/S1461145710000908] [PMID: 20701825]

[5] Williams, J.M.; Galli, A. The dopamine transporter: a vigilant border control for psychostimulant action. *Handb Exp Pharmacol.,* **2006**, *175*, 215-232.

[6] Kosten, T.R.; Wu, G.; Huang, W.; Harding, M.J.; Hamon, S.C.; Lappalainen, J.; Nielsen, D.A. Pharmacogenetic randomized trial for cocaine abuse: disulfiram and dopamine β-hydroxylase. *Biol. Psychiatry,* **2013**, *73*(3), 219-224. [http://dx.doi.org/10.1016/j.biopsych.2012.07.011] [PMID: 22906516]

[7] Ouachikh, O.; Dieb, W.; Durif, F.; Hafidi, A. Anterior ventral tegmental area dopaminergic neurons are not involved in the motivational effects of bromocriptine, pramipexole and cocaine in drug-free rats. *Behav. Brain Res.,* **2014**, *262*, 1-7. [http://dx.doi.org/10.1016/j.bbr.2013.12.021] [PMID: 24361908]

[8] Castells, X; Casas, M; Pérez-Mañá, C. Efficacy of psychostimulant drugs for cocaine dependence. *Cochrane Database Sys. Rev.,* **2010**, *2*, CD007380.

[9] Kalivas, P.W.; Duffy, P. Effect of acute and daily cocaine treatment on extracellular dopamine in the nucleus accumbens. *Synapse,* **1990**, *5*(1), 48-58. [http://dx.doi.org/10.1002/syn.890050104] [PMID: 2300906]

[10] Luoh, H.F.; Kuo, T.B.; Chan, S.H.; Pan, W.H. Power spectral analysis of electroencephalographic desynchronization induced by cocaine in rats: correlation with microdialysis evaluation of dopaminergic neurotransmission at the medial prefrontal cortex. *Synapse,* **1994**, *16*(1), 29-35. [http://dx.doi.org/10.1002/syn.890160104] [PMID: 8134898]

[11] Koob, G.F.; Nestler, E.J. The neurobiology of drug addiction. *J. Neuropsychiatry Clin. Neurosci.,* **1997**, *9*(3), 482-497. [http://dx.doi.org/10.1176/jnp.9.3.482] [PMID: 9276849]

[12] Holman, R.B. Biological effects of central nervous system stimulants. *Addiction,* **1994**, *89*(11), 1435-1441. [http://dx.doi.org/10.1111/j.1360-0443.1994.tb03740.x] [PMID: 7841853]

[13] Hyman, S.E. Addiction to cocaine and amphetamine. *Neuron,* **1996**, *16*(5), 901-904. [http://dx.doi.org/10.1016/S0896-6273(00)80111-7] [PMID: 8630246]

[14] Volkow, N.D.; Wang, G.J.; Fowler, J.S.; Logan, J.; Franceschi, D.; Maynard, L.; Ding, Y.S.; Gatley, S.J.; Gifford, A.; Zhu, W.; Swanson, J.M. Relationship between blockade of dopamine transporters by oral methylphenidate and the increases in extracellular dopamine: therapeutic implications. *Synapse,* **2002**, *43*(3), 181-187. [http://dx.doi.org/10.1002/syn.10038] [PMID: 11793423]

[15] Roncero, C.; Ros-Cucurull, E.; Daigre, C.; Casas, M. Prevalence and risk factors of psychotic symptoms in cocaine-dependent patients. *Actas Esp. Psiquiatr.,* **2012**, *40*(4), 187-197. [PMID: 22851479]

[16] Roncero, C.; Daigre, C.; Grau-López, L.; Barral, C.; Pérez-Pazos, J.; Martínez-Luna, N.; Casas, M. An international perspective and review of cocaine-induced psychosis: a call to action. *Subst. Abus.,* **2014**, *35*(3), 321-327. [http://dx.doi.org/10.1080/08897077.2014.933726] [PMID: 24927026]

[17] Charpeaud, T.; Geneste, J.; Schmidt, J.; Llorca, P.M.; Brousse, G. Disulfiram and addiction: reminders and new perspectives of use. *Therapie,* **2011**, *66*(3), 273-280. [http://dx.doi.org/10.2515/therapie/2011025] [PMID: 21924121]

[18] Schottenfeld, R.S.; Chawarski, M.C.; Cubells, J.F.; George, T.P.; Lappalainen, J.; Kosten, T.R. Randomized clinical trial of disulfiram for cocaine dependence or abuse during buprenorphine treatment. *Drug Alcohol Depend.,* **2014**, *136*, 36-42. [http://dx.doi.org/10.1016/j.drugalcdep.2013.12.007] [PMID: 24462581]

[19] Feldman, H.M.; Reiff, M.I. Clinical practice. Attention deficit-hyperactivity disorder in children and adolescents. *N. Engl. J. Med.,* **2014**, *370*(9), 838-846. [http://dx.doi.org/10.1056/NEJMcp1307215] [PMID: 24571756]

[20] Grabowski, J.; Roache, J.D.; Schmitz, J.M.; Rhoades, H.; Creson, D.; Korszun, A. Replacement medication for cocaine dependence: methylphenidate. *J. Clin. Psychopharmacol.,* **1997**, *17*(6), 485-488. [http://dx.doi.org/10.1097/00004714-199712000-00008] [PMID: 9408812]

[21] Levin, F.R.; Evans, S.M.; McDowell, D.M.; Kleber, H.D. Methylphenidate treatment for cocaine abusers with adult attention-deficit/hyperactivity disorder: a pilot study. *J. Clin. Psychiatry,* **1998**, *59*(6), 300-305. [http://dx.doi.org/10.4088/JCP.v59n0605] [PMID: 9671342]

[22] Schubiner, H.; Saules, K.K.; Arfken, C.L.; Johanson, C.E.; Schuster, C.R.; Lockhart, N.; Edwards, A.; Donlin, J.; Pihlgren, E. Double-blind placebo-controlled trial of methylphenidate in the treatment of adult ADHD patients with comorbid cocaine dependence. *Exp. Clin. Psychopharmacol.,* **2002**, *10*(3), 286-294. [http://dx.doi.org/10.1037/1064-1297.10.3.286] [PMID: 12233989]

[23] Klassen, L.J.; Bilkey, T.S.; Katzman, M.A.; Chokka, P. Comorbid attention deficit/hyperactivity disorder and substance use disorder: treatment considerations. *Curr. Drug Abuse Rev.,* **2012**, *5*(3), 190-198. [http://dx.doi.org/10.2174/1874473711205030190] [PMID: 22571450]

[24] Saiz Ruiz, J.; Gibert, J.; Gutiérrez Fraile, M.; Bobes, J.; Vallejo, J.; Iglesias, C.; Iriarte, V. Bupropion: efficacy and safety in the treatment of depression. *Actas Esp. Psiquiatr.,* **2011**, *39*(39)(Suppl. 1), 1-25. [PMID: 22983817]

[25] Kondo, T. Initial therapy for Parkinsons disease: levodopa vs. dopamine receptor agonists. *J. Neurol.,* **2002**, *249*(249)(Suppl. 2), II25-II29. [PMID: 12375060]

[26] Amato, L; Minozzi, S; Pani, P.P. Dopamine agonists for the treatment of cocaine dependence. *Cochrane Database Syst.,* **2011**, *12*, CD003352-232.

[27] Araújo, J.R.; Martel, F. Sibutramine effects on central mechanisms regulating energy homeostasis. *Curr. Neuropharmacol.,* **2012**,

10(1), 49-52. [http://dx.doi.org/10.2174/157015912799362788] [PMID: 22942877]

[28] Dubuc, I.; Protais, P.; Colboc, O.; Costentin, J. Antagonism of the apomorphine-induced yawning by atypical neuroleptics. *Neuropharmacology,* **1982**, *21*(11), 1203-1206. [http://dx.doi.org/10.1016/0028-3908(82)90181-2] [PMID: 6129594]

[29] Guardia, J.; Casas, M.; Prat, G.; Trujols, J.; Segura, L.; Sánchez-Turet, M. The apomorphine test: a biological marker for heroin dependence disorder? *Addict. Biol.,* **2002**, *7*(4), 421-426. [http://dx.doi.org/10.1080/1355621021000006206] [PMID: 14578019]

[30] Garrett, B.E.; Griffiths, R.R. The role of dopamine in the behavioral effects of caffeine in animals and humans. *Pharmacol. Biochem. Behav.,* **1997**, *57*(3), 533-541. [http://dx.doi.org/10.1016/S0091-3057(96)00435-2] [PMID: 9218278]

[31] Casas, M.; Prat, G.; Robledo, P.; Barbanoj, M.; Kulisevsky, J.; Jané, F. Methylxanthines reverse the adipsic and aphagic syndrome induced by bilateral 6-hydroxydopamine lesions of the nigrostriatal pathway in rats. *Pharmacol. Biochem. Behav.,* **2000**, *66*(2), 257-263. [http://dx.doi.org/10.1016/S0091-3057(00)00189-1] [PMID: 10880677]

[32] Schnackenberg, R.C. Caffeine as a substitute for Schedule II stimulants in hyperkinetic children. *Am. J. Psychiatry,* **1973**, *130*(7), 796-798. [http://dx.doi.org/10.1176/ajp.130.7.796] [PMID: 4712736]

[33] Mally, J.; Stone, T.W. The effect of theophylline on parkinsonian symptoms. *J. Pharm. Pharmacol.,* **1994**, *46*(6), 515-517. [http://dx.doi.org/10.1111/j.2042-7158.1994.tb03840.x] [PMID: 7932051]

[34] Casas, M; Torrens, M; Duro, P. Use of the methylxanthines, caffeine and theophylline, in the treatment of extrapyramidal disorders caused by treatment with neuroleptics. Development of a therapeutic hypothesis. *Encephale,* **1989**, *15Spec No*, 177-180.

[35] Koller, W.C.; Hristova, A.; Brin, M. Pharmacologic treatment of essential tremor. *Neurology,* **2000**, *54*(11)(Suppl. 4), S30-S38. [PMID: 10854350]

[36] Roncero, C.; Casas, M.; Valero, S. EPA-1800-Efficacy and tolerability of oral caffeine with or without biperiden for cocaine detoxification in an inpatient setting: a double blind, randomized, placebo-controlled clinical trial. *Eur. Psychiatry*, *22nd European Congress of Psychiatry,* **2014**, *Vol 1* [http://dx.doi.org/10.1016/S0924-9338(14)78918-7]

[37] Hameedi, F.A.; Rosen, M.I.; McCance-Katz, E.F.; McMahon, T.J.; Price, L.H.; Jatlow, P.I.; Woods, S.W.; Kosten, T.R. Behavioral, physiological, and pharmacological interaction of cocaine and disulfiram in humans. *Biol. Psychiatry,* **1995**, *37*(8), 560-563. [http://dx.doi.org/10.1016/0006-3223(94)00361-6] [PMID: 7619981]

[38] Mutschler, J.; Diehl, A.; Kiefer, F. Pronounced paranoia as a result of cocaine-disulfiram interaction: case report and mode of action. *J. Clin. Psychopharmacol.,* **2009**, *29*(1), 99-101. [http://dx.doi.org/10.1097/JCP.0b013e3181934451] [PMID: 19142124]

[39] Caci, H.; Baylé, F. A case of disulfiram-methylphenidate interaction: implications for treatment. *Am. J. Psychiatry,* **2007**, *164*(11), 1759. [http://dx.doi.org/10.1176/appi.ajp.2007.07060892] [PMID: 17974945]

[40] Grau-López, L.; Roncero, C.; Navarro, M.C.; Casas, M. Psychosis induced by the interaction between disulfiram and methylphenidate may be dose dependent. *Subst. Abus.,* **2012**, *33*(2), 186-188. [http://dx.doi.org/10.1080/08897077.2011.634968] [PMID: 22489591]

[41] Delavenne, H.; Duarte Garcia, F.; Lacoste, J.; Cortese, S.; Charles-Nicolas, A.; Ballon, N. Psychosis in a cocaine-dependent patient with ADHD during treatment with methylphenidate. *Gen. Hosp. Psychiatry,* **2013**, *35*(4), 451.e7-451.e9. [http://dx.doi.org/10.1016/j.genhosppsych.2012.05.010] [PMID: 22739113]

[42] Farooque, M.; Elliott, J. Delayed psychosis induced by bupropion in a former cocaine abuser: a case report. *Prim. Care Companion J. Clin. Psychiatry,* **2010**, *12*(5), PCC.09100943. [PMID: 21274369]

[43] Hahn, M.; Hajek, T.; Alda, M.; Gorman, J.M. Psychosis induced by low-dose bupropion: sensitization of dopaminergic system by past cocaine abuse? *J. Psychiatr. Pract.,* **2007**, *13*(5), 336-338. [http://dx.doi.org/10.1097/01.pra.0000290673.32978.e8] [PMID: 17890983]

[44] The European Monitoring Centre for Drugs and Drug Addiction publishes the European Drug Report 2013: trends and developments *Euro. Surveill.,* **2013**, *18*(22) Avaible on: www.emcdda.europa.eu/publications/edr/trends-developments/2013

[45] Pérez de Los Cobos, J.; Siñol, N.; Puerta, C.; Cantillano, V.; López Z.C.; Trujols, J. Features and prevalence of patients with probable adult attention deficit hyperactivity disorder who request treatment for cocaine use disorders. *Psychiatry Res.,* **2011**, *185*(1-2), 205-210. [http://dx.doi.org/10.1016/j.psychres.2009.03.019] [PMID: 20537723]

[46] Daigre, C.; Roncero, C.; Grau-López, L.; Martínez-Luna, N.; Prat, G.; Valero, S.; Tejedor, R.; Ramos-Quiroga, J.A.; Casas, M. Attention deficit hyperactivity disorder in cocaine-dependent adults: a psychiatric comorbidity analysis. *Am. J. Addict.,* **2013**, *22*(5), 466-473. [http://dx.doi.org/10.1111/j.1521-0391.2013.12047.x] [PMID: 23952892]

[47] Spellicy, C.J.; Kosten, T.R.; Hamon, S.C.; Harding, M.J.; Nielsen, D.A. The MTHFR C677T Variant is Associated with Responsiveness to Disulfiram Treatment for Cocaine Dependency. *Front. Psychiatry,* **2013**, *3*, 109. [http://dx.doi.org/10.3389/fpsyt.2012.00109] [PMID: 23335901]

[48] Torrens, M.; Fonseca, F.; Mateu, G.; Farré, M. Efficacy of antidepressants in substance use disorders with and without comorbid depression. A systematic review and meta-analysis. *Drug Alcohol Depend.,* **2005**, *78*(1), 1-22. [http://dx.doi.org/10.1016/j.drugalcdep.2004.09.004] [PMID: 15769553]

[49] Vorspan, F.; Brousse, G.; Bloch, V.; Bellais, L.; Romo, L.; Guillem, E.; Coeuru, P.; Lépine, J.P. Cocaine-induced psychotic symptoms in French cocaine addicts. *Psychiatry Res.,* **2012**, *200*(2-3), 1074-1076. [http://dx.doi.org/10.1016/j.psychres.2012.04.008] [PMID: 22551940]

[50] Cubells, J.F.; Kranzler, H.R.; McCance-Katz, E.; Anderson, G.M.; Malison, R.T.; Price, L.H.; Gelernter, J. A haplotype at the DBH locus, associated with low plasma dopamine beta-hydroxylase activity, also associates with cocaine-induced paranoia. *Mol. Psychiatry,* **2000**, *5*(1), 56-63. [http://dx.doi.org/10.1038/sj.mp.4000657] [PMID: 10673769]

[51] Kosten, T.R.; Domingo, C.B.; Hamon, S.C.; Nielsen, D.A. DBH gene as predictor of response in a cocaine vaccine clinical trial. *Neurosci. Lett.,* **2013**, *541*, 29-33. [http://dx.doi.org/10.1016/j.neulet.2013.02.037] [PMID: 23458673]

[52] Munoli, R.N.; Kongasseri, S.; Praharaj, S.K.; Sharma, P.S. Bupropion precipitating acute psychosis: a case report. *Am. J. Ther.,* **2014**, *21*(2), e45-e47. [http://dx.doi.org/10.1097/MJT.0b013e31823581c8] [PMID: 23698185]

[53] Kumar, S.; Kodela, S.; Detweiler, J.G.; Kim, K.Y.; Detweiler, M.B. Bupropion-induced psychosis: folklore or a fact? A systematic review of the literature. *Gen. Hosp. Psychiatry,* **2011**, *33*(6), 612-617. [http://dx.doi.org/10.1016/j.genhosppsych.2011.07.001] [PMID: 21872337]

[54] Kraemer, M.; Uekermann, J.; Wiltfang, J.; Kis, B. Methylphenidate-induced psychosis in adult attention-deficit/hyperactivity disorder: report of 3 new cases and review of the literature. *Clin. Neuropharmacol.,* **2010**, *33*(4), 204-206. [http://dx.doi.org/10.1097/WNF.0b013e3181e29174] [PMID: 20571380]

[55] Sherif, P.A.; Murthy, K.K. Psychosis and enuresis during disulfiram therapy. *Indian J. Psychiatry,* **2006**, *48*(1), 62-63. [http://dx.doi.org/10.4103/0019-5545.31622] [PMID: 20703418]

[56] Verbon, H.; de Jong, C.A. Psychosis during and after disulfiram use. *Ned. Tijdschr. Geneeskd.,* **2002**, *146*(12), 571-573. [PMID: 11938582]

[57] Cherland, E.; Fitzpatrick, R. Psychotic side effects of psychostimulants: a 5-year review. *Can. J. Psychiatry,* **1999**, *44*(8), 811-813. [PMID: 10566114]

[58] Nasrallah, H.A. Vulnerability to disulfiram psychosis. *West. J. Med.,* **1979**, *130*(6), 575-577. [PMID: 516699]

[59] Weinshenker, D.; Schroeder, J.P. There and back again: a tale of norepinephrine and drug addiction. *Neuropsychopharmacology,* **2007**, *32*(7), 1433-1451. [http://dx.doi.org/10.1038/sj.npp.1301263] [PMID: 17164822]

[60] Stein, M.D. Medical consequences of substance abuse. *Psychiatr. Clin. North Am.,* **1999**, *22*(2), 351-370. [http://dx.doi.org/10.1016/S0193-953X(05)70081-2] [PMID: 10385938]

[61] Satel, S.L.; Edell, W.S. Cocaine-induced paranoia and psychosis proneness. *Am. J. Psychiatry,* **1991**, *148*(12), 1708-1711. [http://dx.doi.org/10.1176/ajp.148.12.1708] [PMID: 1957934]

[62] Del Cul, A.; Gaillard, R.; Jardri, R.; Fossati, P. [Hallucinations, consciousness and psychosis]. *Encephale,* **2010**, *36*(4), 348-354. [http://dx.doi.org/10.1016/j.encep.2010.07.001] [PMID: 20850607]

[63] Font-Mayolas, S.; Gras, M.E.; Cebrián, N.; Salamó, A.; Planes, M.; Sullman, M.J. Types of polydrug use among Spanish adolescents. *Addict. Behav.,* **2013**, *38*(3), 1605-1609. [http://dx.doi.org/10.1016/j.addbeh.2012.09.007] [PMID: 23254205]

[64] Trape, S.; Charles-Nicolas, A.; Jehel, L.; Lacoste, J. Early cannabis use is associated with severity of Cocaine-Induced Psychosis among cocaine smokers in Martinique, French West Indies. *J. Addict. Med.,* **2014**, *8*(1), 33-39. [http://dx.doi.org/10.1097/ADM.0000000000000003] [PMID: 24481081]

[65] Roncero, C.; Álvarez, F.J. The use of lisdexamfetamine dimesylate for the treatment of ADHD and other psychiatric disorders. *Expert Rev. Neurother.,* **2014**, *14*(8), 849-865. [http://dx.doi.org/10.1586/14737175.2014.932691] [PMID: 24948428]

[66] Levin, F.R.; Mariani, J.J.; Specker, S.; Mooney, M.; Mahony, A.; Brooks, D.J.; Babb, D.; Bai, Y.; Eberly, L.E.; Nunes, E.V.; Grabowski, J. Extended-release mixed amphetamine salts vs placebo for comorbid adult Attention-Deficit/Hyperactivity disorder and Cocaine Use Disorder. *JAMA Psychiatry,* **2015**, *72*(6), 593-602. [http://dx.doi.org/10.1001/jamapsychiatry.2015.41] [PMID: 25887096]

[67] Mooney, M.E.; Herin, D.V.; Specker, S.; Babb, D.; Levin, F.R.; Grabowski, J. Pilot study of the effects of lisdexamfetamine on cocaine use: A randomized, double-blind, placebo-controlled trial. *Drug Alcohol Depend.,* **2015**, *153*, 94-103. [http://dx.doi.org/10.1016/j.drugalcdep.2015.05.042] [PMID: 26116930]

[68] Rush, C.R.; Stoops, W.W.; Sevak, R.J.; Hays, L.R. Cocaine choice in humans during D-amphetamine maintenance. *J. Clin. Psychopharmacol.,* **2010**, *30*(2), 152-159. [http://dx.doi.org/10.1097/JCP.0b013e3181d21967] [PMID: 20520288]

[69] Verma, V. Classic Studies on the Interaction of Cocaine and the Dopamine Transporter. *Clin. Psychopharmacol. Neurosci.,* **2015**, *13*(3), 227-238. [http://dx.doi.org/10.9758/cpn.2015.13.3.227] [PMID: 26598579]