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

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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,

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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].

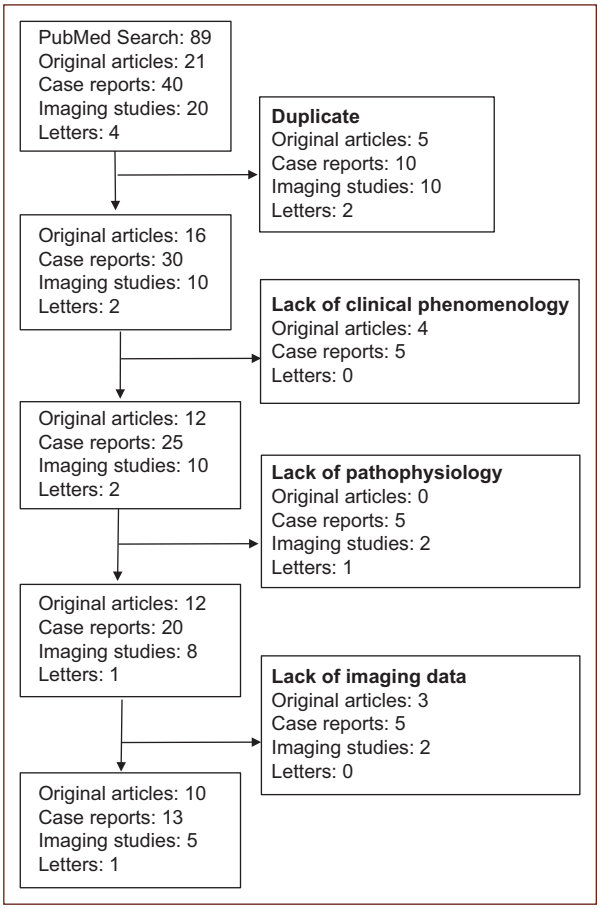

Figure 1. Selection of eligible for the present study.

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

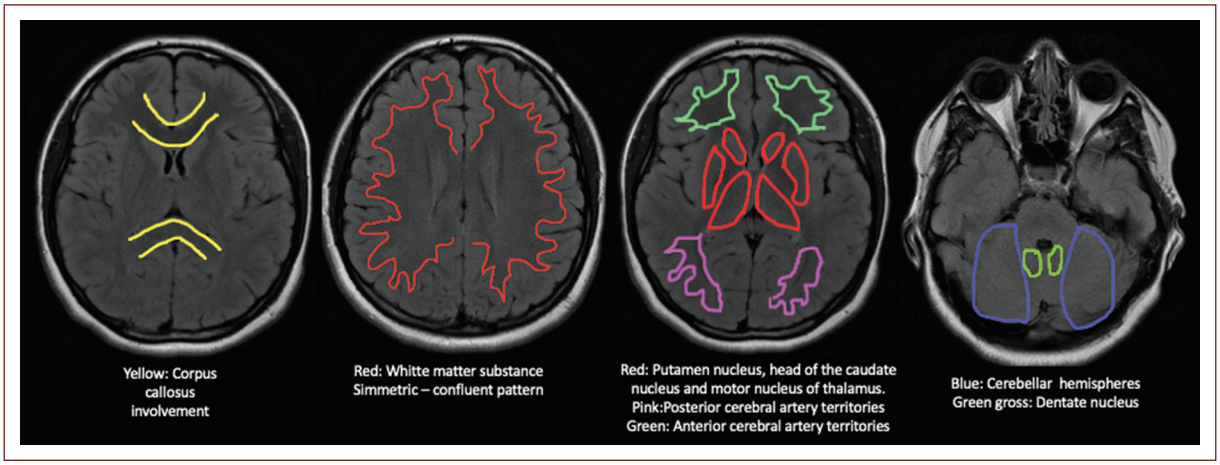

Figure 2. Images from T2 to T2-weighted magnetic resonance imaging show different patterns of injury on subcortical structures (white matter, basal ganglia, cerebellum, and watershed arterial territories. These images are not pathognomonic for opioid use intoxication, which will be seen in other toxic-metabolic 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®.

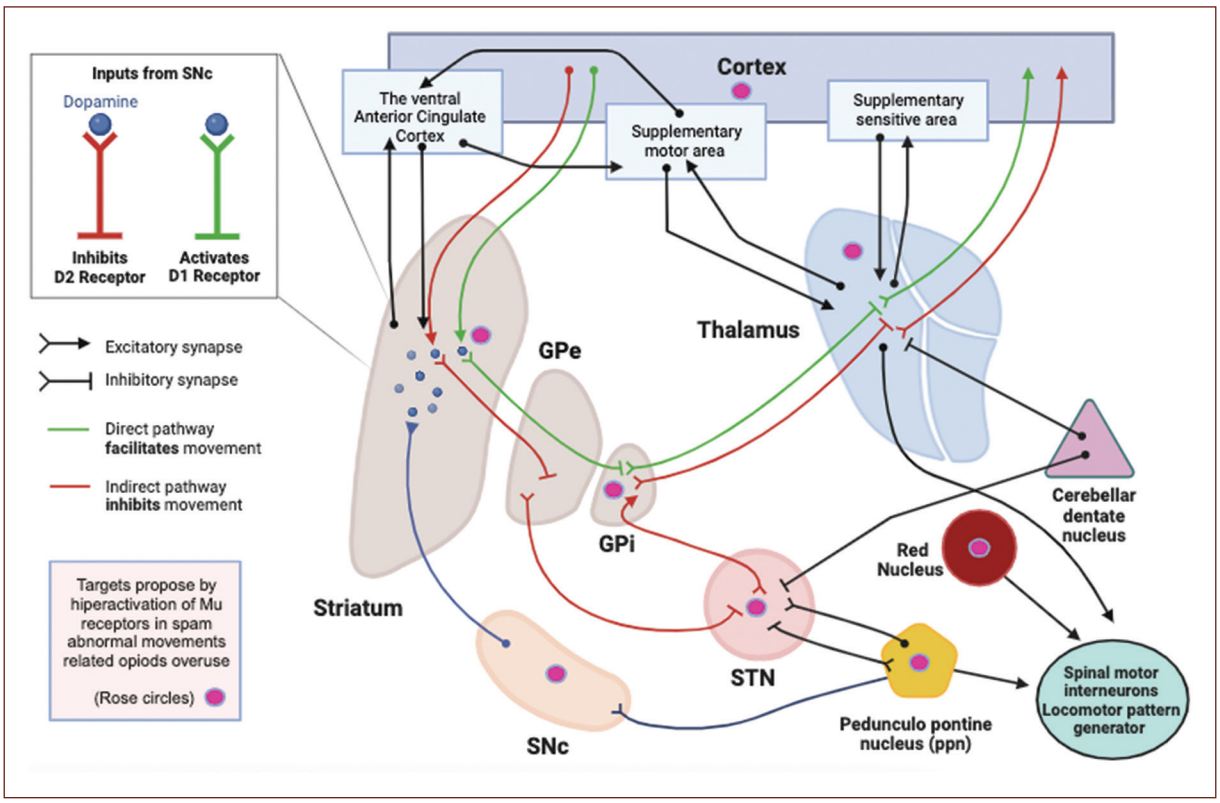

Figure 3. New emerged concepts related to opioid receptors across the distinct compounds of movement "machine" integrated by supratentorial and infratentorial structures. The influence of the Mu receptors in all the pathways over the rest of the neurotransmitter's relays in a excitatory or inhibitory 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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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 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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