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EDITORIAL

A new era in the management of intracerebral hemorrhage is approaching

Se acerca una nueva era en el tratamiento de la hemorragia intracerebral

*Manuel E. Torres-Pérez and Miguel García-Grimshaw**

Stroke Clinic, Department of Neurology and Psychiatry, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

Intracranial hemorrhage (ICH) prevalence has increased since the 1990s in Mexico, especially among young adults (< 50 years)[1]. During the past years, there have been noteworthy advances in the acute management of ischemic stroke, modifying the natural history of this devastating disease[2]. Despite being equally important, ICH is currently perceived as far from showing similar progress, probably due to poor outcomes obtained in most clinical trials and the catastrophic scenarios derived from the current predictive scores, which have sometimes led to discouraging aggressive medical care from the clinical, neuro-interventional, and neurosurgical communities[3].

ICH clinical trials during the past decade have aimed at limiting hematoma expansion, a well-established factor associated with poor clinical outcomes[4]. Most trials have focused on acute intensive blood pressure (BP) control with positive results, as recently demonstrated by the Intensive Ambulance-Delivered Blood-Pressure Reduction in Hyperacute Stroke Trial (INTERACT4), which showed a decrease in the odds of a poor functional outcome (odds ratio 0.75; 95% confidence interval 0.60-0.92) with a target of systolic BP between 130 and 140 mmHg[5].

Besides BP management, temperature, and glucose control are other factors that can improve clinical outcomes, as well as a rapid and goal-directed anticoagulation reversal[6]. The latter is quite relevant in the era of direct oral anticoagulants, especially with the positive results of the ANNEXA-I trial, which showed that among patients with anticoagulation-related ICH, the use of andexanet, a factor Xa inhibitor, resulted in better control of hematoma expansion than usual care[7]. Still, real-life evidence and affordability (especially for low and middle-income countries) analyses are needed, in addition to studies comparing andexanet versus the use of prothrombin complex concentrates.

Until 2024, the role of surgery in ICH has been controversial due to the minimal or null functional benefit of surgical drainage. The Early Minimally Invasive Removal of Intracerebral Hemorrhage (ENRICH) trial has proven the benefits in functional outcomes at 180 days of an early (within 24 h) trans-sulcal minimally surgical technique for lobar hematoma evacuation, the median volume of 54 mL (interquartile range [IQR] 39-72)[8]. Furthermore, the SWITCH study showed that decompressive craniectomy (within 24 h) plus the best medical treatment might be superior to the best medical treatment alone in severe (median volume 55 mL, IQR 45-74) deep ICH (basal ganglia and thalamus) at 180 days[9].

The statement that time is brain is also valid for patients with ICH. The imperative of timely intervention is equal or even greater for this pathology. Therefore, based on the successful experience accumulated in

***Correspondence:**
Miguel García-Grimshaw
E-mail: miguel.garciag@incmnsz.mx

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other domains of neurology, the early combined care model in ICH focused on BP control, glucose, temperature, and anticoagulation reversal, plus the recent positive and encouraging results of the aforementioned trials, which may be supported by future and ongoing minimally invasive surgery trials (ClinicalTrials.gov numbers: NCT05681988, NCT02661672, NCT03342664, NCT04434807)[10], we firmly believe that a new era in the management of ICH is approaching.

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ORIGINAL ARTICLE

Preliminary evaluation of the neuroprotective activity of Cannabidiol in combination with some current medicinal drugs *in vitro*

*Jesús Vélez-Huerta[1], Eder U. Arredondo-Espinoza[1], Karla Ramírez-Estrada[2], Mónica A. Ramírez-Cabrera[1], and Omar González-Santiago[3]**

[1]Laboratory of Molecular Pharmacology and Biological Models; [2]Laboratory of Cell Metabolism; [3]Coordination of Pharmacy Postgraduate. Faculty of Chemical Science, Universidad Autónoma de Nuevo León, Nuevo León, Monterrey, Mexico

Abstract

Objective: *The objective of this study was to evaluate the neurotoxicity and neuroprotective activity of cannabidiol (CBD), valproate, furosemide, metformin, and bilobalide, individually and mixed with CBD in PC12 cells exposed to Glutamate. In addition, antioxidant activity, reactive oxygen species (ROS) production, and caspase-3 activity were evaluated.* **Methods:** *Neurotoxicity and neuroprotection were evaluated with the MTT assay; antioxidant activity, and production of ROS with 2,2-diphenyl-1-picryl-hydrazyl-hydrate, and DCFDA methods, respectively; the apoptosis with caspase-3 activity assay.* **Results:** *CBD 5 μM, and bilobalide 15.3 μM showed neuroprotective activity by ROS inhibition and decreased caspase-3 activity. Metformin 1548.4 μM did not provide significant neuroprotection but decreased ROS generation.* **Conclusions:** *Combining CBD with the study drugs did not improve neuroprotection than the neuroprotection of individual drugs.*

Keywords: *Cannabidiol. Neuroprotection. Cell death.*

Evaluación preliminar de la actividad neuroprotectora del Cannabidiol en combinación con algunos medicamentos in vitro

Resumen

Objetivo: *Evaluar la neurotoxicidad y la actividad neuroprotectora del Cannabidiol, valproato, furosemida, metformina y bilobalida, individualmente y mezclados con Cannabidiol en células PC12 expuestas a Glutamato. Además, se evaluó la actividad antioxidante, la producción de especies reactivas de oxígeno y la actividad de la caspasa-3.* **Métodos:** *La neurotoxicidad y la neuroprotección se evaluaron con el ensayo MTT; la actividad antioxidante, y la producción de ROS con los métodos DPPH, y DCFDA respectivamente; la apoptosis con el ensayo de actividad caspasa-3.* **Resultados:** *El cannabidiol 5 μM, y el bilobalide 15,3 μM mostraron actividad neuroprotectora por inhibición de las especies reactivas del oxígeno y disminución de la actividad de la caspasa-3. La metformina 1548,4 μM no proporcionó una neuroprotección significativa, pero disminuyó la generación de especies reactivas de oxígeno.* **Conclusiones:** *La combinación de Cannabidiol con los fármacos del estudio no mejoró la neuroprotección que la neuroprotección de los fármacos por separado.*

Palabras clave: *Cannabidiol. Neuroprotección. Muerte celular.*

***Correspondence:**
Mónica A. Ramírez-Cabrera
E-mail: monica.ramirezcbr@uanl.edu.mx

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Introduction

Neuroprotection is the prevention of neuronal cell death by intervening and inhibiting the pathogenetic process that causes neuronal dysfunction and death[1]. Compounds with this activity have the potential to treat neurodegenerative diseases. Although some therapies, such as pharmaceutical, herbal agents, surgical methods, exercise, ultrasound, and photobiomodulation[2], have been approved for managing and caring for these diseases, until now there is no cure.

Compounds like bilobalide and the current medicinal drugs valproic acid, furosemide, and metformin have shown neuroprotective effects in some studies, so they have the potential to be pharmacologically repositioned for other therapeutic use. On the other hand, cannabidiol (CBD), the main non-psychoactive phytocannabinoid of marijuana, has been proposed as an alternative for the treatment of several neuropsychiatric and neurological disorders[3]. This molecule has shown a neuroprotective effect through several mechanisms such as anti-inflammatory, immunomodulatory, decreasing inflammatory cytokines.[4]

The search for neuroprotective compounds is needed considering that there is a lack of medicinal drugs that limit neuronal damage; the potential neuroprotection of CBD; and the increased use of non-prescribed CBD products for treating different conditions. The objective of this study was to evaluate the neuroprotective activity of CBD individually and mixed with valproate, furosemide, bilobalide, and metformin in an *in vitro* model of neurotoxicity.

Materials and methods

CBD was purchased from Spex CertiPrep (Metuchen, NJ, USA), valproic acid, bilobalide, metformin, bilobalide, Trolox, glutamate, DCFDA, xanthine oxidase, 2,2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH), dimethyl sulfoxide, MTT, H_2O_2 from Sigma-Aldrich, (St Louis, MO, USA). Furosemide from PiSA Laboratories (Santa Catarina, Mexico), RPMI-1640 medium, and kit EnzChek® Caspase-3 assay Kit #2 from Thermo Fisher Scientific. The PC12 cell line is part of the UANL molecular pharmacology and biological models laboratory catalog.

Cell culture

The PC12 cell was grown in RPMI-1640 medium, 20% fetal bovine serum, and 1% antibiotics (5 mg/mL penicillin, 5 mg/mL streptomycin). They were cultured in 25 cm^2 tissue-culture flasks at 37°C, 5% CO_2, and humidified atmospheric conditions. The medium was replaced every 2 days. Confluent cultures were washed with phosphate-buffered saline and detached with trypsin/ethylenediaminetetraacetic acid solution. Third passage cells with 80% confluence were used for experiments.

The concentrations used for each compound were as follows: CBD 5 μM[5], valproate 433.4 μM (therapeutic dose for seizure in patients with epilepsy and mood disorders)[6], bilobalide 15.3 μM (is the IC_{50} value)[7], furosemide 604.7 μM (is the ED_{50})[8], and metformin 1548.4 μM (neuroprotective against H_2O_2)[9]. Each compound was dissolved in an FBS-free medium.

Neurotoxicity assay

Ten thousand cells were placed in 96-well plates and incubated for 24 h. Compounds were added alone and in a binary combination with CBD at the concentrations previously mentioned and incubated for 24 h. The medium was replaced with [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] (MTT) solution (0.5 mg/mL) and incubated for 3 h. Formazan crystals were solved with a solution of isopropyl alcohol/HCl (10%), and after 30 min, absorbance was measured at 550 nm in a microplate enzyme-linked immunosorbent assay reader ELx800 (Biotek instruments). Results were expressed as a percentage of cell viability[10]. Glutamate (25 mM) was the positive control for neurotoxicity, and glutamate-free cells as a control of 100% cell viability.

Neuroprotection assay

Ten thousand cells were placed in 96-well plates and incubated for 24 h. Then, a 2 h pre-treatment[11] with the compounds alone and mixed with CBD was added. Thereafter, 0.1 mL of glutamate 25 mM[12] was added, and incubated for 22 h. The medium was removed and replaced with MTT solution (0.5 mg/mL). The same protocol for MTT assay was performed. Results were expressed as a percentage of cell viability. Trolox® 50 μM was the positive neuroprotection control[13].

Two different concentrations of each drug, including CBD, were used for the preliminary evaluation of the combinations of CBD with the other studied drugs. The first concentration was the same used for the neuroprotective and neurotoxic assays; the second concentration was ½ of the concentrations previously

mentioned. The increase or decrease in cell viability was compared between the CBD combinations and the individual drugs.

Antioxidant activity

0.1 mL of each drug, alone and mixed with CBD 5 μM was placed in a 96-well plate, then 0.1 mL of 100 μM DPPH[14] solution was added. The microplate was incubated in darkness at room temperature for 15 min, then absorbance was measured at 517 nm. The negative control was wells containing DPPH solution. Results were expressed as a percentage of DPPH inhibition.

Inhibition of reactive oxygen species (ROS) production

Ten thousand cells/well were pretreated with CBD alone and mixed with the other molecules. Then, H_2O_2 (0.1 mM) was added, and incubated for 1 h. Then, 2',7'-dichlorofluorescein diacetate (H_2DCFDA)[15] solution (0.05 mg/mL) was added and incubated for 20 min. Fluorescence was measured at 485 nm of excitation and 530 nm of emission. Negative control was cells treated with H_2O_2 0.1 mM.

Caspase-3 activity

The EnzChek® Caspase-3 Assay Kit#2 was used according to the manufacturer's instructions. The assay was performed only for bilobalide and metformin alone and mixed with CBD. First, 1,000,000 cells were placed in a 35-mm petri dish and exposed to bilobalide and metformin alone and mixed with CBD. Glutamate 25 mM was added and incubated for 2 h. The medium was removed, cells harvested, washed with PBS, lysed, and centrifuged. To 0.05 mL of supernatant, 0.05 mL of the caspase-3 substrate Z-DEVD-R110 was added and set in darkness for 30 min at room temperature. Fluorescence was measured at 496 nm/520 nm excitation and emission in Fluoroskan Ascent (Thermo Fisher). Trolox® 50 μM was the positive control of inhibition of caspase-3, and glutamate 25 mM was the negative control.

Statistical analysis

Data are expressed as mean ± standard error of the mean of three independent experiments performed in triplicate (n = 9). Statistical comparisons were performed using one-way analysis of variance with Tukey's multiple comparisons test. The statistical software GraphPad Prism 5 was used for the analysis. A $p < 0.05$ was considered significant.

Results

Neurotoxicity assay

Individually, CBD and other drugs did not show neurotoxic activity, their cell viability ranging from 77.3 to 106.5%. Furosemide had significantly lower cell viability than CBD (77.3 vs. 106.5%; $p < 0.0001$). Combinations of CBD with other drugs did not show neurotoxicity, and the cell viability was above 80%. All drugs, both individually and combined with CBD, significantly increased cell viability compared to the neurotoxic control, glutamate 25 mM (cell viability 47%; $p < 0.05$); however, the cell viability of the combination of CBD with the other compounds was not better than individual drugs (Fig. 1).

Neuroprotection activity of individual molecules

The pre-treatment of PC12 cells with CBD, and subsequent exposition to glutamate, 25 mM, significantly increases 22.6% cell viability than non-pretreated cells (cell viability = 47%; $p < 0.05$). This neuroprotective activity, however, was lesser than the positive control of neuroprotection Trolox 50 μM (cell viability = 103.4%). Bilobalide (15.3 μM) showed neuroprotection (cell viability = 97.6%) similar to Trolox. The other studied compounds did not show neuroprotective activity (Fig. 2).

Neuroprotection activity of combined molecules

Only the pre-treatment of CBD combined with bilobalide showed neuroprotective activity since significantly increased the viability (108.3%) of glutamate-exposed cells ($p < 0.05$). However, this neuroprotection was not different than neuroprotection of individual compounds (Fig. 2).

Antioxidant activity

All drugs, individually and combined with CBD, showed lower antioxidant activity than Trolox 50 μM (71.35%) ($p < 0.0001$). The values of antioxidant activity ranged from 3.87% to 9.3% with no significant difference among them.

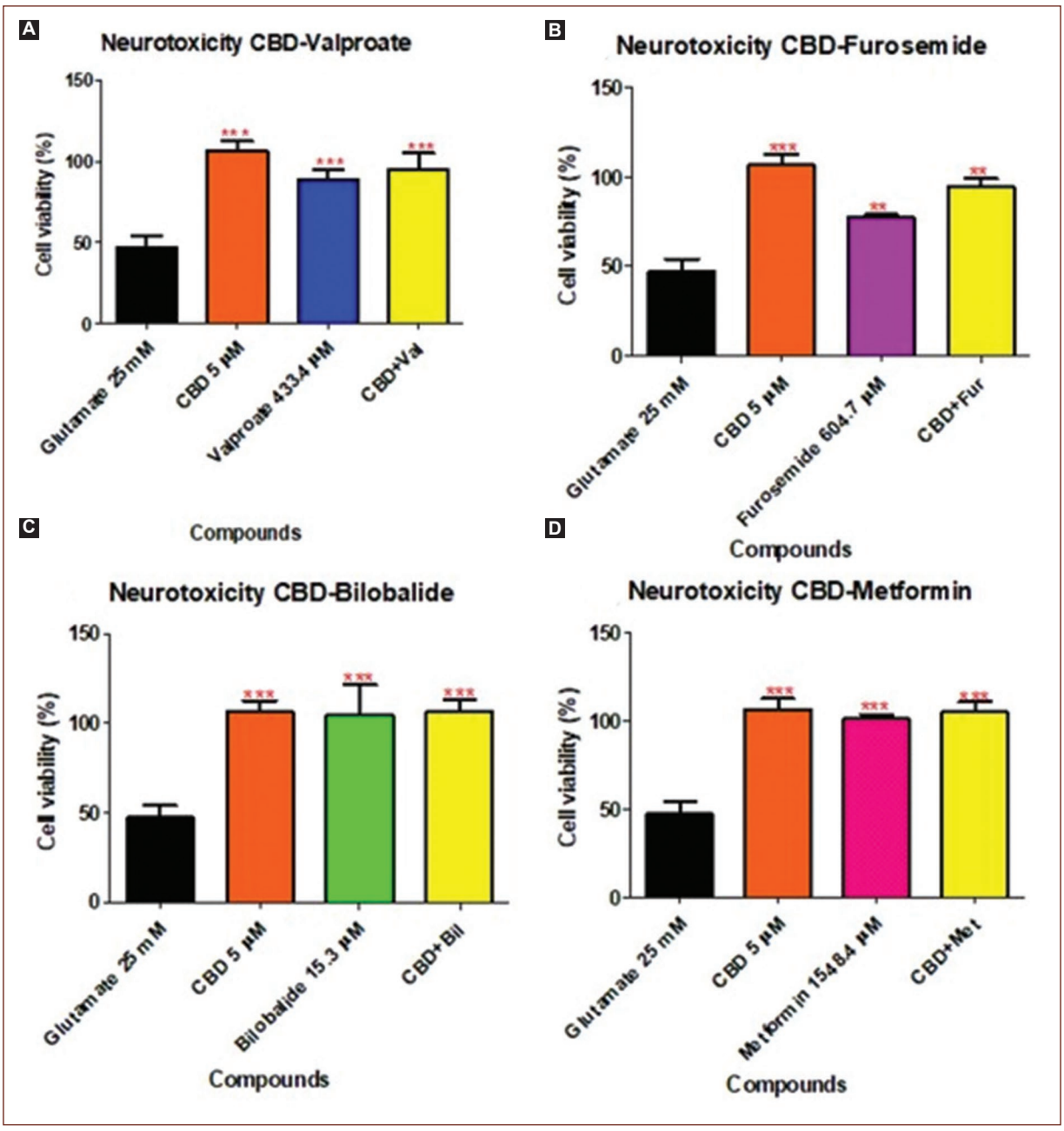

Figure 1. (A-D) Neurotoxic activity of CBD, alone and mixed with current medicinal drugs. ***p < 0.05 with respect to control; CBD: cannabidiol; Val: valproate; Bil: bilobalide: Met: metformin.

Inhibitory activity of ROS production

Only CBD, bilobalide, and metformin decreased the production of ROS (38.2%, 50.1%, and 39.5%, respectively) compared with H_2O_2 0.1 mM. However, these values were minor than Trolox 50 µM (78%) ($p < 0.0001$). The capacity of CBD to inhibit ROS production did not improve when it was mixed with the other molecules (Fig. 3).

Caspase-3 activity

Only CBD, alone and mixed with bilobalide, significantly decreased caspase-3 activity (40.9 and 38.5%, respectively). Although the combination of bilobalide plus CBD significantly decreased caspase 3 activity, this activity was not better than the activity of individual drugs (Fig. 4). There was no difference between the control (Trolox), CBD, and the combination CBD plus bilobalide.

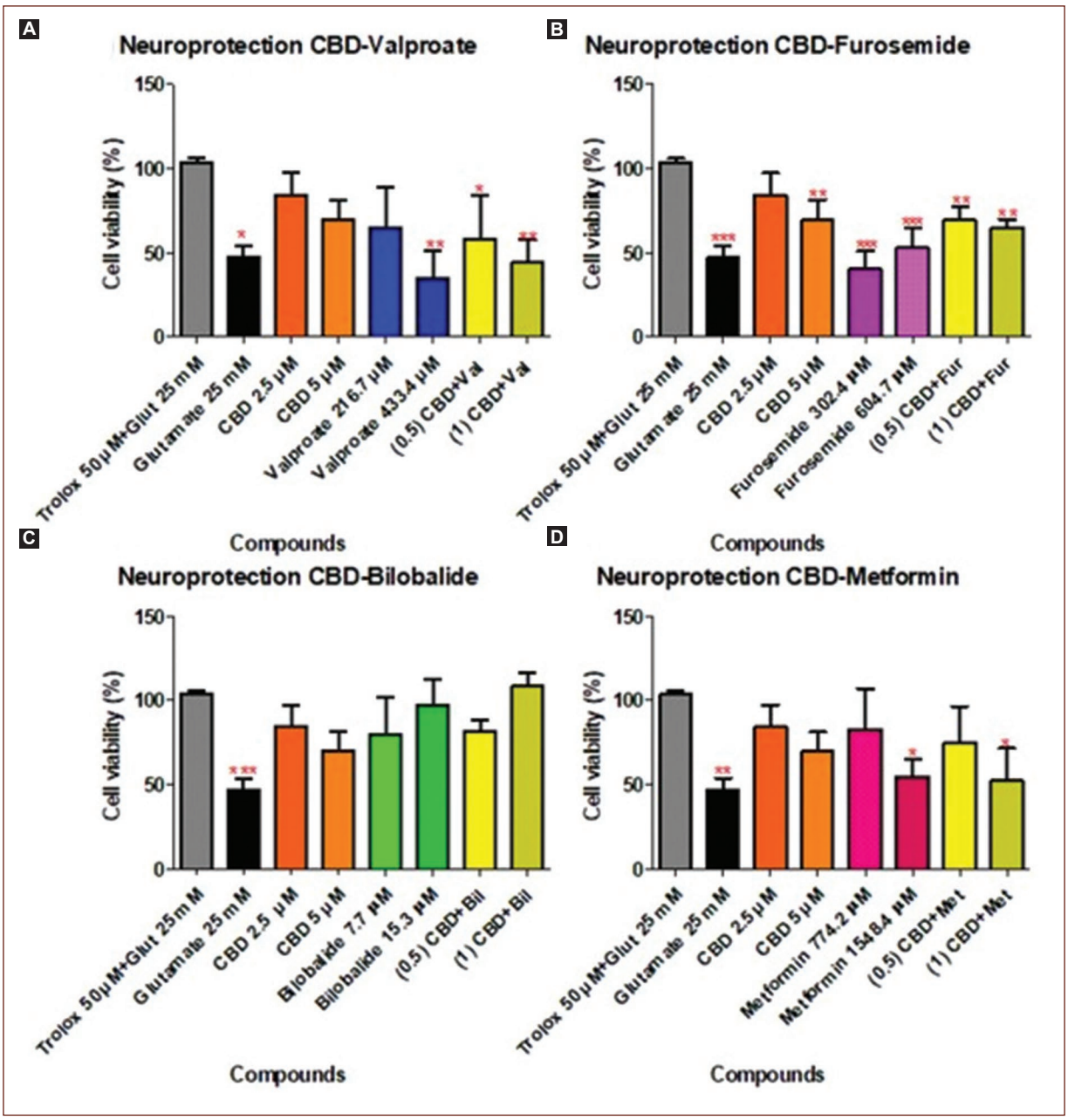

Figure 2. (A-D) Neuroprotection activity of CBD alone and mixed with current medicinal drugs. ***p < 0.05 with respect to control; CBD: cannabidiol; Val: valproate; Bil: bilobalide; Met: metformin.

Discussion

Individually, CBD and the other molecules studied did not showed neurotoxicity in PC12 cells. Previous reports indicate that CBD (10 μM) and valproate (1-5 mM) are neurotoxic in higher doses than used in the present study[16,17]. Bilobalide and metformin (2 mM) do not have neurotoxic activity in the PC12 cells[18,19] and SH-SY5Y cells,[20] respectively, which is similar to the present study. In the case of furosemide, there are no previous studies.

The pre-treatment of CBD showed neuroprotection that was similar to previous studies that use different cells and neurotoxic agent[5]. The mechanisms reported include decreased ROS accumulation, lipid peroxidation, caspase-3, DNA fragmentation, attenuation of intracellular calcium, and inhibition of iNOS and NO production[21,22]. The inhibition of ROS production, and

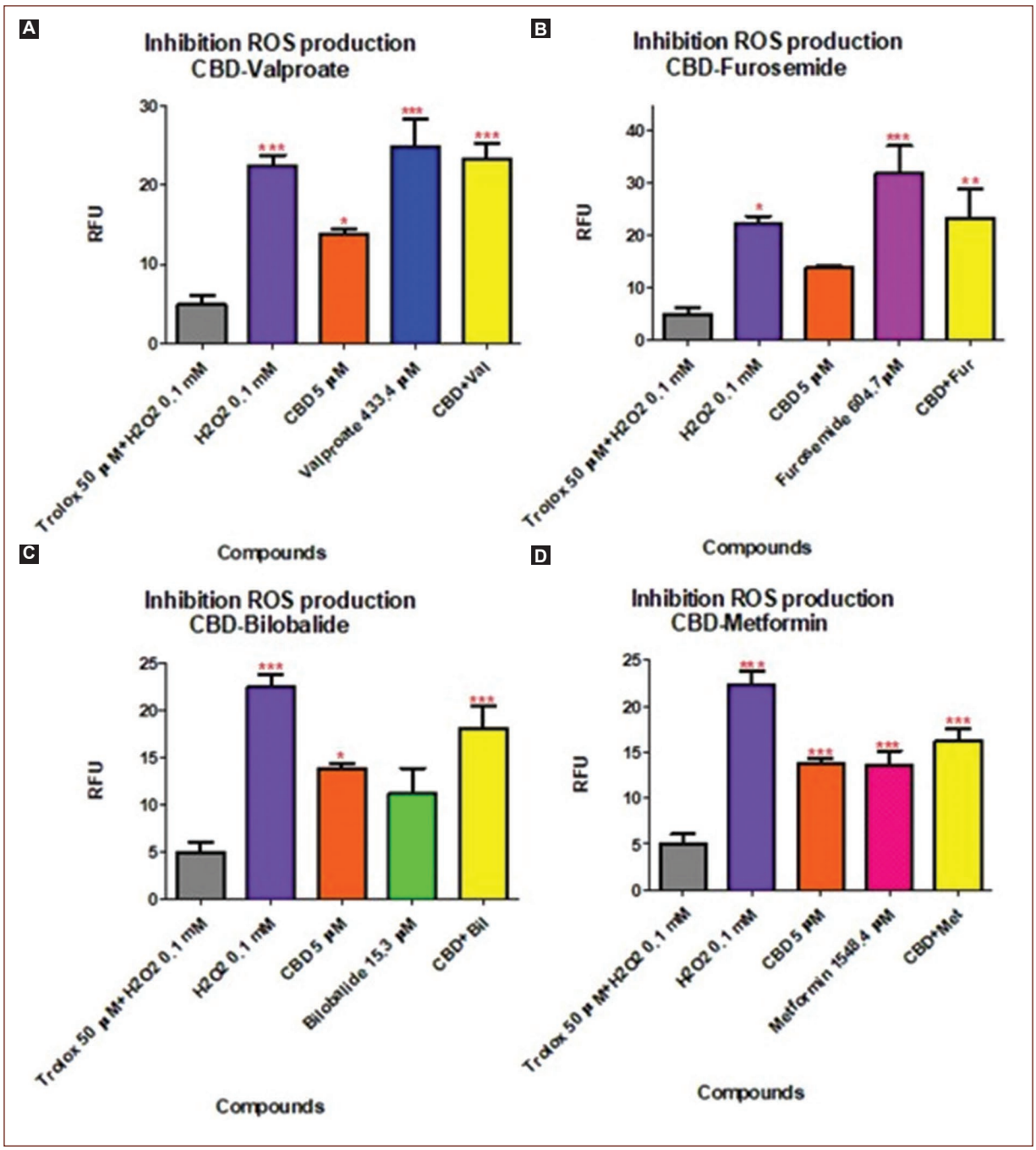

Figure 3. (A-D) Reactive oxygen species production inhibitory activity of CBD alone and in combination with valproate, furosemide, bilobalide, and metformin. ***p < 0.05 with respect to control: CBD: cannabidiol; Val: valproate; Bil: bilobalide; Met: metformin.

decrease in caspase-3 activity (40.9%) observed in the present study also has been reported in SH-SY5Y and PC12 cells[23,24].

Valproate does not show neuroprotective activity, which is contrary to previously reported, this could be due to the different dose and neurotoxic agents used. In a study, valproate (50-400 µM) increases cell viability (> 75%) of PC12 cells exposed to aluminum maltolate (1000 µM), the mechanism was by minor apoptosis, decreased ROS, catalase activity, and reduced mitochondrial membrane potential[25]. In another study with motor neurons treated with glutamate 100 µM,

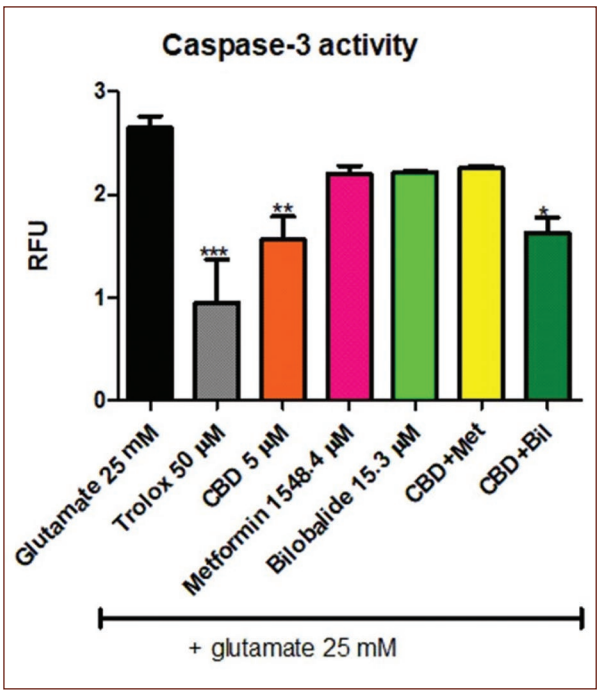

Figure 4. Caspase-3 activity of CBD alone and combined with bilobalide and metformin. **p < 0.05; CBD: cannabidiol; Bil: bilobalide.

valproate increased cell viability through the inhibition of histone deacetylase[26] and acetylation of factor transcription SP1[27,28].

In the present work, furosemide was studied for the 1st time in PC12 cells and did not show neuroprotective activity. This is contrary to reported previously in microglial cell line SIM-A9, where it decreased the proinflammatory microglia phenotype M1 and favored the anti-inflammatory phenotype M2 on cells exposed to lipopolysaccharides (5 ng/mL)[29]. The antioxidant activity was similar to that previously reported, but the inhibition of ROS production was different than reported in SIM-A9 cells[29,30].

As has been previously reported in PC12 cells (25-100 µM), and primary culture of astrocytes (100 µM), bilobalide has neuroprotective activity. Mechanisms include inhibition of ROS production by glucose and oxygen deprivation[31], decreased apoptosis by BAX, and caspase-3 activation induced by ROS[19]. The inhibition of ROS production is similar to that obtained in the present study.

Metformin (1.54 mM) did not show neuroprotective activity which is contrary to other studies and is explained by the different doses used. Higher doses (2 mM) demonstrated neuroprotective activity in PC12 cells and primary culture of hippocampal neurons exposed to H_2O_2 100 µM. The mechanism includes decreased apoptosis and necrosis, less intracellular ROS production, and protected mitochondrial membrane potential by AMPK activation[9]. Antioxidant activity (DPPH inhibition) was lower (5.14% at 1.54 mM) than previously reported, and it is explained by the higher doses used (31% at 20 mM)[32]. The decreased ROS production by metformin (39.4%) is similar to previously reported[9]. Contrary to other studies metformin does not significantly decrease caspase-3 activity and is explained by the different cells and concentrations used[33].

Results showed that CB combined with the studied drugs neither improve nor worsen the neuroprotection of each individual drug. Although with limitations, these results imply that the combinations studied do not produce a beneficial synergic effect in PC12 cells. It is necessary to confirm this with an isobolographic analysis.

There are no studies about the neuroprotective activity of CBD combined with these drugs *in vitro* or *in vivo* models; however, there are some anecdotal findings. In the case of valproate, a clinical case reports that CBD does not modify the antiepileptic effect of valproate[34]. In a clinical trial, CBD plus valproate increased hepatic aminotransferase enzymes[35]. Although the coadministration of CBD and furosemide has not been evaluated, some neuroprotective activity is possible since furosemide has a neuroprotective activity similar to CBD in an *in vivo* binge model induced by ethanol in rats. The combination of CBD plus bilobalide could have pharmacokinetic interaction since both molecules interact with the CYP1A2 isoform. The same could be for the combination of CBD plus metformin since both decrease CYP3A4 expression[36].

Limitations

Only two concentrations of each combination were used in this study. This approach does not permit concluding the type of interactions, such as synergism, summation, potentiation, or antagonism. However, our study permits discarding, in a preliminary way, a beneficial synergic effect of the CBD combination with the study drugs *in vitro*.

Conclusion

CBD and bilobalide present neuroprotective activity in PC12 cells exposed to glutamate 25 mM. The

neuroprotective activity of CBD did not improve when combined with furosemide, valproate, and metformin. Bilobalide, CBD, and metformin decrease ROS production. Only CBD decreases caspase-3 activity.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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ORIGINAL ARTICLE

Clinical and psychophysiological features of smoking and depression (preliminary results)

Sofía Cañizares-Gómez[1,2], Julian V. Reyes-López[1,3], Cintli C. Carbajal-Valenzuela[4], Wendy V. Herrera-Morales[5], Luis Nuñez-Jaramillo[5], Jorge J. González-Olvera[6], Liane Aguilar-Fabré[1], René F. Rodríguez-Valdés[1], Gerardo Trejo-Cruz[2], and Hebert L. Hernández-Montiel[1,3]*

[1]Neurodiagnostic and Neurorehabilitation Unit "Dr. Moisés López González", Autonomous University of Querétaro, Querétaro; [2]Faculty of Medicine, Autonomous University of Querétaro, Querétaro; [3]Faculty of Natural Sciences, Autonomous University of Querétaro, Querétaro; [4]Faculty of Psychology, Autonomous University of Querétaro, Querétaro; [5]Department of Medical Sciences, Division of Health Sciences, Autonomous University of the State of Quintana Roo, Chetumal; [6]National Commission on Mental Health and Addictions. Mexico

Abstract

Objective: *Smoking and depression are two mental health problems that can have a negative effect on a person's overall health. Studies have shown that smoking and mayor depressive disorder (MDD) have a bidirectional relationship. The objective of this study was to deepen the knowledge of the clinical features and psychophysiological bases of heart rate variability (HRV).* **Methods:** *Eighty participants (40% females, 18 and 45 years old) were included and represent a subsample of a randomized clinical trial that explored the therapeutic effects of transcranial magnetic stimulation in patients with depression, suicidal ideation, and smoking. Clinical features were measured in smokers n = 20, MDD n = 20, smokers + MDD n = 20, and controls n = 20 using MINI-plus, the Beck Depression Inventory, the Hamilton Anxiety Scale, the Hamilton Depression Scale, the Fagerström test (FT), the Nicotine Craving Questionnaire (NCQ), co-oximetry and a signal reactivity paradigm with HRV for psychophysiological measures, and the Marlow and Crowne Scale.* **Results:** *Comparison between groups demonstrated that participants with MDD and smokers + MDD had higher scores than the other groups on the depression ($p < 0.001$) and anxiety scales ($p < 0.001$). In the FT, smokers present higher consumption compared to all the groups ($p < 0.001$). In the NCQ, smokers and smokers + MDD had similar behavior with higher scores ($p < 0.001$).* **Conclusions:** *The MDD group had HRV values below the references; smokers and smokers + MDD presented a greater psychophysiological reaction when exposed to the signal reactivity paradigm, and this was reflected in the HRV as they had values below the references.*

Keywords: *Depression. Smoking. Heart rate. Psychophysiology.*

Características clínicas y psicofisiológicas del tabaquismo y la depresión (resultados preliminares)

Resumen

Objetivo: *El tabaquismo y la depresión son dos problemas de salud mental que pueden tener un efecto negativo en la salud general de una persona. Los estudios han demostrado que el tabaquismo y la depresión (TDM) tienen una relación bidireccional. El objetivo de este estudio fue profundizar en el conocimiento de las características clínicas y las bases psicofisiológicas de la variabilidad de la frecuencia cardíaca (VFC).* **Métodos:** *Se incluyeron 80 participantes (40% mujeres,*

***Correspondence:**
Julian V. Reyes-López
E-mail: opdeih@yahoo.com

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18 y 45 años). Las características clínicas se midieron en fumadores n = 20, TDM n = 20, fumadores + TDM n = 20 y controles n = 20 utilizando el Inventario de Depresión de Beck (BDI), la Escala de Ansiedad de Hamilton (HAS), la Escala de Depresión de Hamilton (HDS), la prueba de Fagerström. (FT), Cuestionario de ansia de nicotina (NCQ), Cooximetría y paradigma de reactividad de señales y VFC. **Resultados:** *La comparación entre grupos demostró que los participantes con TDM y fumadores + TDM tuvieron puntuaciones más altas que los otros grupos en la escala de depresión (p < 0,001) y ansiedad (p < 0,001), en el FT los fumadores presentan mayor consumo en comparación con todos los grupos (p < 0,001), en el NCQ los fumadores y fumadores + TDM tuvieron un comportamiento similar con puntuaciones más altas (p < 0,001).* **Conclusiones:** *El grupo TDM tuvo valores de VFC por debajo de las referencias, los fumadores y fumadores + TDM presentaron una mayor reacción psicofisiológica al exponerse al paradigma de reactividad de señales y esto se reflejó en la VFC al tener valores por debajo de las referencias.*

Palabras clave: *Depresión. Tabaquismo. Frecuencia cardíaca. Psicofisiología.*

Introduction

Smoking and depression are two mental health problems that can have a negative effect on a person's overall health. Studies have shown that smoking and depression have a bidirectional relationship, where smoking increases the risk of developing depression and depression increases the risk of becoming a smoker[1-3]. At present, there are several hypotheses that are proposed to explain the high rates of smoking in people with depression; for example, the work of Boden et al. proposes that people turn to tobacco to relieve their symptoms of depression and anxiety. It is suggested that the association between smoking and depression may also be bidirectional, and the comorbidity of both arises from two pathways: (1) common factors of risk and (2) smoking withdrawal symptoms increased anxiety and negative affect may be mistakenly attributed to reflecting genuine mood symptoms, leading to the impression that smoking improves mood[4,5]. As the neurobiological relationship between smoking and depression, different evidence has shown that nicotine facilitates the release of three major monoamines (dopamine, norepinephrine, and serotonin) implicated in the etiology of clinical depression. Furthermore, chronic nicotine treatment has been shown to increase the expression of brain-derived neurotrophic factor and fibroblast growth factor. Positive modulation of these trophic factors by monamines and cyclic adenosine monophosphate is now thought to play a role in the actions of antidepressants and mood stabilizers. The nicotinic receptors are localized in different structures relevant to depression (i.e., cingulate cortex, prefrontal cortex, amygdala, and dorsal raphe nucleus). On the other hand, nicotine has complex effects on the hypothalamic-pituitary-adrenal axis, inducing its activation, and this is associated with the hypercortisolemic state observed in some depressed patients[6-8].

In addition, recent research has shown that smokers have decreased heart rate variability (HRV), which could be related to increased depression[9-13]. HRV refers to the natural variation of the frequency, that is, the difference in the interval between successive cardiac contractions[14,15]. This relationship between smoking, depression, and HRV is an emerging area of research that may have significant implications for the prevention and treatment of these diseases.

HRV can be analyzed through several methods that are based on time domain, frequency domain, geometric measurements, and non-linear variables[15]. Within the temporal domain variables, we can find the standard deviation of RR intervals (RRSD), percentage of successive RR intervals that differ by more than 50 ms (PNN50), SD of the average NN intervals for each 5-min segment of a 24-h HRV recording (SDAN), and RMSSD[15]. The most commonly used is the RMSSD, which is the square root of the mean value of the sum of the squared differences of all successive RR intervals in the measured time. This measure is a cardiac vagal modulation index that is suggested as a method superior to spectral measures because it presents less sensitivity to variations in respiratory patterns and, in turn, is the most appropriate procedure for evaluating short periods in the HRV[16].

The objective of this study was to deepen the knowledge of the psychophysiological bases of HRV in participants who were smokers and had been diagnosed with depression, or both.

The data presented in this article represent a subsample of a randomized clinical trial that explored the therapeutic effects of transcranial magnetic stimulation in patients with depression, suicidal ideation, and smoking. In this article, we show the preliminary results of the influence of depression with and without comorbidity with smoking on HRV and whether said comorbidity affects tobacco consumption.

Methodology

Participants: a total of 80 participants, between 18 and 45 years of age, of both sexes were included, 20 of whom had a diagnosis of depression, 20 were smokers, 20 were both smokers and had a diagnosis of depression, and 20 were control participants. All of them attended the Neurodiagnostic and Neurorehabilitation Unit[1] of "Dr. Moisés López González", which is part of the University Health System of the Autonomous University of Querétaro (UAQ), and agreed to sign an informed consent letter, which was previously explained to them. All participants were diagnosed according to the DSM-5 criteria (APA 2013). This study was approved by the bioethics committee of the UAQ's Faculty of Medicine under number 11343. The clinical trial registration number is NCT05694754 (ClinicalTrials.gov PRS).

Instruments

Mini International Neuropsychiatric Interview (MINI Plus): a brief and highly structured interview of the main psychiatric disorders of the ICD-10 and DSM IV; it is structured in formats and algorithms and is modular by diagnostic categories[17]. Used in this work as a support instrument for the diagnosis of depression and the exclusion of other psychiatric disorders.

Marlow and Crowne Social Desirability Scale: a 33-item self-applied scale that allows us to evaluate the participants need to respond in a culturally accepted way. It produces values between 0 and 33, in which a higher score indicates greater desirability, understood as response bias[17,18].

Beck depression inventory (BDI): a self-applicable test consisting of 21 items for the evaluation of depressive clinical symptoms. The cutoff points range from 0 to 9 (absent or minimal), 10 to 16 (mild), 17 to 29 (moderate), and 30 to 36 (severe)[19].

Hamilton anxiety scale (HAS): a hetero-applicable instrument consisting of 14 items for the assessment of the severity of symptoms of anxiety states; it is divided into two subscales: psychic anxiety and somatic anxiety. A higher score indicates a higher intensity[20].

Hamilton Depression Scale (HDS): consisting of 21 items for the assessment of the severity of depressive symptoms. It provides a global score for the severity of the depressive symptoms and a score for three indexes, which are melancholy, anxiety, and sleep. The cutoff points range from 0 to 7 (without depression), 8 to 13 (mild depression), 14 to 18 (moderate depression), 19 to 22 (severe depression), and higher than 23 (very severe depression)[20].

Fagerström test: a short and simple test consisting of six questions that assess dependence on tobacco users. The score ranges from 0 to 10 in such a way that the higher the score, the greater the dependence[21].

Nicotine Craving Questionnaire (NCQ): a 12-item questionnaire to assess the degree of craving, with five response options ranging from 1 (completely disagree) to 5 (completely agree)[22].

Co-oximetry: it is a spectrophotometric technique to detect the loss in the oxygenation capacity of hemoglobin, which consists of determining the level of carbon monoxide (CO) in the air exhaled by an individual. The device used to perform this test is called a co-oximeter, a high-precision monitor that measures the concentration of CO in parts per million (ppm).

The co-oximeter indicator stabilizes and marks the exact number of ppm of CO in the subject's exhaled air.

HRV: it performed using the signal reactivity paradigm, which consists of presenting blocks of images that were chosen from the International Smoking Imaging Series (with neutral counterparts), Version 1.2. In this test, the participant is subjected to a series of visual stimuli while wearing a Polar H10 chest strap sensor and a Bluetooth transmitter used for HRV measurement. The test consists of four blocks of images: two blocks of tobacco images and two blocks of neutral images, which in turn are interspersed. Each block of images consisted of 25 images; each image appeared for 6 s on the screen, for a total of 150 s per block.

Statistical analysis

A statistical analysis was performed using the IBM SPSS Statistics 25 software as well as the GraphPad Prism 6 software. The mean of the clinical and psychophysiological scores was compared between various groups of the tested variables using a one-way ANOVA. For *post hoc* analysis, the Fisher's LDS method was employed, and the significance level was set at $p < 0.05$.

Results

Table 1 shows the sociodemographic data of the four groups and the clinical results. It was found in the BDI that the major depressive disorder (MDD) group had a higher score than the other groups ($p < 0.001$); likewise, the smokers + MDD group showed differences in regard to the other groups ($p < 0.001$). Furthermore, it

1 In Spanish: *Unidad de Neurodiagnóstico y Neurorehabilitación*.

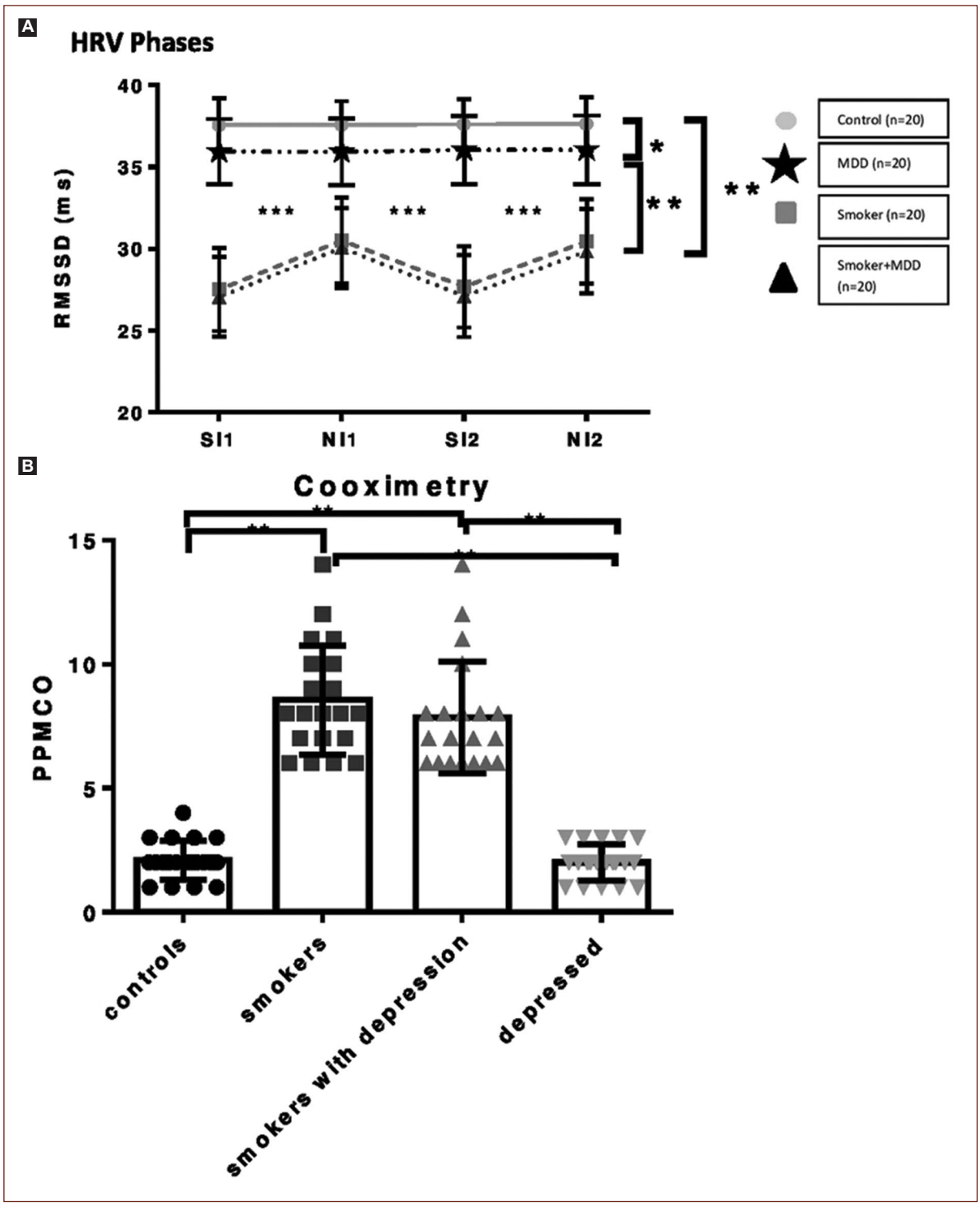

Figure 1. A: in this figure, we can see the comparison between HRV groups throughout the four phases of the signal reactivity paradigm. On the X-axis, we can see the four blocks of the reactivity signal paradigm and on the Y-axis, we can observe the media of the RMSSD (ms). **B:** the comparison between the groups of the values obtained in the co-oximetry test is shown. On the X-axis, we can observe the four groups and on the Y-axis, we can see the PPMCO. SI1 (smoking images 1), NI1 (Neutral images 1), SI2 (smoking images 2), NI2 (Neutral images 2), RMSSD ms (square root of the mean value of the sum of the squared differences of all successive RR intervals in the measured time expressed in milliseconds) PPMCO (particles per million of carbon monoxide); * = $p < 0.05$, ** = $p < 0.001$, *** = $p < 0.0001$.

Table 1. Sociodemographics and clinical results

Variables	Groups			
	Control (n = 20)	Smokers (n = 20)	Smokers+MDD (n = 20)	MDD (n = 20)
Gender	♂ = *38%* ♀ = *62%*	♂ = 35% ♀ = 65%	♂ = 45% ♀ = 55%	♂ = 33% ♀ = 67%
Age	$\bar{X}$ = 37.66 ± 6.39	$\bar{X}$ = 36.26 ± 8.02	$\bar{X}$ = 35.83 ± 8.41	$\bar{X}$ = 34.93 ± 7.24
Years of study	$\bar{X}$ = 18.08 ± 2.42	$\bar{X}$ = 17.3 ± 3.17	$\bar{X}$ = 17.66 ± 2.62	$\bar{X}$ = 16.85 ± 2.06
Depressive episodes throughout life	$\bar{X}$ = 0	$\bar{X}$ = 0	$\bar{X}$ = 7.08 ± 3.39	$\bar{X}$ = 6.38 ± 1.83
Duration of most recent depressive episode (months)	$\bar{X}$ = 0	$\bar{X}$ = 0	$\bar{X}$ = 8.49 ± 5.59	$\bar{X}$ = 5.38 ± 3.04

Clinical variables	Groups					
	Control	Smokers	Smokers + MDD	MDD	F	p-value
	M (SD)	M (SD)	M (SD)	M (SD)		
BDI	#^1.6 (0.82)	#^1.8 (1.2)	#35 (5.2)	30.8 (3.3)	648.601	< 0.001
HDS	#^1.35 (1.30)	#^1.7 (1.7)	30.8 (3.4)	30.4 (8.1)	273.716	< 0.001
HAS	#^2 (0.97)	#^2.2 (1.2)	*25.2 (3.7)	28.1 (4.8)	399.212	< 0.001
Fagerström	***^0 (0)	#^9.3 (2.4)	7.4 (1.9)	***^0 (0)	191.462	< 0.001
Craving	***^0 (0)	#37.4 (4.8)	37.3 (4.6)	***^0 (0)	820.738	< 0.001

MDD: mayor depressive disorder; M: media; SD: standard deviation; $\bar{X}$: mean.
* = p < 0.05 compared with MDD group.
*** = p < 0.0001 compared with smokers group.
^ = p < 0.0001 compared with smokers + MDD group.
# = p < 0.0001 compared with MDD group.

was observed in the HDS that the MDD and smokers + MDD groups had a higher score than the other groups (p < 0.001).

As for the HAS, the MDD and smokers + MDD show differences with higher scores (p < 0.0001) compared with the other groups, and MDD shows higher scores than smokers + MDD (p < 0.05).

However, in the Fagerström test, smokers presented a higher consumption compared to all the groups (p < 0.001).

In the NCQ, both smoker and smokers + MDD groups showed similar behavior in the scores, which were higher than the other groups (p < 0.001).

Fig. 1A shows that both the smokers and smokers + MDD groups have below-reference HRV values and significant differences with the control and MDD groups (p < 0.001 in both cases); the MDD group shows a reference value lower than the control group (p = 0.023). The within intragroup analysis shows that smokers and smokers + MDD have differences in the HRV along the signal reactivity paradigm, with lower values in the blocks of smoking images in comparison with the neutral image blocks (p < 0.001 for both groups).

Fig. 1B shows that the smokers and smokers + MDD groups show a higher concentration of PPMCO in co-oximetry (p < 0.001) compared with the other groups.

Discussion, Conclusions, and Limitations

To the best of our knowledge, this is the first study carried out in a Mexican population in which the psychophysiological component of HRV was evaluated in these groups of patients. The results of this study are consistent with the reports of Schiweck, Sgoifo, Kircansky, and Kindwell, where they found a reduction in HRV in subjects with depression[13,23,24]. Based on the results of this study, we can observe that participants in the smokers and smokers + MDD groups, who presented a significant reduction in HRV during all phases of the signal reactivity paradigm (neutral images and smoking imaging blocks) compared with the control and MDD groups, had a psychophysiological reaction that has been described by Ashare, Soares, and Erblich[11,25,26].

Having carried out the analyses, we can conclude that the participants with MDD showed below-reference HRV values. In a similar manner, participants in the

smokers and smokers + MDD groups presented a greater psychophysiological reaction when exposed to the signal reactivity paradigm, which was a below-reference HRV value. These findings are similar to those reported by Kroczek et al. who show changes in spectral measures of HRV during smoking cue exposition[27].

Our results have potential clinical importance since exploring the different dimensions in which smoking and depression can manifest themselves allows us to search for new and better diagnostic and evaluation alternatives for the different dimensions that may be affected. For example, the associations between some symptoms of MDD measured by HDS and HRV have already been reported. In this sense, melancholic features of MDD were related to HRV parameters using frequency methods[28] and temporal parameters (SDNN and RMSSD)[29]. The existent evidence shows a relationship between HRV and the severity of depression; for example, patients with more severe depression tend to have a lower HRV than those with less severe depression[29,30].

Some limitations should be noted, especially the sample sizes; had they been larger, we could have formed subgroups based on cigarette consumption. In the same way, we need to deepen the analysis of the HRV by including more variables.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript or for the creation of images, graphics, tables, or their corresponding captions.

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ORIGINAL ARTICLE

12-year effectiveness and safety of botulinum toxin type A for the treatment of blepharospasm and hemifacial spasm

Héctor J. Colorado-Ochoa[1]* *and Victoria G. Tenorio-González*[2]

[1]*Neurología;* [2]*Medicina Interna. Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado (ISSSTE), Veracruz, Mexico*

Abstract

Objective: *The objective of this study was to perform a long-term evaluation of the efficacy and safety of treatment with botulinum toxin A (BoNT-A) in patients with blepharospasm (BS) and hemifacial spasm (HFS) from January 2007 to December 2019.* **Methods:** *In each application of BoNT-A, the date of treatment, number of units applied, and time elapsed since the previous application were recorded. Outcome data was: mean latency of the clinical effect, mean duration of the clinical effect, mean improvement on Jankovic rating scale, side effects were self-reported, and evaluated 2 weeks after injection, including non-responding patients to BoNT-A for two consecutive sessions. The comparison between the first and last dose of BoNT-A was analyzed by Student's t-test, for which a value of $p < 0.05$ was considered statistically significant.* **Results:** *A total of 136 patients were analyzed; 60 had BS, 76 had HFS, and 75% were female. The duration between onset and referral for BoNT-A treatment was 18 ± 3 months, and the mean age at the time of the first therapeutic injection was 50 ± 12 years. The mean dose per session was 16 ± 4 for BS and 36 ± 12 for HFS. The therapeutic interval for injections was 4.4 ± 1 month. The mean latency of the clinical effect was 8 ± 3 days, the mean duration of the clinical effect was 112 ± 9 days, and the mean improvement on the Jankovic scale was 2 ± 1 points. Side effects were observed in 9 patients (6.6%), that is, ptosis (7 patients) and hematoma (2 patients).* **Conclusions:** *BoNT-A is a safe and effective long-term treatment for BS and HFS.*

Keywords: *Facial dystonia. Blepharospasm. Hemifacial spasm. Botulinum toxin type A.*

Eficacia y seguridad durante 12 años de la toxina botulínica tipo A para el tratamiento del blefaroespasmo y el espasmo hemifacial

Resumen

Objetivo: *Realizar una evaluación de largo plazo de la eficacia y seguridad del tratamiento con Toxina Botulínica A (BoNT-A) en pacientes con Blefaroespasmo y Espasmo Hemifacial entre Enero 2007 y Diciembre 2019.* **Métodos:** *En cada aplicación de BoNT-A se registraron la fecha de tratamiento, número de unidades aplicadas, y el tiempo transcurrido desde la última aplicación. Los datos de desenlace fueron: el promedio de latencia del efecto clínico, el promedio de duración del efecto clínico, el promedio de mejoría en la Escala de Valoracion de Jankovic, los efectos secundarios fueron reportados por el paciente y evaluados 2 semanas después de la inyección, incluyendo pacientes no respondedores en 2 sesiones terapeúticas consecutivas. Las comparaciones de resultados entre la primera y la última dosis de BoNT-A fueron analizadas con la prueba t de Student, considerandose estadísticamente significativo un valor $p < 0.05$.*

Correspondence:
Héctor J. Colorado Ochoa
E-mail: hector_neuro@yahoo.com

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Resultados: *De un total de 136 pacientes analizados, 60 tenían blefaroespasmo, 76 tenían espasmo hemifacial, y 75% fueron femeninos, La duración entre el inicio y la referencia para tratamiento con BoNT-A fue de 18 ± 3 meses, la edad al momento de la primera inyección terapeútica fue de 50 ± 12 años de edad. El promedio de dosis por session fue 16 ± 4 en casos de blefaroespasmo, y 36 ± 12 en pacientes con espasmo hemifacial. El intervalo entre sesiones terapeúticas fue de 4.4 ± 1 meses. El promedio de latencia del efecto clínico fue de 8 ± 3 días, el promedio de duración del efecto clínico fue de 112 ± 9 días, y el promedio de mejoría en la Escala de Jankovic fue de 2 ± 1 puntos. Los efectos secundarios se observaron en 9 pacientes (6.6%) que presentaron ptosis (7 pacientes) y hematoma (2 pacientes).* **Conclusiones:** *BoNT-A es segura y efectiva en la terapeutica de largo plazo en pacientes con blefaroespasmo y espasmo hemifacial.*

Palabras clave: *Distonía facial. Blefaroespasmo. Espasmo hemifacial. Toxina botulínica tipo A.*

Introduction

Blepharospasm (BS) and hemifacial spasm (HFS) are two of the most frequent forms of focal cranial dystonia that chronically affect quality of life[1].

BS is a chronic focal dystonia with excessive involuntary contractions of the orbicularis oculi muscle[2]. The prevalence of BS is 4.24/100,000 inhabitants, affecting more women (4.78/100,000 inhabitants) than men (3.08/100,000 inhabitants)[3].

HFS is characterized by unilateral, intermittent, tonic, or clonic contractions of muscles innervated by the facial nerve[4]. In Rochester and Olmsted County, Minnesota, from 1960 to 1984, the prevalence rate in women was 14.5/100,000, and 7.4/100,000 in men. Most patients were between 40 and 79 years of age[5].

Different treatments have been used to treat BS and HFS, such as baclofen, gabapentin, orphenadrine, clonazepam, phenytoin carbamazepine, levetiracetam with insufficient results; microsurgery has an 80-90% rating success, but 25% of patients relapse in 2 years and has potential complications such as hearing loss, unilateral facial palsy, cerebral hemorrhage. The advent of botulinum toxin A (BoNT-A) has improve the treatment results on both conditions. BoNT-A injection is now a first-line treatment for HFS[1].

At present, it is not known whether the clinical efficacy of botulinum toxin decreases with time and repeated treatment sessions and if there is a possible loss of efficacy in clinical settings. Future studies comparing any form of BoNT-A should address the comparative proportion of participants who develop a nonresponse secondary to treatment[6].

Immune resistance tends to occur in the first 1-4 years of treatment, and the formation of antibodies seems less likely after that period[7]. Patients positive for antibodies against BoNT-A tend to have an earlier age of onset, higher mean dose per visit and higher cumulative dose than patients negative for antibodies[7].

The longest studies of treatment with BoNT-A refer to follow-ups of 15.8 years[7] and 16 years[8]. The present study was designed to retrospectively evaluate the efficacy and safety of BoNT-A in a cohort of the Mexican population treated for chronic BS and HFS.

Materials and methods

Design and participants

This study has a retrospective longitudinal design. Patients who attended the Botulinum Toxin Clinic at the ISSSTE Veracruz Hospital (Hospital ISSSTE Veracruz) from January 2007 to December 2019 were identified. Subjects were eligible if they were between 18 and 80 years of age, had a diagnosis of BS or HFS, had received treatment for 12 years, and had received at least one injection per year. The exclusion criteria were as follows: previous surgical treatment, incomplete data, or patients who did not attend follow-up for 12 months or more. Informed consent was obtained from all patients. This study complied with the ethical principles for research on human subjects in accordance with the Declaration of Helsinki.

Procedures

The injections were prepared as follows: dilution of BoNT-A (500 units or 100 units, regardless of brand) in 1 mL of 0.9% saline solution in a 1 mL syringe; a dilution of 100 units was obtained in a 1 mL syringe with 100 graduation marks. Patients were scheduled to return 2 weeks after the injection to observe the results. The BoNT-A brand names supplied over 12 years, 1 at a time, by Hospital Pharmacy were Botox® (Allergan) Onabotulinum toxin A, Xeomeen® (Merz) Incobotulinum toxin A, and Dysport® (Ipsen) Abobotulinum toxin A.

Measurement of results

From the records of the patients included in the study, data on sex, age at the time of the first treatment injection, duration between onset and referral for BoNT-A treatment, unilateral or bilateral symptoms, and focal or multisegmental manifestations were recorded.

For each application of BoNT-A, the date of treatment, number of units applied, and time elapsed since the previous application was recorded.

Follow-up schedule was: Evaluation 2 weeks after injection, and reinjection every 3 months at each follow-up visit, patients were asked about the results of the previous session.

For the evaluation of the effectiveness and long-term safety, dose per session, number, and location of injections, latency (defined as the time between the injection and the first sign of improvement), duration (defined as the interval between treatment and the recurrence of symptoms intense enough to lead the patient to receive another application), presence of side effects were evaluated by patient self-report and clinical evaluation at the 2-week follow-up visit, after every treatment session.

The data were analyzed and grouped by BS and HFS and are presented as the mean dose per session, interval between injections, mean latency of the clinical effect, mean initial latency, mean last latency, mean duration of the clinical effect, mean initial duration of the clinical effect, mean last duration of the clinical effect, mean improvement in the Jankovic scale[6], mean initial improvement in the Jankovic scale, mean last improvement in the Jankovic scale, and percentage of side effects. The Jankovic rating scale measures clinical features at basal and follow-up evaluation of severity and improvement, allowing to assess the efficacy of BS and HFS therapy.

Results

In the Botulinum Toxin Clinic of the ISSSTE Veracruz Hospital, the records of 141 patients were identified. Five patients lost to follow-up were excluded from the study. One hundred and thirty-six patients treated for 12 years between January 2007 and December 2019 who met the inclusion criteria (60 with BS and 76 with HFS) were analyzed. The mean duration from onset to referral for treatment with BoNT-A was 18 ± 3 months. Table 1 shows the demographic characteristics of the patients included in the study.

Table 1. Demographic characteristics of the long-term follow-up group consisting of 136 patients treated with BoNT-A for 12 years

Variable	Data (%)
Total patients (n)	136
Age at first injection	50 ± 12 years
Sex, n (%), female/male	102 (75) / 34 (25)
Blepharospasm	60 (44.1)
Hemifacial spasm	76 (55.9)
Unilateral symptoms	124 (91.1)
Bilateral symptoms	12 (8.8)
Focal symptoms	134 (98.5)
Multisegmental	2 (1.4)
BS, mean units per session	16 ± 4
HFS, mean units per session	36 ± 12
Treatment interval between injections	4.4 ± 1 months

BoNT-A: botulinum toxin A; BS: blepharospasm; HFS: hemifacial spasm. Data are presented as the mean ± standard deviation.

BS (n = 60)

Table 2 provides the mean and standard deviation of the measurements associated with the first and last applications of BoNT-A for the treatment of BS. In all the items analyzed, there was a statistically significant difference between the two measurements.

The mean dose per treatment session was 16 ± 4 U. Importantly, no primary resistance was detected, and no secondary resistance was reported with the first or last application of BoNT-A.

The comparison between the initial and final values allowed the identification of an increase in the dose of 2 units accompanied by a latency period shorter than 0.6 days, a 7-day increase in the duration of therapeutic effect, and an improvement in the Jankovic scale of 0.6. The interval between injections was slightly lower by 3 days at the final evaluation session.

HFS (n = 76)

Table 2 provides the mean and standard deviation of the measurements associated with the first and last application of BoNT-A for the treatment of HFS.

The mean dose of BoNT-A was 36 ± 12 U. In patients with HFS, there were no patients with primary resistance,

Table 2. Long-term follow-up of patients with BS and HFS treated with BoNT-A for 12 years. Analysis using student's t-test

Parameter	Initial	Final	p-value
Blepharospasm (n = 60)			
BoNT-A (units)	16 ± 2.7 (SD)	18 ± 2.1 (DE)	0.0001
Treatment interval (months)	4.4	4.3	0.0012
Latency (days)	9.2 ± 3.1	8.6 ± 4.5	0.020 (*)
Duration (days)	107 ± 6	114 ± 7	0.0001
Improvement in the Jankovic scale	2.7 ± 1.3	3.3 ± 0.3	0.0001
Primary resistance (%)	0	0	NS
Secondary resistance (%)	0	0	NS
Hemifacial spasm (n = 76)			
BoNT-A (units)	38 ± 7.1 (SD)	41 ± 6.3 (SD)	0.069 (*)
Treatment interval (months)	4.2	4.1	0.0001
Latency (days)	9.4 ± 3.1	9.2 ± 3.7	0.44 (*)
Duration (days)	109 ± 8	116 ± 5	0.0001
Improvement in the Jankovic scale	2.5 ± 1.5	3.1 ± 0.9	0.0001
Primary resistance (%)	0	0	NS
Secondary resistance (%)	0	0	NS

BoNT-A: botulinum toxin A; BS: blepharospasm; HFS: hemifacial spasm. Data are presented as the mean ± standard deviation (SD). (*) NS, not significant.

and no secondary resistance was reported with the first or last application of BoNT-A.

Comparing the units applied, there was a non-significant increase of 3 units and a non-significant decrease of 0.2 in days of latency; however, there was a significant difference in the decreased application interval of 0.1 months, in the duration of therapeutic effect, which increased by 7 days, and in the improvement in the Jankovic scale, which increased by 0.6 points.

Table 3. Side effects

Parameter	Initial	Final	p-value
Blepharospasm (n = 60)			
Ptosis	1	1	NS
Hematoma	1		NS
Hemifacial spasm (n = 76)			
Ptosis	3	2	NS
Hematoma		1	NS

Side effects

Side effects occurred with very low frequency in both groups. In the population with BS, 2 patients (3.3%) presented side effects after the initial injection, and 1 patient (1.6%) presented side effects after the last injection. In the population with HFS, 3 patients (3.9%) presented side effects from the first injection, and 3 patients (3.9%) presented side effects from the last injection. Table 3 lists the side effects recorded.

Discussion

Although botulinum toxin has been considered the first-line treatment for BS and HFS[1], few studies have considered the long-term follow-up of patients who receive BoNT-A. The analyzed cohort exclusively included Mexican patients from a hospital in the state of Veracruz.

This cohort had a predominance of women (3:1), similar to previous studies long-term studies that had a predominance of female patients[9]. Patients were referred to treatment on average 18 ± 3 months after the onset of symptoms.

In the present retrospective study, only one physician (HCO) treated the patients, and both investigators participated design and implementation of the research. In general, a study includes the results from the first session, reporting the changes observed during the follow-up, but Czyz[10] used the fourth visit as the "initial visit" to control for the confounding factor of the dosing adjustment phase, which usually starts with a dose of BoNT-A that is progressively modified over time, depending on changes in the spasm, the needs of the patient, the latency to improvement, the duration of improvement and the side effects.

The degree of improvement has been reported using several different methods: percentage of patients who

improved; number of injections needed for improvement; and percent improvement in spasms, as assessed using quantitative scales ranging from 0 to 7 or using a percentage from 0% to 100%. It has also been evaluated using a visual analog scale, as a subjective satisfaction scale to determine the degree of spasm remission[8].

In this study, the BS group the mean dose per treatment session was 16 ± 4 units, similar to previous long-term reports that indicate a dose range of 7.5U -140 U for onabotulinum toxin A and of 40U-400 U for abobotulinum toxin A[11].

HFS patients in this study were treated with 15 U or 25 U of onabotulinum toxin A[12], with a mean dose of 36 ± 12 units, results that are similar to previous long-term literature with no significant difference in response rate and duration of improvement.

With respect to the purpose of this study, there was an increase in the final dose at the 12th year, compared to the initial dose of BoNT-A, similar to the majority of long-term reports.

For the treatment of BS, in this study, the increase in the mean dose from 16 U to 18 U of BoNT-A was significant; the duration of the effect was significantly longer, improvements in the score for the Jankovic scale were significant, the latency time was shorter by 0.6 days, and the treatment interval decreased by 0.1 months, at the last evaluation of 12 years of follow-up.

With respect to the follow-up at 12th year for the treatment of HFS comparing with the first evaluation, the present study found a non-significant increase in the mean dose from 38 U to 41 U of BoNT-A, improvements in the score for the Jankovic scale with 0.6 points and an increase in the duration of therapeutic effect, by 7 days, similar to other long-term reports that indicate an increase in the dose of BoNT-A over-time with[11,13,14] or without[10] statistical significance.

The treatment interval in this study was 4.4 ± 1 months, 123 days/17.6 weeks, similar to the period between therapeutic sessions previously reported for long-term studies[10,15,16].

The mean latency to obtain therapeutic effect in this report was 8 ± 3 days, a finding similar to that reported in the literature, that is, 2-14 days[8,10,17,18].

In this study, the mean duration of the clinical effect was 112 ± 9 days, with an initial duration of 109 ± 6 days and a final duration of 137 ± 7, similar to long-term reports in the literature[8,10,17,18]. The longer final duration of therapeutic effect in this study, as mentioned previously, can be explained in part by a longer-lasting effect detected in patients with HFS, as reported in the literature[15].

The mean improvement in this report, evaluated with the Jankovic scale, was 3.1 ± 1.4 points, with an initial improvement of 3.0 ± 0.9 points and an improvement with the last injection of 3.3 ± 0.7 points, similar to previous long-term reports of 2.5 ± 1.5 points for the first injection and 3.4 ± 0.9 points for the last[7]. Despite the differences in the study designs using different scales and methods, other long-term studies report overall improvement with BoNT-A treatment in 73.7[8]-89% of patients[14], and improvement in 96% of patients with BS and 98% of those with HFS[13], findings that confirm that in long-term studies, apart from the method to evaluate improvement, treatment with BoNT-A offers an adequate lasting effect for patients with BS and HFS.

Treatment with BoNT-A is very safe. A meta-analysis that included 2,309 subjects reported mild to moderate adverse effects in 25% of the group treated with BoNT-A (353/1,425 patients), compared to 15% in the control group (133/884 patients)[7]. In this study, there were side effects in 9 patients (6.6%), that is, ptosis in 7 (77.7%) and hematoma in 2 (22.2%). The general profile of side effects in this study is consistent with that reported in the literature of long-term follow-up, that is, 5-30%[10]. The highest frequency of side effects in this report occurred with the initial treatment, 4.4%, and the lowest frequency of side effects was observed with the last treatment 2.2%.

Contrast of hypotheses, it is assumed that variables with $p > 0.05$ follow a normal distribution and that variables with $p < 0.05$ do not follow a normal distribution. The justification for the use of the Student's t-test was to contrast if a significant difference could be found in the variable mean result between the two measurements.

A major concern with BoNT-A, especially with prolonged treatment, is the possibility of developing antibodies against BoNT-A. In a study with 303 patients, 17 of the 169 (10.4%) who discontinued treatment had stopped responding, nine of them due to blocking antibodies, as analyzed by the mouse protection assay[7]. In the present study, the identification of antibodies against BoNT-A was not performed, which is a limitation of this study.

The results from this study support the conclusion that BoNT-A, as a first-line treatment for focal facial dystonia, is an effective and safe treatment in a long-term cohort of the Mexican population with BS and HFS treated for 12 years.

Limitations of this study include the retrospective nature of analysis without a control group and without blinding, and the lack of antibody detection for BoNT-A. This long-term follow-up study in a real-world scenario did not intend to compare results between BoNT-A

brands, because indeed, the BoNT-A brand names (Botox®, Xeomeen®, Dyspor®t) were supplied over 12 years, 1 at a time, by Hospital Pharmacy, according to the institutional annual material purchase plan.

The long-term follow-up in a real-world scenario might be seen as strength of this study. Future trials should study also the quality of life, injection techniques, and immunogenicity.

Discussion

HES patients in this study were treated with a mean dose of 36 + 12 units, results that are similar to previous long term literature with no significant difference in response rate and duration of improvement12.

Conclusion

BonT-A is a safe and effective long-term treatment for BS and HFS in this real-world scenario follow-up. Future long-term trials, should address quality of life, iniection techniques, and immunogenity.

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The authors declare that this work was carried out with the authors' own resources.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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REVIEW ARTICLE

Movement disorders in opioid users observed in the social networks: a systematic review

Ariadna Domínguez-García, Gonzalo Hernández-Armesto, Eduardo Argüelles-González, Ulises Rodríguez-Ortiz, Mayela Rodríguez-Violante, Daniel Rebolledo-García, and Amin Cervantes-Arriaga*

Neurodegenerative Diseases and Movement Disorders Laboratory, National Institute of Neurology and Neurosurgery "Manuel Velasco Suarez", Mexico City, Mexico

Abstract

The significance of social networks in medical education, particularly in the field of movement disorders, is immeasurable. The current trend revolves around the emergence of new-onset pandemics, such as the COVID-19 virus or the rising use of consumer opioids. This phenomenon is evident across social networks, where non-professional videos depicting individuals experiencing abnormal movement disorders, such as upright postures and gait issues, are widely shared. These videos often feature people living on the streets in various locations throughout the United States and other major cities worldwide. The phenomenology of movement disorders involves closely observing patients in the examination room to identify the clinical phenotype and distinguish between hyperkinetic and hypokinetic disorders. This initial step is crucial in the assessment of any movement disorder. Given the limited availability of literature discussing the clinical features of opioid users, our research strategy involved exploring articles in the PubMed database that met the PRISMA criteria for 2020. Specifically, we sought articles addressing the clinical phenomenology and pathophysiology related to movement disorders from 1980 to the present. Our objective was to investigate cases, propose potential theories regarding implicated mechanisms, and explore the role of opioids in the movement circuits within the basal ganglia.

Keywords: *Social networks. Phenomenology spectrum. Movement disorders. Basal ganglia physiology. Opioid users.*

Trastornos del movimiento en consumidores de opioides observados en las redes sociales: una revisión sistemática

Resumen

La importancia de las redes sociales para el aprendizaje en medicina, especialmente en el campo de los trastornos del movimiento, es incalculable. La tendencia actual es el desarrollo de pandemias de inicio reciente (por ejemplo, el virus COVID-19 o el aumento de opioides entre consumidores) que se observa a través de las redes sociales, donde se suben videos sobre personas que viven en las calles de Estados Unidos y otras ciudades importantes en el mundo, y que muestran trastornos anormales del movimiento, como posturas erguidas y trastornos de la marcha. La fenomenología en trastornos del movimiento se centra en observar al paciente en la sala de examen para determinar el fenotipo clínico (trastornos hiperquinéticos o hipocinéticos) como primer paso en la evaluación de cualquier trastorno del movimiento. Por lo tanto, debido a la escasez de documentos escritos en la literatura médica sobre las características clínicas de los usuarios de opioides,

***Correspondence:**
Daniel Rebolledo-García
E-mail: daniel.rebolledo@innn.edu.mx

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decidimos investigar en la base de datos PubMed artículos seleccionados bajo los criterios PRISMA 2020 sobre la fenomenología clínica y la fisiopatología relacionada con los trastornos del movimiento desde 1980 hasta la actualidad, abordando los casos y la teoría posible sobre el mecanismo implicado y el papel de los opioides en los circuitos del movimiento en los ganglios basales. Nuestro objetivo fue investigar casos, proponer teorías potenciales sobre los mecanismos involucrados y explorar el papel de los opioides en los circuitos de movimiento dentro de los ganglios basales.

Palabras clave: *Redes sociales. Espectro fenomenológico. Trastornos del movimiento. Fisiología de los ganglios basales. Usuarios de opiáceos.*

Introduction

During the fentanyl crisis in the United States and globally, there has been a notable rise in videos circulating on social platforms such as X®[1-4] or TikTok®[5-8]. These videos depict individuals exhibiting abnormal postures while standing and walking, characterized by a flexion of the thoracic over the lumbar column. This posture bears a resemblance to the camptocormia phenomenon observed in other etiologies, including patients with Parkinson's disease.

Social networks on the internet have become significant as they provide a platform for observing amateur videos that showcase a rich phenomenology in movement disorders, contributing to the continuous learning of neurologists[9]. Ultimately, this avenue enables us to document the clinical findings associated with well-established, reemerging, and newly identified neurological diseases on a day-to-day basis.

The notion of illegal substances affecting the basal ganglia is not a novel concept. At present, our understanding characterizes these substances as capable of inducing movement disorders, particularly in opioid users. Medical databases contain case reports and experimental models in mice aimed at elucidating the pathophysiology that impacts the circuits connecting the motor cortex, basal ganglia, cerebellum, and thalamus, leading to spasms in motor patterns during general movement. It is essential to clarify that, in this context, "spam" refers to the current understanding of abnormal movement disorders, encompassing bizarre involuntary and voluntary motor patterns that interfere with both general and voluntary movement[10]. Additional reports from hospital centers with expertise in managing these patients have noted that, beyond cognitive and behavioral changes associated with opioid withdrawal, many patients may also develop hypokinetic and hyperkinetic movement disorders[11,12]. Consequently, we conducted a comprehensive review of the medical literature to characterize the opioid user population and delineate both typical and novel phenotypes in movement disorders.

Material and methods

We performed research from medical literature between three independent investigators in the PubMed database; the primary objective was to find articles related to the pathophysiology and clinical phenomenology of movement disorders in opioid users. Keywords used were "opioids," "parkinsonism," "ataxia," "chorea," "dystonia," "myoclonus," "movement disorders," and "fentanyl" between 1980 and present. Synonyms and related terms were used interchangeably. The article review was based on the findings of these terms in article titles and abstracts. The inclusion criteria were original articles, imaging studies, case reports, and letters to editors related to movement disorders in opioid users. There was no geographical restriction on the origin of the reviews. Exclusion criteria were duplicate articles, lack of imaging data, clinical phenomenology, and pathophysiology. Finally, papers were eliminated due to a poor description of the primary objective. The approach was supported by PRISMA 2020 guidelines for standardizing the information (Fig. 1).

Results

Demographics findings

The distribution of the papers selected was from North America (n =), South America (n =), Asia (n =), Europe (n =), and Oceania (n =). Regions across the world that reported these conditions were North-America n = 12 (United States n = 10, Canada n = 2), Europe n = 6 (France n = 2, Austria n = 1, United Kingdom n = 1, Denmark n = 1, Germany n = 1), Asia n = 4 (India n =, Arabia Saudita n = 1, Japan n = 1, Korea n = 2), Africa n = 1 (South-Africa n = 1), and Oceania n = 1 (Australia n = 1). The average age was 20-60 years, and the male-female ratio was 2:1. Other demographic features were omitted because the whole cases were individual reports[13-17].

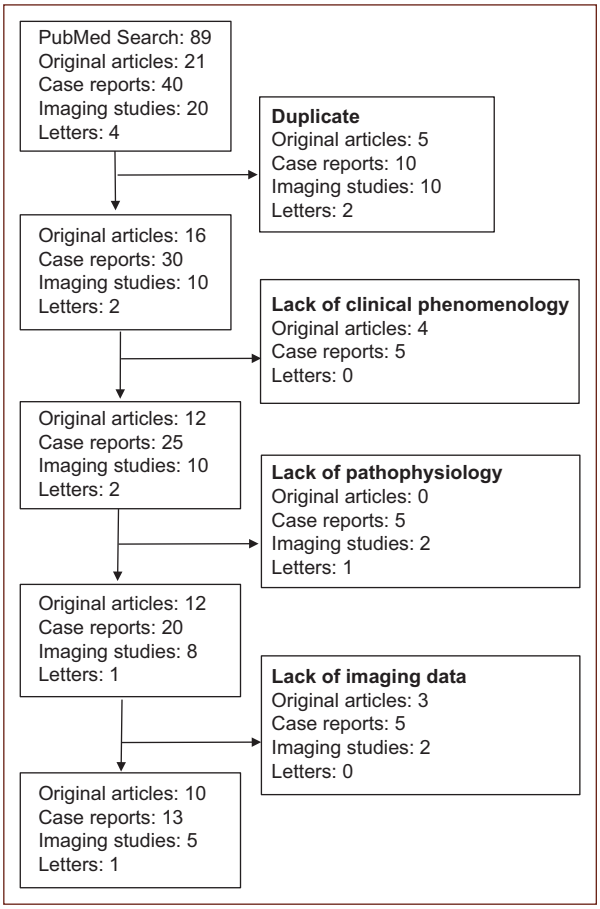

Figure 1. Selection of eligible for the present study.

Clinical features of movement disorders related to opioid use

The clinical presentations that were reviewed in the articles selected were heterogeneous. Many patients developed hyperkinetic and hypokinetic movement disorders (Table 1). On the other hand, other neurological symptoms have been described as headache, cognitive impairment (ideomotor apraxia), language disorders, confusion, delirium, psychotic flares, and diverse degrees of consciousness as minimal consciousness states or degrees in vegetative states. The myoclonus and chorea were the most common movement disorders described in case reports. Interestingly, many cases were seen in the surgical sceneries (transoperative and post-operative states) and the time of inpatient care[18-23].

Locations of neuroimaging abnormalities

The brain regions that were most affected in the cases revisited were the white matter substance (22.9%), caudate nucleus (12.5%), putamen (18.7%), thalamus (6.25%), cerebellar hemispheres (16.6%), dentate nucleus (6.25%), and cortex (14.5%) (Table 2). There was less affectation in the thalamic nucleus, corpus callosum, and watershed artery territories (middle cerebral artery with anterior and posterior artery branches), which suggests a role of a concomitant hypoxemic and unstable hemodynamic state that explains the distribution of the injury (similar to anoxic-ischemic states) in these regions (Fig. 2)[24-30].

Table 1. Phenomenology in movement disorders described in legal and illegal opioids-users

Hyperkinetic movement disorders (n = 26)	Hypokinetic movement disorders (n = 13)
Myoclonus (7, 26.9%) Dystonia (5, 19.2%) Chorea (6, 23%) Dyskinesia (2, 7.6%) Akathisia (2, 7.6%) Ataxia (4, 17.39%)	Parkinsonism (5, 38.4%) Catatonia (5, 38.4%) Postural instability (3, 18.75%)

While the findings may not entirely fulfill all criteria, the neuroimaging pattern observed in the studies bears resemblance to the cerebellar hippocampal and basal nuclei transient edema with restricted diffusion (CHANTER) syndrome[30]. This is a rare radiographic pattern observed in acute intoxication by other substances, such as cocaine. However, patients with CHANTER syndrome typically experience unconscious states, including coma, drowsiness, encephalopathy, or varying degrees of vegetative states, with a generally fatal prognosis in the short term.

In contrast, opioid users exhibit a broad spectrum of sequelae, encompassing cognitive, motor, gait, and behavioral long-term changes, with different functional outcomes on the Rankin-modified scale. This is evident in the case series by Alambyan et al.[31], where scores ranged between 2 and 5. It is important to note that, in this study, the prevalence of mortality was higher compared to other series.

Theories propose about the pathophysiology related to neuronal damage induced by opioid use

In the classical model, the dopaminergic system was believed to regulate all the input and output pathways within the movement system, originating from basal ganglia circuits. However, moving beyond this traditional perspective, there is recognition of a complex

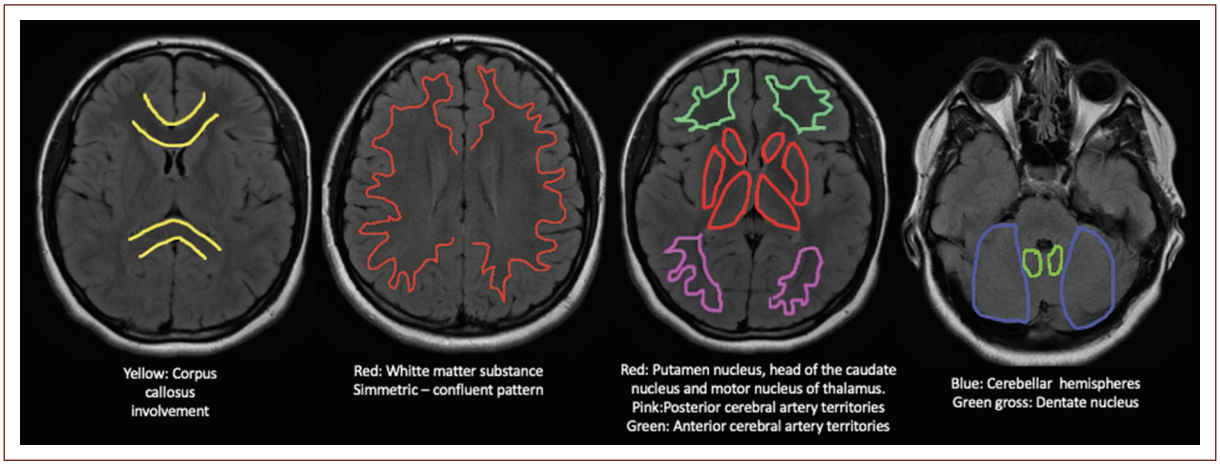

Figure 2. Images from T2 to T2-weighted magnetic resonance imaging show different patterns of injury on subcortical structures (white matter, basal ganglia, cerebellum, and watershed arterial territories. These images are not pathognomonic for opioid use intoxication, which will be seen in other toxic-metabolic states from many etiologies, but suggest the possible role of opioids in brain damage[24-30]. Modified with Biorender.com.

Table 2. Summary of locations of brain regions abnormalities

Location/Imaging modality	CT scan (n = 15)	MRI scan (n = 33)
Supra-ganglionic white matter	3	8
Caudate nucleus	2	4
Putamen	4	5
Thalamus	1	2
Cortex (frontal and/or parietal)	3	4
Cerebellar hemispheres	1	7
Dentate nucleus	1	2

CT: computed tomography; MRI: magnetic resonance imaging.

interaction involving various neuronal groups, including GABAergic, cholinergic, noradrenergic, glutamatergic, serotoninergic, and opioid neurons. These groups function as interneurons, serving as afferent or efferent relays within the motor system. This intricate network is distributed along the cortex- striatum-pallidal pathway, interconnected with the substantia nigra, subthalamic nucleus (STN), and ventral motor nucleus of the thalamus. This thalamic nucleus serves as a major efferent motor modulator pathway, influencing the firing rate to either inhibit or stimulate the motor cortex, thereby regulating normal voluntary movement[32].

On the other hand, infratentorial stimulation from the red nucleus and the cerebellar deep nucleus (dentate nucleus) also projects input fibers onto the thalamus. This input increases the GABAergic tone while suppressing the cholinergic and glutamatergic excitatory tone within the thalamocortical network. This modulation serves to dampen aberrant patterns in movement influenced by both the hyperdirect and indirect pathways. Dysregulation in these pathways could result in abnormal firing rate patterns, leading to hypo-or hyperactivation of the thalamus. Consequently, such abnormalities in thalamic activity can manifest as hyperkinetic and hypokinetic movement disorders, illustrating the various ways in which these disturbances interfere with normal movement[33].

Furthermore, the efferent final way through the pedunculopontine nucleus (ppn) that manipulates the motor interactions inside the way of the reticulospinal nucleus, red nucleus, and the system interactions from the corticospinal tract motor neurons, and lower motor neurons perhaps supports the theory that an increasing in the GABAergic input over the ppn[34] (if we remember the relays, the GPi are in overactivity with the global GABAergic tone that inhibits the ventral motor in thalamus) could affect the gait (increment in the muscle tone, slow the agonism and antagonism activities in muscle contraction leading the freezing of gait (FOG) phenomenon that it is described in the parkinsonism states) and the postural stability (anti-gravidity muscles controlled by the red nucleus), although the pathophysiology of FOG should be explained by a decrease in the noradrenergic tone and a lack in the directly connections between the thalamus and the ppn[35].

The physiology outlined earlier may not fully elucidate the underlying reasons for the spectrum of movement disorders associated with opioid use or overuse. However, the various reports reviewed demonstrate a significant focus on the role of mu receptors in different neuron centers within the movement system.

In classic experiments involving monkeys (and incidentally in humans) exposed to the compound 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, it was initially hypothesized that only the striatum and substantia nigra pars reticulata could be affected. Contrary to this hypothesis, clinical results from patients undergoing deep brain stimulation procedures revealed bidirectional relays within these pathways and circuits. Sometimes, the observed effects were opposite to expectations; for instance, paradoxical dyskinesias were obtained when the STN was electrically stimulated during micro-registration through surgery, despite successful electrode tip placement.

These diverse cases underscore the notion that the dopaminergic system does not operate in isolation. Instead, there exists a complex interaction between the neurotransmitter panel and the neuron cores[36].

For example, if the mu receptor in the striatum is overstimulating in opioid users (there are many biases related to what opioids are used, concentration, other added substances, and time in exposition), the hyper-direct and indirect pathways will lead to a hypoactivation in the GPi plus the STN hyperstimulation firing rate over the thalamus project over the cortex stimulates the begin of hyperkinetic abnormal movements as dystonia or chorea; in an inverse scenario, the way inhibits in excess the SNT firing rates and leads to hypokinetic disorders as Parkinsonism; and if there is an influence between the cortical motor supplementary area and the ventral Anterior Cingulate Cortex-striatum-thalamic circuit, this could induce the development of catatonia state by a phenomenon of clogging into this specific circuit because the patients cannot decide what motors or executive functions directs the sequence (absence of cognitive or motor continuing tasks) and execute process, feature found in these cases (Fig. 3). These examples illustrate that the dysregulation of mu receptors in a particular region may exert either positive or negative effects on firing rates, with inhibitory or excitatory outcomes. This dysregulation can modulate the depolarization of the GABAergic neuronal team throughout the system[37]. While observing the spectrum of clinical phenomenology may aid in recognizing the affected part of the basal ganglia system, it is not a foolproof method. In movement disorders, the general consensus is that each case is unique and differs from others, even if both individuals have the same affected areas. For instance, in cases of spongiform leukoencephalopathy associated with heroin derivatives, there is no consistent pattern in clinical phenomenology, despite a notable similarity in neuroimaging findings.

Discussion

During our leisure time on an ordinary day, my team and I browsed through the X® social network (formerly Twitter) and TikTok®, where we came across various videos showcasing abnormal postures and gait disorders in individuals living on the streets of US cities who are fentanyl users. Upon initial observation, the phenomenology seemed to predominantly feature a hypokinetic phenotype, but in other videos, we noticed a peculiar hyperkinetic movement disorder. The gait of fentanyl users appeared slow, characterized by a reduced swing in both arms. In addition, they tended to maintain a fixed posture for extended periods, reminiscent of patients with catatonia. It is noteworthy, however, that the phenomenon of FOG has not been observed in these instances.

On the flip side, the spectrum of neuroleptic malignant syndrome associated with opioid medical use, which represents an acute facet of catatonia, has been recently documented by Ketigian[23]. However, there have been no reports of isolated catatonia in individuals with chronic fentanyl use. Similarly, our literature review did not reveal any reports of camptocormia associated with chronic fentanyl use.

We posit that the clinical phenomenology observed in the videos may signify a novel phenotype of manifestations associated with opioid toxicity affecting the pathways and relays within the functional circuit of the basal ganglia. This circuit is known to play a crucial role in standing posture, gait, and the FOG phenomenon. The alterations in normal physiology observed could potentially be attributed to the toxic effects of chronic exposure to neuronal fentanyl. An open question remains regarding whether these findings will have an impact on the development of neurodegenerative diseases in this population in the years to come.

We hypothesize that the neuroimaging findings in these patients may exhibit similarities in structural injuries comparable to those observed in individuals who engage in “chasing the Dragon,” for instance. However, we were unable to locate case reports in the recent medical literature that specifically addressed the patients depicted in the amateur videos from X® or TikTok®.

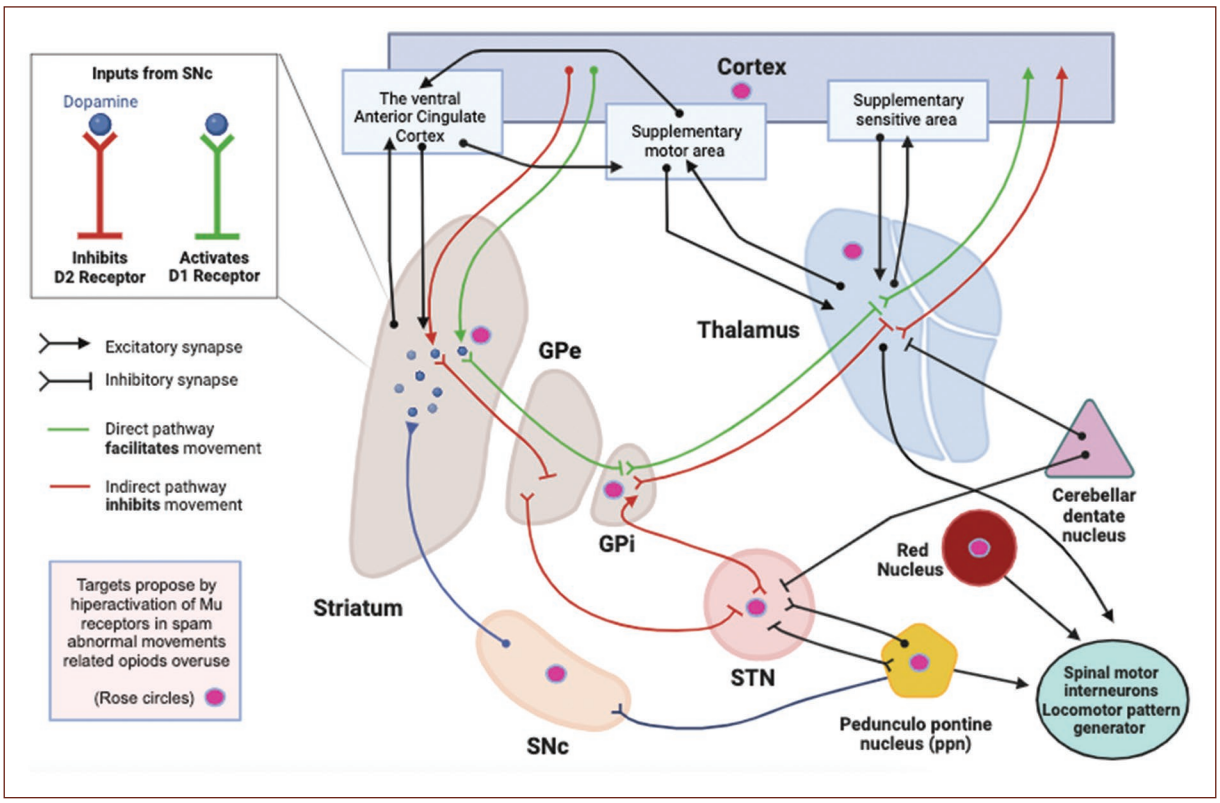

Figure 3. New emerged concepts related to opioid receptors across the distinct compounds of movement "machine" integrated by supratentorial and infratentorial structures. The influence of the Mu receptors in all the pathways over the rest of the neurotransmitter's relays in a excitatory or inhibitory outputs and inputs regional circuits explains the spectrum of movement disorders developed by opioid users. Modified with Biorender.com.

Conclusions

The movement disorders associated with opioid users constitute a captivating field that could enhance our understanding of the physiology and pathophysiology underlying the motor system within the circuits and pathways governed by the basal ganglia. Additionally, it contributes to a more comprehensive understanding of the clinical spectrum and extensive phenomenology resulting from strategic injuries in this system. Moving forward, longitudinal observational studies will be crucial to assessing the long-term neurological disorders stemming from the abuse of this drug and its impact on the gait of affected individuals.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines, depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript or for the creation of images, graphics, tables, or their corresponding captions.

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