Chapter 39

Mirtazapine: Multitarget strategies for treating substance use disorder and depression

Susana Barbosa-Méndez[a], Luis Enrique Becerril-Villanueva[b], María Dolores Ponce-Regalado[c], and Alberto Salazar-Juárez[a]

[a]*Laboratorio de Neurofarmacología Conductual, Microcirugía y Terapéutica Experimental, Subdirección de Investigaciones Clínicas, Instituto Nacional de Psiquiatría "Ramón de la Fuente", México DF, México,* [b]*Laboratorio de Psicoinmunología, Dirección de Neurociencias, Instituto Nacional de Psiquiatría "Ramón de la Fuente", México DF, México,* [c]*Laboratorio de investigaciones en Biociencias, Departamento de Ciencias de la Salud, Centro Universitario de los Altos, Universidad de Guadalajara, Guadalajara, Mexico*

List of abbreviations

α1-NER, α2-NER	norepinephrine receptor
$\alpha_4\beta_2$, α_7, β_3 nAChR	nicotine receptor
5-HT	serotonergic system
5-HT_{2A}R, 5-HT_{2c}R, 5-HT_3R	serotonin receptors
ACh	holinergic system
CB_1R	cannabinoids receptor
CPP	conditioned place preference
D_1R, D_2R	dopamine receptors
DA	dopamine neurons
DAT	reuptake dopamine transporter
DD	dual diagnosis
DRN	dorsal raphe nucleus
GABA	GABAergic system
$GABA_A$R	GABA receptor
GLU	glutamatergic system
GLUR	glutamate receptor
GLUT	glutamate transporter
H_1R	histamine receptor
i.p.	intraperitoneal administration
LC	locus coeruleus
M_1mAchR	muscarinic receptor
MDD	major depressive disorder
MLCS	mesocorticolimbic dopaminergic system
MOR, DOR, KOR	opioid receptors
NAcc	nucleus accumbens
NE	noradrenergic system
NET	reuptake norepinephrine transporter
PFC	prefrontal cortex
SERT	reuptake serotonin transporter
SUD	substance use disorder
VTA	ventral-tegmental area
WHO	World Health Organization

Introduction

Major depressive disorder (MDD) is considered a serious health problem by the World Health Organization (WHO), especially when its duration and intensity affect the work, family, and/or school activity of the sufferer. That is why MDD is one of the main causes of morbidity worldwide (Walker, McGee, & Druss, 2015). The main characteristics of MDD in adults and adolescents are: a recurrent and/or long-lasting depressed and/or an hedonic mood, a decrease in interest in everyday activities, significant weight loss or gain, without dieting, insomnia or hypersomnia, agitation, psychomotor retardation, fatigue, loss of energy, feeling of worthlessness, excessive or inappropriate guilt, decreased ability to think and concentrate, decreased decision-making, thoughts of death and suicidal thoughts without a specific plan, or structured suicide attempt (Table 1).

Substance use disorder (SUD)

Individuals with substance use disorder (SUD) show symptoms that are common in some mental illnesses, such as anxiety states, impulsiveness, psychotic episodes and/or mania, and obsessive-compulsive disorder as well as those related to mood. SUD is characterized by an excessive desire for the consumption of psychoactive substances, and the consequent withdrawal symptoms, a progressive loss of interests or pleasures not associated to substance use, and an increase in tolerance and craving for consumption (Santucci, 2012).

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TABLE 1 Antidepressants used in the treatment of comorbid depression with substance abuse.

Antidepressant (dose)	Mood disorder diagnosis	Drug use disorder
Citalopram (40 mg/day)	MDD	Alcohol dependence or abuse
Fluoxetine (20–60 mg/kg)	MDD	Alcohol, cocaine, nicotine or opioid dependence, or abuse
Desipramine (100–300 mg/kg)	MDD	Alcohol or cocaine dependence or abuse
Nefazodone (300–500 mg/kg)	MDD	Alcohol dependence or abuse
Sertraline (100–200 mg/kg)	MDD	Nicotine or opioid dependence or abuse
Viloxazine (400 mg/kg)	MDD	Alcohol dependence or abuse
Imipramine (150–300 mg/kg)	MDD	Cocaine or opioid dependence or abuse
Gepirone (116–25 mg/kg)	MDD	Alcohol or cocaine dependence or abuse
Ritanserin (10 mg/kg)	MDD	Alcohol or cocaine dependence or abuse
Bupropion (300 mg/kg)	MDD	Cocaine or nicotine dependence or abuse
Mirtazapine (30–60 mg/kg)	MDD	Alcohol or cocaine dependence or abuse
Doxepin (100–200 mg/kg)	MDD	Nicotine or opioid dependence or abuse
Nortriptyline (100 mg/kg)	MDD	Nicotine dependence or abuse
Paroxetine (20–40 mg/kg)	MDD	Nicotine dependence or abuse

MDD-SUD comorbidity

Comorbidity is a fundamental characteristic of MDD. While several symptoms are considered diagnostic, others are frequently a sequel to MDD or part of other psychiatric disorders, as SUD.

Currently, dual diagnosis (DD) has been established between SUD and other mental illnesses (Ng, Browne, Samsom, & Wong, 2017) as MDD.

Neurobiological mechanisms of DD (MDD-SUD)

The neural substrate associated to DD is the mesocorticolimbic dopaminergic system (MCLD). This system is directly interconnected to the serotonergic (5-HT), noradrenergic (NE), GABAergic (GABA), cholinergic (ACh), glutamatergic (GLU), and endogenous opioid systems in the brain, among others. MCLD consists of a series of interconnected neural structures, in close communication with each other: ventral-tegmental area (VTA), nucleus accumbens (NAcc) in its two portions (core and shell), dorsal striatum, prefrontal cortex (PFC), and axis structures through which the reinforcing effect of a psychoactive drug is processed.

From the molecular point of view, in the dopaminergic (DA) neurons located in these brain structures, different types of membrane receptors associated with psychoactive drugs are colocated: nicotine ($\alpha_4\beta_2$, α_7, β_3 nAChR), cannabinoids (CB_1R), opioids (MOR, DOR, KOR), and alcohol ($GABA_AR$), among others. In addition, a high density of the dopamine transporter (DAT) and different subtypes of dopamine receptors (D_1R and D_2R) are located at the terminals of these DA neurons. Due to the interconnections that MLCS shows with other brain structures, receptors and/or transporters for serotonin (5-$HT_{2A}R$, 5-$HT_{2c}R$, 5-HT_3R, and SET), norepinephrine (α1-NER, α2-NER, and NET), acetylcholine ($\alpha_4\beta_2$, α_7, and β_3 nAChR), and glutamate (GLUR and GLUT), among others are also colocated in DA neurons, which are neurotransmission systems responsible for modulating by the drug reinforcing effect.

Mirtazapine

Mirtazapine is an atypical antidepressant approved by the Food and Drug Administration (FDA) for the treatment of moderate to severe MDD and a wide range of symptoms associated with it (Croom, Perry, & Plosker, 2009).

This drug is a part of the group of tetracyclic antidepressants carrying out effects through the combination of noradrenergic and serotonergic mechanisms (Anttila & Leinonen, 2001). Its mechanism of action is complex since it involves the simultaneous interaction of mirtazapine with different subtypes of adrenergic (α_1-NER and α_2-NER) and serotonergic (5-$HT_{1A}R$, 5-$HT_{2A/C}R$, 5-$HT_{2C}R$, and 5-HT_3R) receptors; although it is also capable of interacting with histamine (H_1R) and acetylcholine (M_1mAchR) receptors (de Boer, 1996).

Mirtazapine potentiates serotonergic neurotransmission through the postsynaptic antagonism of 5-HT_{2A} and 5-HT_3 receptors, resulting in increased excitation of dorsal raphe nucleus (DRN) neurons. Furthermore, the blockade of presynaptic α_2-NERs, which normally inhibit serotonergic and noradrenergic terminals in the locus coeruleus (LC), promotes the release of NE and leads to increased adrenergic activation in the α_1-NERs in the DRN, which enhances the release of 5-HT. This ability to stimulate DRN is complemented by antagonism in α_2-NERs located in serotonergic neurons, which also leads to intensified DRN

activity and a surge in 5-HT flow (Haddjeri, Blier, & de-Montigny, 1998).

On the other hand, mirtazapine is not able to block the reuptake systems of dopamine (DAT), serotonin (SERT), and norepinephrine (NET) in the brain and has a low affinity for dopamine receptors (D_1R and D_2R), while it is a potent antagonist of histaminergic (H_1) receptors and a moderate antagonist of M_1mAchR muscarinic cholinergic receptors and α_1-adrenergic receptors (Anttila & Leinonen, 2001).

Mirtazapine-SUD

For the past decades, several antidepressants have been explored as possible therapeutic drugs to relieve SUD (Torrens, Fonseca, Mateu, & Farré, 2005). In fact, several clinical trials have evaluated the efficacy of various antidepressants to reduce withdrawal symptoms and drug craving, and/or prevent relapse during early withdrawal. However, the results of these studies have not been conclusive since they have reported that only some of the patients who received the medications during withdrawal from psychoactive drugs showed improvement and/or relief of any withdrawal symptoms (Lima, Reisser, Soares, & Farrell, 2010).

In general, these studies suggest that the symptomatology of SUD is heterogeneous and that one of the main limitations of antidepressants used in the SUD treatment is that they generally act selectively on a receptor subtype and only alleviate some symptoms of SUD. Therefore, molecules capable of acting simultaneously on several receptor subtypes (multitarget drugs), in different brain nuclei are required to simultaneously reduce different withdrawal symptoms and also prevent relapses.

Preclinical studies

Pioneer studies in rodents show that mirtazapine administration to Sprague-Dawley rats reduced morphine-induced reward effects and the acquisition of morphine dependence (Kang et al., 2008). In addition, in a series of studies, Graves et al. demonstrated that Sprague-Dawley rats treated with mirtazapine showed an attenuation in the establishment and expression of the conditioned place preference (CPP) to morphine and methamphetamine. Other studies described that rats dosed with mirtazapine showed a reduction in the reacquisition of methamphetamine self-administration and the expression of methamphetamine-induced locomotor sensitization (Graves & Napier, 2012; Graves, Rafeyan, Watts, & Napier, 2012; Herrold et al., 2009; McDaid et al., 2007; Voigt, Mickiewicz, & Napier, 2011; Voigt & Napier, 2012).

In addition, it was reported that Wistar rats dosed with mirtazapine (30 mg/kg, i.p., daily, 30 days) during withdrawal showed a significant decrease in induction and expression of locomotor sensitization, CPP expression, duration of locomotor effect, and self-administration induced by different doses of cocaine, heroin, or nicotine (Barbosa-Méndez, Jurado, et al., 2017; Barbosa-Méndez, Leff, et al., 2017; Barbosa-Méndez, Matus-Ortega, Jacinto-Gutiérrez, & Salazar-Juárez, 2018; Barbosa-Méndez & Salazar-Juárez, 2018a; Fig. 1). These results support the efficacy of mirtazapine in reducing the behavior reinforcement effect induced by a wide variety of drugs.

In addition, these studies demonstrated that (1) the dose, (2) the duration of the dosage, and (3) the stage of drug withdrawal in which mirtazapine is administered are key parameters (dosing schedule) on which the efficacy of

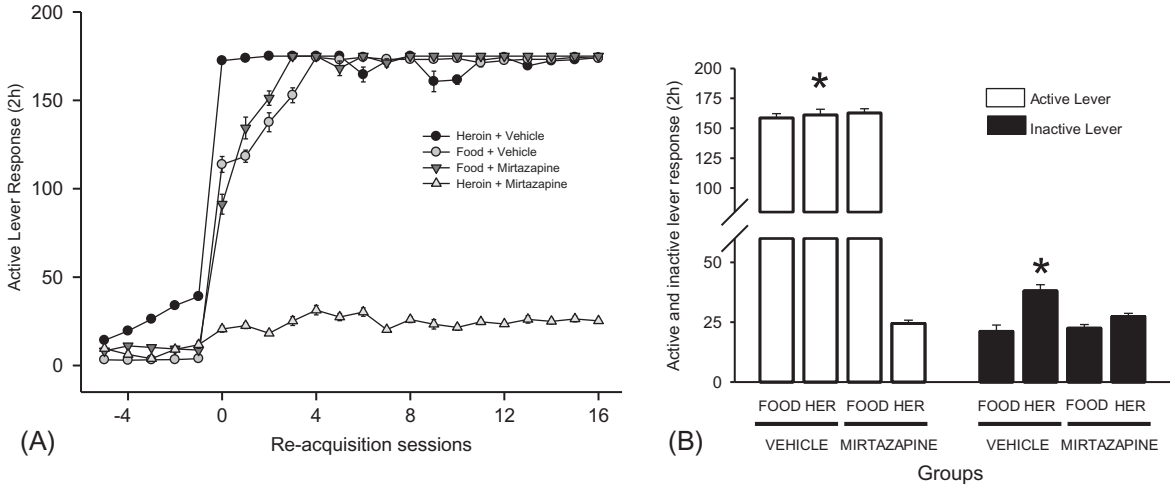

FIG. 1 Mirtazapine decreases heroin self-administration. The heroin + vehicle and heroin + mirtazapine groups received saline and mirtazapine, respectively, during extinction (30 days) and were then exposed to the reacquisition of heroin self-administration. The heroin + mirtazapine group also received mirtazapine during reacquisition (10 days). (A) Cocaine seeking during reacquisition in which a decrease in active lever pressures in the animals of the heroin + mirtazapine group is observed. (B) Mean active lever pressures during the reacquisition phase. Two-way ANOVA followed by a post hoc Tukey's test. (*) indicates that significant differences ($P < 0.01$) were found in the heroin + mirtazapine group, compared to the heroin + vehicle group.

mirtazapine depends as a therapeutic agent for the treatment of SUD (Barbosa-Méndez, Matus-Ortega, Flores-Zamora, Jurado, & Salazar-Juárez, 2017).

(1) *Dose*. Studies in rats showed that the administration of low doses of mirtazapine (0.5, 1, or 5 mg/kg) produced a significant attenuation in the maintenance of methamphetamine-induced CPP (Graves & Napier, 2011; Graves, Persons, Riddle, & Napier, 2012; Herrold et al., 2009), as well as a decrease in methamphetamine-seeking behavior (Graves & Napier, 2012; Graves, Rafeyan, et al., 2012). Other authors reported that the effectiveness of 5 mg/kg mirtazapine to attenuate methamphetamine-induced CPP in rats depended on the contextual signals associated with the administration of mirtazapine (Voigt et al., 2011; Voigt & Napier, 2012) rather than the dose used. Other studies reported that a dose of 10 or 15 mg/kg of mirtazapine not attenuate the expression of methamphetamine-, cocaine-, or nicotine-induced locomotor sensitization in rats (Barbosa-Méndez, Matus-Ortega, Flores-Zamora, et al., 2017; Bhatia, Szabo, Fowler, Wetsel, & Lee, 2011).

In 2008, Kang et al. reported that mirtazapine (30 mg/kg i.p.) attenuated morphine-induced CPP in rats. In addition, we have reported that 30 mg/kg of mirtazapine administered to rats previously treated with cocaine or nicotine decreased the expression of locomotor sensitization (Barbosa-Méndez, Jurado, Matus-Ortega, et al., 2017; Salazar-Juárez et al., 2016), CPP (Barbosa-Méndez et al., 2018), and reacquisition of self-administration to cocaine, heroin, or nicotine (Barbosa-Méndez, Leff, et al., 2017; Barbosa-Méndez & Salazar-Juárez, 2018a). The daily dosage (30 mg/kg) of mirtazapine reduced the toxic effects generated by a sublethal cocaine dose. However, when increasing the dose to 60 mg/kg, no behavioral effects were significantly different from those generated by a 30 mg/kg dose (Barbosa-Méndez, Matus-Ortega, Flores-Zamora, et al., 2017).

(2) Dosage duration. On the other hand, clinical studies have described that the pharmacological action of antidepressants is slow and their therapeutic effects become evident after weeks of treatment.

Studies in rodents have described the effects of acute administration of mirtazapine and found that rats dosed 15 min before cocaine administration showed a decrease in reward effects and the acquisition of morphine-induced dependence (Kang et al., 2008). In addition, rodents administered with mirtazapine 24 h before cocaine showed attenuation in the establishment of morphine- or methamphetamine-induced CPP (Graves, Persons, et al., 2012; Voigt & Napier, 2012).

Other studies reported that rats administered with mirtazapine for periods from 3 to 15 days showed a decrease in self-administration, locomotor sensitization, and maintenance of CPP induced by methamphetamine (Graves & Napier, 2011; Herrold et al., 2009; Voigt et al., 2011).

However, a recent study described the effects of chronic administration of mirtazapine in rodents and found that rats administered with mirtazapine for 15 days did not show attenuation of the expression of cocaine- or nicotine-induced locomotor sensitization (Barbosa-Méndez, Matus-Ortega, Flores-Zamora, et al., 2017). In contrast, animals pretreated with cocaine and dosed with mirtazapine for 30 days showed a significant decrease in cocaine self-administration, the expression of cocaine-induced locomotor sensitization, and CPP (Barbosa-Méndez et al., 2018; Salazar-Juárez et al., 2016). In addition, the study reported that a longer treatment with mirtazapine (60 days) significantly improved the decrease in the expression of cocaine-induced locomotor sensitization, compared to that generated by the administration of mirtazapine for 30 days (Barbosa-Méndez, Matus-Ortega, Flores-Zamora, et al., 2017).

(3) *Drug-withdrawal stage*. Some clinical studies have suggested that the early withdrawal phase is an important therapeutic window. Animal studies have reported that the administration of mirtazapine in the first days of drug withdrawal (10 days) reduced methamphetamine-induced CPP (Graves & Napier, 2011; Herrold et al., 2009; Voigt et al., 2011). However, an important limitation of these studies was the lack of follow-up on the effect of mirtazapine, even after withdrawing the medication.

We have previously (2016) described that (1) mirtazapine and cocaine showed an enhancement of cocaine-induced locomotor activity in dosed simultaneously during the active consumption phase; contrastingly, (2) the treatment with mirtazapine for $\geq$30 days during drug withdrawal caused a permanent decrease in the expression of cocaine-induced locomotor sensitization, even in the absence of mirtazapine (Salazar-Juárez et al., 2016). These findings suggest that the first 30 days of drug withdrawal are essential for mirtazapine to exert permanent therapeutic effects.

Sedation: Clinical and preclinical studies have shown that sedation generated during treatment with mirtazapine is dose-time dependent (Salazar-Juárez et al., 2016; (Salazar-Juárez et al., 2017)Sasada et al., 2013). Pioneer studies showed that $\leq$15 mg/kg doses of mirtazapine produced hyperphagia and weight gain, while doses of $\geq$60 mg/kg produced hypoactivity, drowsiness, and reduced exploratory

activity as well as altered behavioral responses (de Boer, 1996(Iwamoto et al., 2013)).

Several clinical studies have shown that an initial dose of ≤15 mg/kg of mirtazapine acts as a potent histamine block that induces clear sedation and drowsiness (Grasmäder et al., 2005), while a dose of ≥30 mg/kg is associated with a decrease in sedative antihistamine activity due to enhanced noradrenergic transmission. In addition, the acute treatment with mirtazapine has been reported to produce temporary sedative effects.

Sasada et al. (2013) reported that the sedative effects induced by mirtazapine (7.5 or 15 mg/kg) disappeared after repeated administrations to healthy volunteers. Other studies indicated that sedation induced by 15 mg/kg mirtazapine decreased overtime (Grasmäder et al., 2005).

A recent study revealed that a single dose of ≤15 mg/day of mirtazapine administered to rats decreased spontaneous locomotor activity, balance, and motor coordination for several days. In contrast, animals dosed with ≥30 mg/day of mirtazapine showed sedation within 20 min after administration. The effect gradually decreased and reached reference levels at 60 min to 2 days until the animals no longer showed signs of sedation. This suggests that the chronic administration of ≥30 mg/kg of mirtazapine doses does not cause sedation (Salazar-Juárez et al., 2016).

Drug withdrawal: Preclinical studies have described that rodents exposed to different withdrawal periods showed an increase in anxiety- and depressive-like behavior. Kang et al. (2008) reported that mirtazapine decreased the severity of symptoms during morphine withdrawal in rats.

In a recent study, Wistar rats pretreated with cocaine underwent a 60-day cocaine-withdrawal period during which depression- and anxiety-like behaviors were evaluated in open field, elevated plus maze, light-dark box, forced swimming tests, and spontaneous locomotor activity. This study found that the chronic treatment with 30 or 60 mg/kg of mirtazapine decreased the depression- and anxiety-like behaviors induced by different doses of cocaine (10, 20, and 40 mg/kg) during the 60 days of cocaine withdrawal (Barbosa-Méndez & Salazar-Juárez, 2019a).

On the other hand, in a double-blind, placebo-controlled clinical trial whose participants were DD in patients with alcohol or cocaine dependence, the treatment with mirtazapine produced a significant decrease in depressive symptoms at week 2 and in all subsequent evaluations (weeks 3, 4, 6, 8, 10, and 12) during a 12-week study (Afshar et al., 2012; Cornelius et al., 2012, 2013, 2016b). Other double-blind, placebo-controlled clinical trials have shown that mirtazapine significantly improved the symptoms of depression, anxiety, insomnia, and dysphoria that appear during benzodiazepine, methamphetamine, and cocaine withdrawal (Afshar et al., 2012; Cruickshank et al., 2008; Kongsakon, Papadopoulos, & Saguansiritham, 2005).

Clinical trials

A pioneering study in patients with benzodiazepine abuse showed that the administration of mirtazapine (60 mg/day) stopped benzodiazepine abuse in the streets, including the reduction of cocaine abuse (Zueco-Pérez, 2002).

Subsequently, other randomized, double-blind, placebo-controlled trials reported that 50% of the subjects treated with mirtazapine (30 mg/day) for 12 weeks showed a decrease in methamphetamine use (Colfax et al., 2011; de Bejczy & Söderpalm, 2015; McGregor, Srisurapanont, Mitchell, Wickes, & White, 2008). Studies in patients with alcohol use disorder showed that the dose of 30 or 45 mg/day of mirtazapine for 8–11 weeks reduced alcohol consumption (Brunette, Akerman, Dawson, O'Keefe, & Green, 2016; Liappas, Paparrigopoulos, Tzavellas, & Christodoulou, 2003; Liappas, Paparrigopoulos, Tzavellas, & Rabavilas, 2005).

However, other studies found no effect of mirtazapine treatment on cocaine or alcohol use (Afshar et al., 2012; Cornelius et al., 2016a). Afshar et al. (2012) found no significant differences in the urine positive cocaine tests between the placebo and mirtazapine group at week 11. In an open trial, Cornelius et al. (2012, 2016a, 2016b) found no evidence of the efficacy of mirtazapine in reducing the level of alcohol consumption in patients with alcohol use disorder.

Furthermore, double-blind, placebo-controlled clinical trials in which patients dependent on cocaine or alcohol were treated with 30 or 45 mg/day of mirtazapine for 4–14 weeks showed a decrease in drug craving as compared to patients treated with placebo (Brunette et al., 2016; Cornelius et al., 2016a; Graves, Rafeyan, et al., 2012; Yoon et al., 2006; Zueco-Pérez, 2002). However, Afshar et al. (2012) reported that the daily treatment with 45 mg of mirtazapine for 12 weeks failed to reduce cocaine craving.

On the other hand, clinical studies have described that mirtazapine dosed for several weeks is well tolerated and does not cause serious side effects (Afshar et al., 2012; Brunette et al., 2016; Kongsakon et al., 2005; McGregor et al., 2008; Yoon et al., 2006). These studies demonstrated that an initial dose of 15 mg/day followed by 30 mg/day of mirtazapine to treat methamphetamine-dependent withdrawal symptoms resulted in a safe and well-tolerated dose, which produced a significant decrease in the frequency of methamphetamine use (Colfax et al., 2011; McGregor et al., 2008).

As mentioned above, emotional and cognitive adverse symptoms are considered as the main factors that trigger the relapse to chronic drug abuse. Thus, effectively dealing these symptoms is one of the main objectives that a treatment against SUD must meet.

In an open trial study, McGregor et al. (2008) reported the efficacy of mirtazapine (60 mg/day for 10 days) in hospitalized patients. It significantly reduced the symptoms of methamphetamine withdrawal, such as agitation, fatigue, irritability, paranoid and suicidal ideation, anhedonia, and vivid dreams; it also decreased symptoms of depression and anxiety. Other double-blind, placebo-controlled clinical studies showed that mirtazapine significantly improved depression, anxiety, insomnia, minimized physical and subjective discomfort, and dysphoric symptoms that appear during benzodiazepine and alcohol withdrawal (Altintoprak, Zorlu, Coskunol, Akdeniz, & Kitapcioglu, 2008; Chandrasekaran, 2008; Cruickshank et al., 2008; Kongsakon et al., 2005; Liappas, Paparrigopoulos, Malitas, Tzavellas, & Christodoulou, 2004). In addition, the treatment with 45 mg/day of mirtazapine, administered for 12 weeks in outpatients, increased the amount of sleep and decreased depression in patients with depression and cocaine dependence (Afshar et al., 2012).

Preclinical studies in models of polydrug

Epidemiological studies have indicated that a common practice among drug users is the simultaneous mixing or use of two or more drugs. These studies state that nicotine is a drug commonly used by cocaine dependents. In animals, the concurrent self-administration of cocaine and nicotine has been reported to increase the response rate in rhesus macaques (Mello & Newman, 2011) and increase dopamine release in rats (Gerasimov et al., 2000). We have reported that the combination of cocaine and nicotine increases the self-administration and consumption pattern of both drugs (Fig. 2) and enhances locomotor activity and the induction and expression of locomotor sensitization in rats (Barbosa-Méndez & Salazar-Juárez, 2018b).

In addition, we found that mirtazapine decreases the induction and expression of locomotor sensitization induced by the concurrent administration of cocaine and nicotine (Barbosa-Méndez & Salazar-Juárez, 2019b).

Selective agent therapies

The role of adrenergic and serotonergic systems in the development and consolidation of SUD has been well documented.

Several preclinical studies have shown that the individual treatment with 5-HT_2, 5-HT_3, or α_2NE receptor antagonists has not generated consistent and permanent results. Occasionally, the administration of 5-HT_{2A} receptor antagonists such as ketanserin or M100907, 5-HT_{2C} receptor agonists, (Ro60-0175), 5-HT_3 receptor antagonists such as tropisetron, and ondansetron or α_2NE receptor antagonists (yohimbine) for several days during drug withdrawal caused a decrease in dopamine release and an attenuation in the induction and expression of locomotor sensitization, in self-administration and reacquisition of CPP induced by drugs like as cocaine and nicotine (Zayara et al., 2011). However, the treatment with these antagonists or agonists has also failed to decrease self-administration and drug-generated hyperactivity (Schenk et al., 2016).

Multitarget therapy

Drugs such as cocaine simultaneously affect several neurotransmission systems and alter the functioning of different subtypes of monoaminergic and non-monoaminergic receptors. Mirtazapine decreases many behavioral effects of drugs by simultaneously antagonizing the 5-HT_{2A}, 5-HT_{2C}, and 5-HT_3 receptors, and even the α_2NE. However, its limitations include the low affinity shown by the α_1NE and α4β2nAch cholinergic receptors, which have been reported to be involved in the development and establishment of the reinforcement effects induced by drugs such as cocaine, nicotine, and even opioids.

To compensate for this pharmacological shortcoming, different strategies have been carried out: (1) coadministration of mirtazapine with some α_1NE or α4β2nAch cholinergic receptor antagonists (Barbosa-Méndez, Matus-Ortega, & Salazar-Juárez, 2017; Barbosa-Méndez & Salazar-Juárez, 2019b), (2) development of a new multitarget drug capable of acting on the different receptor subtypes (Millan, 2006), and (3) development of a new pharmaceutical formulation containing mirtazapine and another/other antagonist(s) (Ranjan et al., 2011; Vysloužil et al., 2016).

In 2017, we reported that the coadministration of mirtazapine and prazosin (α_1NER antagonist) for 30 days during drug withdrawal significantly reduced the expression of cocaine sensitization, compared with the individual treatment with mirtazapine or prazosin (Barbosa-Méndez, Matus-Ortega, & Salazar-Juárez, 2017). In addition, we have found that the coadministration of mirtazapine and mecamylamine potentiated the effect of mirtazapine on the expression of locomotor sensitization induced by cocaine, nicotine, and even the combination of both drugs (Barbosa-Méndez & Salazar-Juárez, 2019b).

These results suggest that coadministration of mirtazapine and other monoamine and non-monoamine antagonists generated promising results, especially in the absence of new selective or multitarget drugs specifically designed to treat SUD.

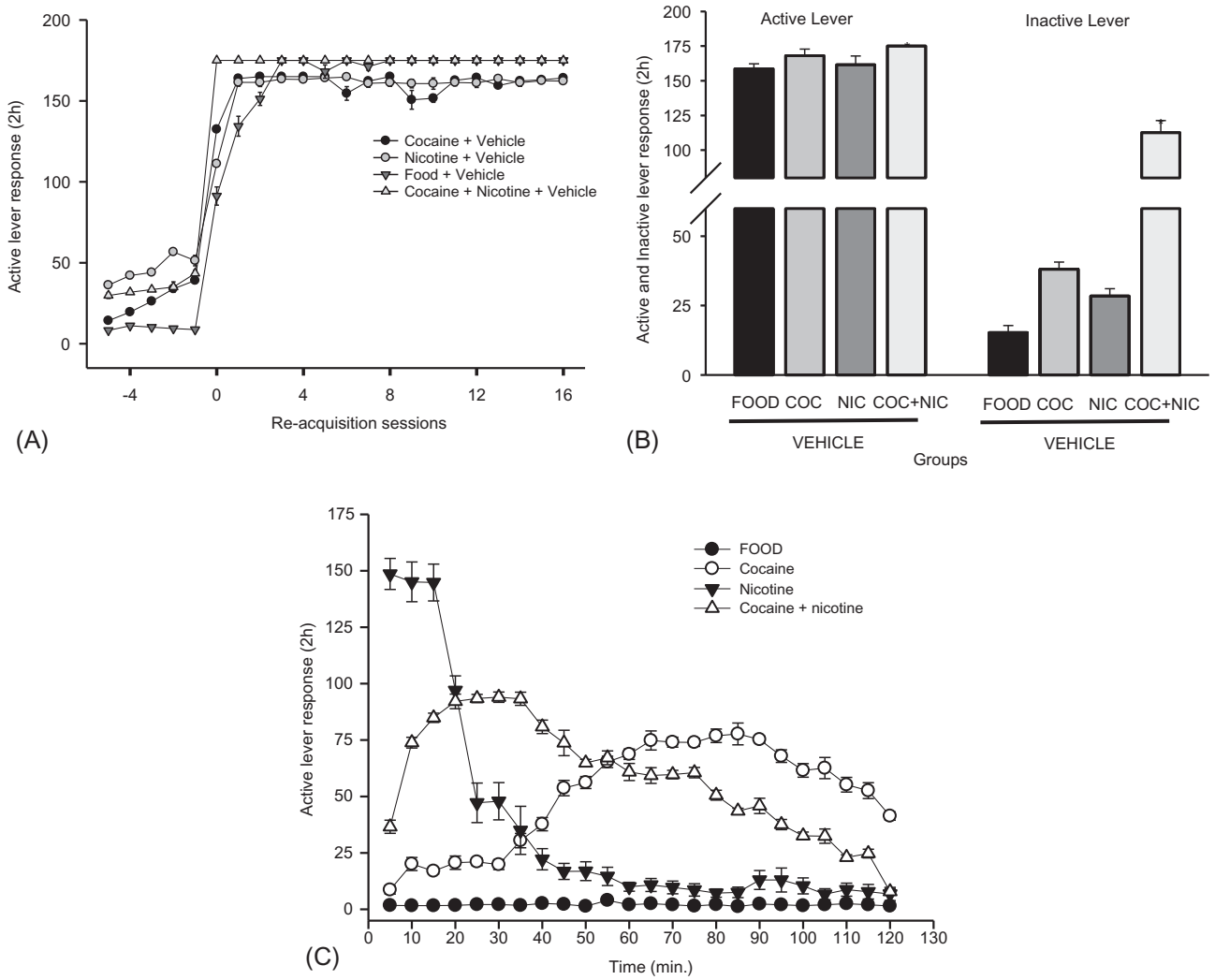

FIG. 2 The cocaine+nicotine mixture increases self-administration. (A) Concurrent administration of cocaine and nicotine increases the number of active lever pressures. (B) Mean active and inactive lever pressures. Two-way ANOVA followed by a post hoc Tukey's test. (*) indicates that significant differences ($P < 0.01$) were found in the cocaine+nicotine+vehicle group, compared to the cocaine+vehicle and nicotine+vehicle group. (C) The cocaine+nicotine mixture modifies the consumption pattern of the drug. Nicotine is consumed in the first 20 min of the test and cocaine at 40 min, while the cocaine+nicotine mixture was consumed during the 120-min test.

Conclusion and future perspectives

In view of the high prevalence of DD and the absence of effective medications for its treatment, there remains an urgent need to discover new and improved medications, whether they be highly selective or multitarget agents.

The use of drugs that selectively interact with specific targets involved in the etiology of DD has not been very successful; however, drugs that have multitarget mechanisms of action can incorporate monoaminergic (DA, 5-HT, and NE) and non-monoaminergic action mechanisms (ACH, GLU), which opens a range of possibilities to improve the treatment of DD and other complex CNS disorders.

Mirtazapine has a complex action mechanism that covers the characteristics of a multitarget drug, which as evidenced by coadministration studies with monoaminergic agents (prazosin, α_1NER) and non-monoaminergic agents ($\alpha4\beta2$nAChR) can be used as a key molecule to design new drugs.

Key facts

- MDD is a highly prevalent disorder, affecting more than 350 million people worldwide.
- SUD affects 330 million users around the world, leading to 166,000 direct deaths per year; approximately 5%–

6% of the population between ages 15 and 64 has consumed an illegal substance on at least one occasion.
- Dual diagnosis is considered as a serious public health problem, with a prevalence of 11%–27% of the world's population.
- Several preclinical and clinical studies have described the efficacy of mirtazapine in mitigating various behavioral alterations characteristic of SUD.
- Mirtazapine is a multitarget drug, which has demonstrated efficacy in preclinical and clinical studies, supporting its use in different clinical trials.

Summary points

- Several clinical studies have shown that MDD is a strong risk factor for the development of other health problems such as SUD.
- Mirtazapine is an atypical antidepressant approved by the FDA for the treatment of moderate to severe MDD; due to its sedative, antiemetic, anxiolytic, and appetite-stimulating effects, mirtazapine has also been used in the treatment of other psychiatric disorders.
- Mirtazapine dosed for 30 days during drug withdrawal significantly reduced the induction and expression of locomotor sensitization and CPP, the duration of locomotor effect, and self-administration induced by different doses of cocaine, heroin, methamphetamines, or nicotine.
- Several clinical trials show that mirtazapine decreased withdrawal symptoms, use, and drug craving.
- Mirtazapine is a multitarget molecule, which not only is able to reduce the reinforcing effect of various psychoactive substances through its complex mechanism of action but can also simultaneously decrease withdrawal symptoms; these evidences support the use of mirtazapine in future clinical trials.

Mini-dictionary of terms

Substance use disorder Substance use disorder is a psychiatric disorder characterized by the intense desire and uncontrolled consumption of large amounts of a substance, leading to noncompliance and/or abandonment of important work, social, academic, or domestic activities.

Dual diagnosis Dual diagnosis is characterized by the comorbidity of a conventional psychiatric disorder with the use of psychoactive substances.

Self-administration Self-administration is a pharmacological procedure that models various aspects of SUD under controlled laboratory conditions in which the animal self-administers psychoactive substances based on drug functioning as a reinforcer that maintains the seeking and intake of the psychoactive substance.

Behavioral sensitization Behavioral sensitization is the process whereby repeated, intermittent stimulant administration produces a progressively greater and enduring-behavioral response.

CPP CPP is a pharmacological procedure used to evaluate the efficacy of the reinforcement of psychoactive substances using classical or Pavlovian conditioning procedures.

Polydrug abuse Polydrug abuse is the simultaneous use of the effects of more than one psychoactive substance in a short period of time.

Drug withdrawal Drug withdrawal is the abrupt discontinuation or decrease in intake of psychoactive substances and the symptoms that characterize this stage.

Dosing program Dosing program is the set of pharmacological parameters (dose, route administration, days, etc.) under which a drug or medication will be administered.

Multitarget drug Multitarget drug is a drug that can act on multiple pharmacologically relevant targets for the generation of a therapeutic effect.

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