Cocaine-induced Movement Disorder: A Literature Review

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Abstract: This study aims to describe movement disorders secondary to cocaine use. To our knowledge, while these presentations have been previously reported in the literature, a comprehensive review has not been published yet. We searched six databases from 1986 to 2022 without language restriction. Case reports, case series, and literature reviews have been analysed to find associations between cocaine use and movement disorders. The present study encompasses epidemiology, clinical manifestations, pathophysiology, and diagnostic challenges of abnormal movements associated with cocaine use. This review highlights the importance of proper initial evaluation and investigation taking into account the broad spectrum of differential diagnoses and exclusion of primary movement disorders. The role of the dopaminergic system in movement disorders is reviewed. Cocaine use is associated with movement disorders such as dystonia, parkinsonism, akathisia, and tics. The complex interaction of multiple factors, including other neurological conditions, such as Tourette syndrome, and additional substances of abuse is discussed. The presentation of these manifestations is often heterogeneous and does not follow a specific pattern. In this way, future research is needed to improve our understanding of the pathophysiological mechanisms and develop novel drug targets for these disorders. Increased awareness among the general public and policymakers could translate into reduced stigma and improved care.

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Introduction

Substance use disorder (SUD), or drug addiction, is a complex condition involving genetic, psychiatric, biological and social factors in which affected individuals are unable to control the use of a given substance. This occurs with legal or illegal substances and leads to immediate or late devastating consequences, which often ensue in financial loss, social isolation, stigmatization, unemployment and considerable personal suffering and social burden. This condition is prevalent worldwide in societies of different cultures and stages of economic development. In the United States alone, SUD affects approximately 40 million people, and the annual medical cost attributed to SUD-related hospitalization is estimated at 13.2 billion dollars. Between 2006 and 2014, there was a 40% increase in substance use-related emergency department visits. In a large study examining emergency department visits and inpatient encounters, approximately 10% of all hospitalizations were due to a substance use disorder, and the mean medical cost of a primary SUD diagnosis was over $9,000 (Peterson et al., 2021). Moreover, SUD results in increased vulnerability to infectious diseases, including COVID-19, which translates to an increased healthcare burden. A significant proportion of SUD patients experience homelessness, and more than 50% of the incarcerated population in the United States suffers from SUD (Manhapra et al., 2021). Unfortunately, SUD patients are less likely to have access to healthcare professionals because of the stigmatization related to this condition. Nonetheless, social support is limited, and the marginalization associated with SUDs often leaves individuals unable to break out of the vicious cycle (Volkow, 2020).

A voluntary motor function requires planning, coordination, and execution. If either of these processes or a combination of them is impaired, a movement disorder emerges. Movement disorders are complex and varied. A considerable number of movements noted during the physical examination of an individual will fall under a spectrum, which includes dystonia, akathisia, athetosis, choreiform movements, tremors, bradykinesia, myoclonus, rigidity, and ataxia. Movement disorders are highly variable in presentation and often require careful observation for proper diagnosis. While some, such as neuroleptic malignant syndrome, constitute neurological emergencies, others required extended periods of follow-up for appropriate treatment in the outpatient setting, such as Parkinsonian tremors. Functional neurological disorders are often prevalent in referrals for the specialist and an important differential diagnosis in the movement disorders clinic. Patients with these disorders should also be followed-up and treated accordingly. Movement disorders can be inherited or acquired, and multiple syndromes ranging from Huntington's to MPTP-induced have been described (Rissardo et al., 2023a). Most movement disorders affect the dopaminergic system and the deeper gray matter regions of the brain. Abnormal movements can significantly impact an individual's quality of life and represent a major healthcare expenditure in the United States.

While novel approaches are promising and have shown to improve the lives of patients suffering from movement disorders, such as deep brain stimulation in Parkinson's disease, the newly emerging involuntary abnormal movements secondary to illicit substance use represent a significant challenge in terms of development of new therapeutic strategies (Rissardo et al., 2023b).

The association of movement disorders with substance abuse is well known. Tremors during withdrawal in the setting of alcohol use disorder is a classic example. This symptom can be alleviated with benzodiazepines but also occurs in benzodiazepine withdrawal. Many other psychoactive substances can induce motor symptoms. These presentations are highly variable according with different substances, and even for the same substance. Thus, objective characterization of these disorders is extremely challenging. For example, both central nervous system depressants, such as opioids, and stimulants, such as cocaine, can cause myoclonus. MPTP, a known neurotoxic and street-drug contaminant, is associated with parkinsonism and its wide range of motor alterations (Kopin, 1987). Recent studies suggest that methamphetamine use can cause athetotic and choreiform movements that mimic Huntington's disease (Rissardo et al., 2023a). In addition, novel synthetic drugs are making their way into patient populations, sometimes disguised as harmless products such as herbal supplements, bath salts, and others, which can lead users to underestimate their potency. These drugs are still poorly understood and have unpredictable immediate and long-term effects (Wang and Hoyte, 2019).

Cocaine, one of the most common drugs of abuse in the 21st century, is an alkaloid extracted from *Erythroxylum coca*, a plant used in South America for thousands of years. Referred to as the divine plant of the Incas, the coca held a mythical status in their society. Its effect against fatigue and as an appetite suppressant was first recorded in the XV century by the early explorer Amerigo Vespucci. Coca leaves were traditionally chewed for their stimulant properties and played an important role in religious and healing practices (Matuskey, 2012). While this traditional use continues to exist in parts of South America, the coca plant is now notoriously recognized as emblematic of cartel violence. The international process of cocaine prohibition began in 1912 with the Hague Opium Convention. In 1914, federal regulation was introduced in the United States, followed by increasing restrictions that attempted to limit cocaine use to medical and scientific purposes. The Drug Enforcement Administration (DEA) of the United States classifies cocaine as a Schedule II drug (Das, 1993). In the 1970s, the cocaine trade and smuggling led to the rise and fall of one of the most notorious criminals, Pablo Escobar, and made cocaine a top player in the drug scene of America. Cocaine is mainly produced in Peru, Colombia, and Bolivia and is then trafficked to multiple other destinations. In 2019 alone, over 1,400 tons of cocaine were seized internationally (Drake and Scott, 2018).

With approximately 2 million regular users in the United States, cocaine is responsible for 40% of all substance abuse-related emergency department visits (Bravo et al., 2022). Because of stigma, omission, and underreporting, the actual

number of cocaine users may be much higher than estimated. The all-cause mortality from cocaine abuse is high, and the past decade has seen a marked increase in deaths secondary to overdose. On average, regular or problematic cocaine users have an excess mortality risk six times the expected rate for age-matched on-users (Peacock et al., 2021). Cocaine use disorder (CUD) is a serious and urgent public health problem, and the lack of Food and Drug Administration (FDA)-approved treatments is concerning (Kampman, 2019).

Cocaine was first isolated in 1859. In 1884, Carl Koller used this substance in ophthalmic procedures, making cocaine the first local anesthetic in modern medicine. During the same period, Sigmund Freud conducted his studies on cocaine, defending its therapeutic use. Cocaine was later used in many other prescriptions ranging from headaches to toothaches. Examples of adverse effects began to appear. A publication from 1911 mentions motor alterations when cocaine was applied in combination with adrenaline in a tonsillectomy and adenoidectomy. The patient's "*body showed a tendency to become flexed backward, and the eyeballs rolled upwards while the pupils dilated widely. This was at once followed by a violent convulsive seizure, epileptiform in character, with powerful twitching and contraction of the muscles of the limbs and face, and marked retraction of the head*" (Wishart, 1911). This case alone illustrates a wide variety of motor alterations, and while adrenaline administration is a confounding factor, opisthotonos, torticollis, and seizures were all observed when cocaine was used alone (Scharf, 1989; Fines et al., 1997).

The route of cocaine administration may be intravenous, ocular, inhaled, or by contact with any mucous membrane (oral, intranasal, rectal). In the context of drug abuse, cocaine is usually self-administered by snorting cocaine hydrochloride powder or by smoking its freebase form, crack. Individuals with stable living conditions often use cocaine powder, while crack cocaine is associated with heavy use, homelessness, and unstable living situations.

Cocaine abuse directly or indirectly affects multiple organs, from dentition and facial structures to the homeostasis of the nervous, gastrointestinal, respiratory, renal, and cardiovascular systems (Havakuk et al., 2017; Peacock et al., 2021; Bravo et al., 2022). Mental health is significantly impaired, as cocaine affects social functioning and cognition across multiple dimensions, such as working memory, attention span, flexibility of thought, and even empathy (Frazer et al., 2018). Common cardiovascular manifestations include hypertension, tachycardia, and ischemia, with possible myocardial infarction, arrhythmias, and heart failure secondary to vasoconstriction and increased oxygen demand due to stimulation of contractility. Bronchoconstriction, pulmonary edema, and pneumothorax can occur secondarily to cocaine's irritant nature, especially if smoked. Acute pulmonary syndrome manifesting as hemoptysis, pain, and lung infiltrates is a rare but dreaded complication. Cocaine may cause acute kidney injury, renal infarction, malignant hypertension, and rhabdomyolysis secondary to hemodynamic changes. Ischemic and hemorrhagic strokes occur because of blood pressure dysregulation, and seizures

occur because of chronic low-intensity stimulation of the limbic system, known as kindling, even after a single use. Hepatotoxicity, mostly as hepatocellular necrosis, fatty acid infiltration, and alterations to amino acid pathways due to abnormal oxidative stress regulation, have been reported. Increased susceptibility to emergency conditions such as neuroleptic malignant syndrome and serotonin syndrome, which are life-threatening conditions, are occasionally encountered in clinical practice (Frazer et al., 2018; Bravo et al., 2022).

The extent of cocaine's effects and their ramifications on different systems is not fully understood. Cocaine's primary mechanism of action is the inhibition of dopamine, norepinephrine, and serotonin reuptake by their respective transporters in presynaptic neurons. The accumulation of these neurotransmitters in the synaptic cleft and consequent activation of postsynaptic receptors, results in several responses. Increased serotonin signalling could contribute to euphoria, overall mood elevation, and susceptibility to seizures. Increased norepinephrine activity results in the typical manifestations of sympathetic overdrive. Increased dopaminergic activity along the mesocorticolimbic impacts the regulation of several important cognitive and affective functions, such as motivation, learning, and emotions. The circuits formed in this pathway constitute the so-called "reward system". In this system, dopaminergic neurons originating in the ventral tegmental area relay to other brain locations. These neurons and their projections in the nucleus accumbens, throughout the limbic system, and prefrontal cortex are implicated, for example, in the euphoric sensation experienced by cocaine users (Bravo et al., 2022). Disruptions in the reward system explain most of the characteristic patterns followed in CUD, with cocaine-seeking behaviour, habit formation, withdrawal, cravings, and ultimately addiction.

While the action of each monoamine in different brain areas can infer its effect, these substances do not work in separate compartments but interact in several points. Cocaine's effects are even more complex considering N-methyl-D-aspartate, sigma, and kappa opioid receptors are also modulated, which may alter their expression and distribution (Bravo et al., 2022). All these systems and their delicate balance are affected and could influence the increased psychomotor activity typical of cocaine use (Figure 1).

Cocaine use disorder is a multifactorial condition, genetic and environmental exposure have an impact on cocaine use patterns. Relatives of those affected by CUD are 4.4 times more likely to develop the condition. Epigenetic modifications in circuits of the cortico-striato-thalamo-cortical system have a role in relapse and drug cravings. Interestingly, only 20% of cocaine users develop CUD, which could be due to genetic susceptibility. For example, the NSF gene, associated with synaptic vesicle turnover, has polymorphic copy number variations that can influence cocaine dependence with an inverse relationship (Fernandez-Castillo et al., 2022).

Like addiction, movement disorders are complex phenomena. Psychostimulants like cocaine alter the function of the basal ganglia directly or indirectly, similar to the mechanism of commonly known and understood movement disorders.

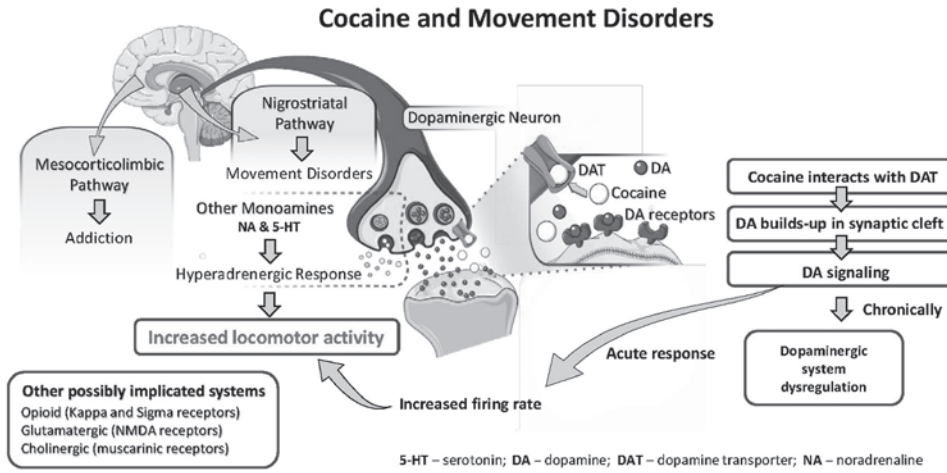

Figure 1 – Hypothetical pathophysiology of movement disorders caused by cocaine use. The figure was partly generated using Servier Medical Art, provided by Servier, licensed under an unported Creative Commons Attribution 3.0 license.

Broadly, tremors, dystonia, ataxia, dyskinesia, bruxism, parkinsonism, stereotypical movements, choreoathetosis, restlessness, and tics are some of the movements. The present review aims to investigate the cases of movement disorder secondary to cocaine use reported in the literature.

Methodology

Search strategy

We searched six databases to locate all the existing reports on movement disorders secondary to cocaine published from 1986 to 2022 in electronic form. Excerpta Medica (Embase), Google Scholar, Latin American and Caribbean Health Sciences Literature (Lilacs), Medline, Scientific Electronic Library Online (Scielo), and ScienceDirect were searched. Search terms were "parkinsonism, tics, dyskinesia, dystonia, stuttering, myoclonus, restless legs syndrome, akathisia, tremor, chorea, restlessness, ataxia, ballism, hyperkinetic, hypokinetic, bradykinesia, movement disorders." These terms were combined with "cocaine and coca" (Table 1).

Inclusion and exclusion criteria

Case reports, case series, original articles, letters to the editor, bulletins, and poster presentations published from 1986 to 2023, without language exclusion criteria, were included to ensure a thorough review. In the cases where the non-English literature was beyond the authors' proficiency (English, French, and Spanish) or when the

Table 1 – FreeText and MeSH search terms in the US National Library of Medicine

Category	Search term	Results
Movement disorder	(“cocaine”[MeSH Terms] OR “cocaine”[All Fields] OR “cocaine s”[All Fields] OR “cocaines”[All Fields] OR “cocainics”[All Fields]) AND (“movement disorders”[MeSH Terms] OR (“movement”[All Fields] AND “disorders”[All Fields]) OR “movement disorders”[All Fields])	577
Parkinsonism	(“cocaine”[MeSH Terms] OR “cocaine”[All Fields] OR “cocaine s” [All Fields] OR “cocaines”[All Fields] OR “cocainics”[All Fields]) AND (“parkinson disease”[MeSH Terms] OR (“Parkinson”[All Fields] AND “disease”[All Fields]) OR “parkinson disease”[All Fields] OR “parkinsons”[All Fields] OR “Parkinson”[All Fields] OR “parkinson s”[All Fields] OR “parkinsonian disorders”[MeSH Terms] OR (“parkinsonian”[All Fields] AND “disorders”[All Fields]) OR “parkinsonian disorders”[All Fields] OR “parkinsonism”[All Fields] OR “parkinsonisms”[All Fields] OR “parkinsons s”[All Fields])	554
Dyskinesia	(“cocaine”[MeSH Terms] OR “cocaine”[All Fields] OR “cocaine s” [All Fields] OR “cocaines”[All Fields] OR “cocainics”[All Fields]) AND (“dyskinesiae”[All Fields] OR “dyskinesias”[MeSH Terms] OR “dyskinesias”[All Fields] OR “dyskinesia”[All Fields])	373
Ballism	(“cocaine”[MeSH Terms] OR “cocaine”[All Fields] OR “cocaine s” [All Fields] OR “cocaines”[All Fields] OR “cocainics”[All Fields]) AND (“dyskinesias”[MeSH Terms] OR “dyskinesias”[All Fields] OR “ballism”[All Fields])	355
Restlessness	(“cocaine”[MeSH Terms] OR “cocaine”[All Fields] OR “cocaine s” [All Fields] OR “cocaines”[All Fields] OR “cocainics”[All Fields]) AND (“psychomotor agitation”[MeSH Terms] OR (“psychomotor”[All Fields] AND “agitation”[All Fields]) OR “psychomotor agitation” [All Fields] OR “restlessness”[All Fields] OR “restless”[All Fields])	102
Tremor	(“cocaine”[MeSH Terms] OR “cocaine”[All Fields] OR “cocaine s” [All Fields] OR “cocaines”[All Fields] OR “cocainics”[All Fields]) AND (“tremor”[MeSH Terms] OR “tremor”[All Fields] OR “tremors” [All Fields] OR “tremoring”[All Fields] OR “tremorous”[All Fields])	99
Akathisia	(“cocaine”[MeSH Terms] OR “cocaine”[All Fields] OR “cocaine s” [All Fields] OR “cocaines”[All Fields] OR “cocainics”[All Fields]) AND (“akathisias”[All Fields] OR “psychomotor agitation”[MeSH Terms] OR (“psychomotor”[All Fields] AND “agitation”[All Fields]) OR “psychomotor agitation”[All Fields] OR “akathisia”[All Fields])	82
Dystonia	(“cocaine”[MeSH Terms] OR “cocaine”[All Fields] OR “cocaine s” [All Fields] OR “cocaines”[All Fields] OR “cocainics”[All Fields]) AND (“dystonia”[MeSH Terms] OR “dystonia”[All Fields] OR “dystonias”[All Fields] OR “dystonic disorders”[MeSH Terms] OR (“dystonic”[All Fields] AND “disorders”[All Fields]) OR “dystonic disorders”[All Fields])	72

Category	Search term	Results
Ataxia	(“cocaine”[MeSH Terms] OR “cocaine”[All Fields] OR “cocaine s” [All Fields] OR “cocaines”[All Fields] OR “cocainics”[All Fields]) AND (“ataxia”[MeSH Terms] OR “ataxia”[All Fields] OR “ataxias” [All Fields])	50
Chorea	(“cocaine”[MeSH Terms] OR “cocaine”[All Fields] OR “cocaine s” [All Fields] OR “cocaines”[All Fields] OR “cocainics”[All Fields]) AND (“chorea”[MeSH Terms] OR “chorea”[All Fields] OR “choreas” [All Fields])	38
Bradykinesia	(“cocaine”[MeSH Terms] OR “cocaine”[All Fields] OR “cocaine s” [All Fields] OR “cocaines”[All Fields] OR “cocainics”[All Fields]) AND (“hypokinesia”[MeSH Terms] OR “hypokinesia”[All Fields] OR “bradykinesia”[All Fields])	23
Myoclonus	(“cocaine”[MeSH Terms] OR “cocaine”[All Fields] OR “cocaine s” [All Fields] OR “cocaines”[All Fields] OR “cocainics”[All Fields]) AND (“myoclonus”[MeSH Terms] OR “myoclonus”[All Fields])	17
Hyperkinetic	(“cocaine”[MeSH Terms] OR “cocaine”[All Fields] OR “cocaine s” [All Fields] OR “cocaines”[All Fields] OR “cocainics”[All Fields]) AND (“hyperkinetic”[All Fields] OR “hyperkinetics”[All Fields])	16
Hypokinetic	(“cocaine”[MeSH Terms] OR “cocaine”[All Fields] OR “cocaine s” [All Fields] OR “cocaines”[All Fields] OR “cocainics”[All Fields]) AND (“hypokinesia”[MeSH Terms] OR “hypokinesia”[All Fields] OR “hypokinetic”[All Fields])	16
Tics	(“cocaine”[MeSH Terms] OR “cocaine”[All Fields] OR “cocaine s” [All Fields] OR “cocaines”[All Fields] OR “cocainics”[All Fields]) AND (“tics”[MeSH Terms] OR “tics”[All Fields])	16
Restless legs syndrome	(“cocaine”[MeSH Terms] OR “cocaine”[All Fields] OR “cocaine s” [All Fields] OR “cocaines”[All Fields] OR “cocainics”[All Fields]) AND (“restless legs syndrome”[MeSH Terms] OR (“restless”[All Fields] AND “legs”[All Fields] AND “syndrome”[All Fields]) OR “restless legs syndrome”[All Fields])	7
Stuttering	(“cocaine”[MeSH Terms] OR “cocaine”[All Fields] OR “cocaine s”[All Fields] OR “cocaines”[All Fields] OR “cocainics”[All Fields]) AND (“stammerers”[All Fields] OR “stammers”[All Fields] OR “stutterer”[All Fields] OR “stutterer s”[All Fields] OR “stutterers” [All Fields] OR “stuttering”[MeSH Terms] OR “stuttering” [All Fields] OR “stammer”[All Fields] OR “stammering”[All Fields] OR “stutter”[All Fields] OR “stuttered”[All Fields] OR “stutters” [All Fields] OR “stutterings”[All Fields])	5
Total		**2402**

English abstract did not provide enough data, such as articles in Dutch and Japanese, Google Translate services were used (De Vries et al., 2018).
The authors independently screened the titles and abstracts of all articles from the initial search. Disagreements between authors were solved through discussion. Cases where the cause of movement disorder was already known, and the motor symptoms were not worsened or were not related to cocaine were excluded. Additionally, cases not accessible by electronic methods, including after a formal request e-mailed to the authors, were excluded.

Data extraction

For cocaine, a total of 2,402 articles were found; 2,001 were inappropriate, and 352 were unrelated to the subject, duplicate, inaccessible electronically, or provided insufficient data (Figure 2). Data abstraction was carried out. When provided, we extracted author, department, year of publication, country of occurrence, number of patients affected, patient's comorbidities, time from first cocaine dose until movement disorder occurrence (movement disorder onset), time from cocaine withdrawal to symptoms improvement (movement disorder recovery), patient's status at follow-up, neuroimaging features, electrodiagnostic studies, and significant findings of clinical history and management. Two independent authors extracted

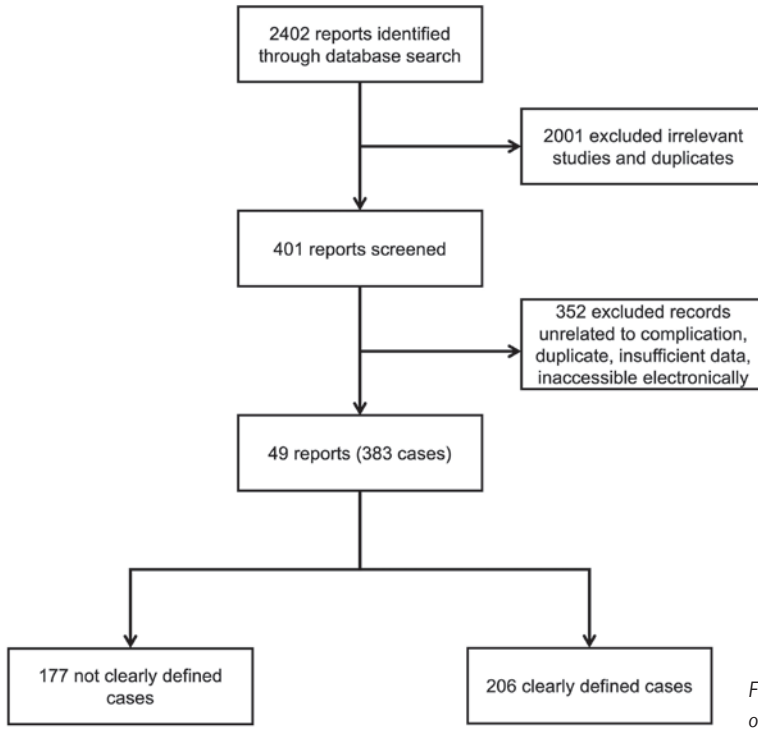

Figure 2 – Flowchart of the screening process.

the data, double-checked to ensure matching, and organized accordingly if the movement disorder was associated with cocaine use.

Statistical analysis
Categorical variables were represented as proportions; continuous variables were represented as means, standard deviation (SD), median, and range.

Definitions
The clinical characteristics and definitions of movement disorders such as parkinsonism, tics, dyskinesia, dystonia, stuttering, myoclonus, restless legs syndrome, akathisia, tremor, chorea, ataxia, and ballism were obtained from Rissardo et al. (2023a).

Results

A total of 49 studies containing 383 cases of movement disorder associated with cocaine were found in the literature (Table 2) (Kumor et al., 1986; Mesulam, 1986; Factor et al., 1988; Merab, 1988; Choy-Kwong and Lipton, 1989; Scharf, 1989; Pascual-Leone and Dhuna, 1990; Rebischung et al., 1990; Farrell and Diehl, 1991; Habal et al., 1991; Hegarty et al., 1991; Cardoso and Jankovic, 1993; Attig et al., 1994; Casas Parera et al., 1994; Daras et al., 1994; Horwitz and Van Harten, 1994; Beltran and Coker, 1995; Bauer, 1996; Daniels et al., 1996; Elkardoudi-Pijnenburg and Van Vliet, 1996; Catalano et al., 1997; Dhopesh et al., 1997; Domingo and Martínez, 1997; Fines et al., 1997; Gingrich et al., 1998; Van Harten et al., 1998; Bartzokis et al., 1999; Weiner et al., 2001; O'Suilleabhain and Giller, 2003; Supervía et al., 2006; Duggal, 2007; Henderson et al., 2007; Kamath and Bajaj, 2007; Maat et al., 2008; Vinkers et al., 2010; Anbarasan et al., 2011; Pinto et al., 2013; Doobay et al., 2017; Narula et al., 2017; Gibb and Nacopoulos, 2018; Illés et al., 2019; Van Esch et al., 2019; Ángel et al., 2021; Mascia and Defazio, 2021; Yeoh et al., 2022; Audi et al., 2023; Kim et al., 2023; Rajmohan et al., 2023; Srichawla et al., 2023). The abnormal movements encountered were 88 dyskinesia, 73 dystonia, 22 parkinsonism, 12 tics, nine catatonias, and two opsoclonus-myoclonus symptoms. A mixture of movement disorders was observed in 177 cases. Most of the individuals reported were from the male sex, accounting for 85.63%.

Discussion

Overview
Cocaine is associated with hyperkinetic movements such as dystonia, myoclonus, chorea, and tics. These effects are well known in the literature and are termed

Table 2 – Literature review of movement disorders associated with cocaine use

Reference	Age /Sex	Comorbidities	Cocaine route, mixture of drugs	Clinical manifestations	Notes
Parkinsonism					
Bauer (1996)	34 (mean) /13 M and 6 F	None	Cocaine dependent, cocaine and alcohol codependent	Hand-tremor	Hand-tremor was not visually obvious but required recording devices
Domingo and Martínez (1997)	35/M	None	Intranasal and intravenous cocaine, cannabis use previously	Tremor, loss of facial expression, and axial mobility	–
O'Suilleabhain and Giller (2003)	38/M	Hepatitis C and moderate depression	Intranasal, smoking (freebase), MDMA, amphetamine, alcohol	Bradykinesia, rigidity. decreased blink rate, left arm tremor at rest, postural arm tremor bilaterally – features suggesting hemiparkinsonism	The clinical features described in this report could be secondary to MDMA use
Illés et al. (2019)	44/M	Gastroesophageal reflux disease and first-degree heart block	Intranasal insufflation	Asymmetric (right) postural hand tremor (isometric tremor syndrome)	Patient' son was evaluated for restless leg syndrome at 13 years of age. Magnetic resonance imaging of the brain for the patient showed the absence of a swallow tail sign indicating Parkinson's disease
Dystonia					
Kumor et al. (1986)	29.5 (mean) /7 M	None	Intravenous cocaine	Acute dystonia – torticollis, oculogyric crisis, truncal involvement	The subjects/ volunteers received cocaine within 72 hours of haloperidol. Although there were no control groups, 6/7 patients developed dystonic reactions
Merab (1988)	35/M	None	Cocaine, unknown route	Facial dystonia	–

Reference	Age /Sex	Comorbidities	Cocaine route, mixture of drugs	Clinical manifestations	Notes
Choy-Kwong and Lipton (1989)	15/F	Adjustment disorder with depressed mood	Freebasing cocaine	Acute dystonia, torticollis, extensor posturing, high pitched vocalization	–
Rebischung et al. (1990)	29.5 (mean) /3 F	None	Freebasing cocaine	Dystonic posturing of head and extremities	Symptoms appeared during the cocaine withdrawal phase
Farrell and Diehl (1991)	29/M	None	Smoke form, crack cocaine	Painful spasms of the masseter muscle	–
Hegarty et al. (1991)	35 (mean) /25 M and 20 F	None	Intranasal, intravenous, freebasing cocaine	Acute dystonia	Prior neuroleptic use did not impact dystonic reaction significantly
Casas Parera et al. (1994)	Undetermined age, multiple subjects	None	Unknown route of cocaine consumption	Seizures and paroxysmal dystonic reactions	–
Horwitz and Van Harten (1994)	25/M	None	Unknown route of cocaine consumption	Acute dystonia	–
Beltran and Coker (1995)	3 hours after birth /M	None	Prenatal exposure – mother used inhalation crack cocaine during the third trimester	Episodic abnormal tonic posturing with head and neck deviation; episodic dorsiflexion	–
	2 months /M	None	Intrauterine cocaine exposure – mother inhaled cocaine	Torticollis (left-sided)	–
	2 months /M	None	Inhalation cocaine in mother – intrauterine exposure	Torticollis (right-sided)	–
Catalano et al. (1997)	34/F	None	Crack cocaine	Acute onset facial (facial muscles and jaw) dystonia	Symptoms resolved immediately with intravenous diphenhydramine
Fines et al. (1997)	32/M	None	Intranasal inhalation of cocaine	Extension of the head, hips, trunk arched forward	Symptoms resolved with diphenhydramine administration
	19/M	None	Intranasal inhalation of cocaine	Acute dystonia (torticollis)	–
Van Harten et al. (1998)	25/M	Mild intellectual disability	Cocaine, unknown route	Severe dystonia	–

Reference	Age /Sex	Comorbidities	Cocaine route, mixture of drugs	Clinical manifestations	Notes
Duggal (2007)	37/M	Psychotic disorder not otherwise specified	Intranasal insufflation	Trismus, trouble swallowing, shortness of breath (pharyngolaryngeal dystonia)	Ziprasidone was considered the primary agent causing dystonia with cocaine use as a risk factor
Henderson et al. (2007)	58/M	Bipolar disorder type II, depression with psychotic features, attention-deficit/hyperactivity disorder, hepatitis C, hypertension	Unspecified route of cocaine use	Jaw muscle dystonia, hands dystonia	Dystonia could be secondary to aripiprazole without the effect of cocaine
Vinkers et al. (2010)	45/M	None	Crack cocaine	Late onset, persistent torticollis	Structural changes in dopamine receptors are conjectured to cause long-term effects
Pinto et al. (2013)	7/M	None	Potential ingestion/inhalation	Exaggerated posturing of extremities, rhythmic movements, fixed rightward case	Cocaine was used by the patient's parents, and they were charged with child neglect in both these cases
	4/M	None	Ingestion of cocaine	Extended right arm, head turned to right (dystonia)	–
Ángel et al. (2021)	33/M	Congenital deafness	Cocaine, unknown route	Severe dystonia – status dystonicus	–
Mascia and Defazio (2021)	46/M	Bipolar disorder, arterial hypertension	Intranasal cocaine insufflation	Involuntary lateral flexion of trunk – referred to as PISA syndrome, Parkinsonism	–
Dyskinesia					
Habal et al. (1991)	24/F	None	Crack cocaine	Slow abnormal involuntary movements of the head (athetosis) of upper extremities and trunk	–

Reference	Age /Sex	Comorbidities	Cocaine route, mixture of drugs	Clinical manifestations	Notes
Habal et al. (1991)	34/F	None	Crack cocaine	Slow, purposeless involuntary movement of the trunk and bilateral upper extremities (athetosis), eye blinking, lip smacking	–
Daras et al. (1994)	34/F	None	Crack cocaine	Lip smacking, eye blinking, choreoathetoid movements of extremities	–
	24/F	None	Crack cocaine	Slow head movements, writhing movements of arms, trunk, and legs	–
	21/F	None	Crack cocaine	Gait ataxia, chorea of head and arms	–
	29/F	None	Crack cocaine	Akathisia, wringing movements of the hand	–
	58/F	None	Intranasal cocaine	Buccolingual dyskinesia, arm, and leg choreoathetoid movements	–
	38/M	None	Crack cocaine	Bradykinesia, mild chorea of fingers	–
	46/M	None	Crack cocaine	Rotations of the shoulder, movements of hand and feet	–
Bartzokis et al. (1999)	39.8 (mean) /71 M	None	Crack cocaine, smoked	Choreoathetoid movements, predominantly non-facial	AIMS was used in the grading of abnormal movement. Younger subjects had higher scores on the AIMS
Weiner et al. (2001)	34/F	Substance use disorder	Intranasal cocaine, intravenous cocaine, alcohol, opiates, and barbiturates	Serpentine movements of the trunk, dystonia, spasms of the abdominal wall, and rocking movements of the body initially associated with pleasurable	–

Reference	Age /Sex	Comorbidities	Cocaine route, mixture of drugs	Clinical manifestations	Notes
				sensations which later were unpleasant	
Supervía et al. (2006)	22/M	None	Cocaine, unknown route	Choreiform movements of the neck and upper extremities	–
Kamath and Bajaj (2007)	60/M	Hepatitis C, intravenous heroin use, subacute bacterial endocarditis, deep venous thrombosis	Intravenous cocaine	Choreiform movements of all extremities, orofacial dyskinesia	–
Doobay et al. (2017)	32/M	Hypertension, major depressive disorder	NA	Choreoathetoid movements of the head, arm, trunk, and shoulders	The patient was started on selective serotonin reuptake inhibitors for depression four weeks before presentation
Narula et al. (2017)	69/F	Type II diabetes mellitus	Crack cocaine inhalation	Choreoathetoid movements of bilateral upper extremities with left greater than right	–
Gibb and Nacopoulos (2018)	35/M	None	Cocaine ingestion	Buccal lingual dyskinesias and choreiform movements present in all extremities, intermittent tics	First-time cocaine use by the subject
Audi et al. (2023)	27/M	None	Intravenous cocaine and fentanyl, cannabis (likely smoke form)	Choreiform movements of left upper extremity	Chorea was noted after the patient developed anoxic brain injury secondary to drug use. Chorea failed to resolve initially with aripiprazole. The symptoms were attributed to fentanyl withdrawal, and his chorea was resolved with fentanyl

Reference	Age /Sex	Comorbidities	Cocaine route, mixture of drugs	Clinical manifestations	Notes
Rajmohan et al. (2023)	48/M	None	Cocaine/amphetamine/dextro-amphetamine	Writhing movements of the toe, left greater than right	Symptoms persisted months after discontinuation of substances
Tics					
Mesulam (1986)	27/M	Tourette's syndrome with obsessive-compulsive symptoms	Intranasal cocaine	Motor and vocal tics that were under remission	Patient's long-standing tics were controlled with haloperidol and his tics worsened with cocaine lasting a few hours
Factor et al. (1988)	21/M	Tourette's syndrome	Intranasal cocaine	Increased motor and vocal tics	Increased amplitude of tics with cocaine was associated with euphoria
Pascual-Leone and Dhuna (1990)	38/F	Tourette's syndrome	Intranasal cocaine	Recurrence of previous tics – jerking of neck and arms and barking noises, new onset facial tics	First-time cocaine exposure
	21/M	Tourette's syndrome	Crack cocaine, intranasal cocaine (chronic exposure)	Grunting noises, severe jerking tics of face, extremities, and neck	The patient was a chronic user of intranasal cocaine, but tics re-emerged after crack cocaine use
	28/F	None	Intranasal cocaine	Eye blinking, shoulder shrugging, head-turning, grunting, throat clearing	NA
	38/F	None	Intravenous cocaine	Right-sided facial and lower extremity jerks	Motor and vocal tics presented after a large dose of intranasal cocaine
Cardoso and Jankovic (1993)	21/M	Tourette's syndrome, attention deficit hyperactivity disorder	Intranasal cocaine	Wiggling of nose, upward rolling of eyes, right shoulder circumduction	–
	28/M	Tourette's syndrome	Intranasal cocaine	3 times increase in vocal and motor tics including coprolalia, copropraxia, and new paranoid delusions	–

Reference	Age /Sex	Comorbidities	Cocaine route, mixture of drugs	Clinical manifestations	Notes
Cardoso and Jankovic (1993)	31/F	None	Intranasal cocaine	Tenfold increase in head and hand tremor, cervical and axial dystonia	–
	30/M	Depression, paranoid schizophrenia	Intranasal cocaine	Generalized dystonia with axial involvement	–
Attig et al. (1994)	35/F	None	Intranasal and crack cocaine	Grunting, nostril-flaring, jerking of arms and head	–
Daniels et al. (1996)	49/M	Motor and vocal tics	Crack cocaine	Uncontrollable eye blinking	Within a day of abstinence, symptoms resolved
Opsoclonus-myoclonus					
Scharf (1989)	26/F	None	Intranasal cocaine	Myoclonic jerking of trunk, extremities, opsoclonus (conjugate, clockwise rotary)	Patient had an episode of isolated seizure with cocaine a few years ago
Elkardoudi-Pijnenburg and Van Vliet (1996)	29/M	Migraine and hypertension	Chronic heroin use, incidental cocaine misuse	Conjugated beats in all directions mimicking nystagmus, myoclonic jerks of the trunk	Patient was a chronic opioid user and cocaine use was incidental
Catatonia					
Gingrich et al. (1998)	36/F	None	Cocaine	Mutism, staring, slow purposeless hand gestures and resistance to movement	–
Anbarasan et al. (2011)	35/F	None	Crack cocaine vapor inhalation	Echolalia, speech latency, rigidity, gait ataxia, disorganized behaviour	A diagnosis of cocaine-induced leukoencephalopathy was made
Van Esch et al. (2019)	54/F	Psychosis	Cocaine and methadone	Disorganization, disorientation, confusion that progressed to rigidity, stupor, stupor, echolalia	–
Yeoh et al. (2022)	31 (mean)/4 M and 1 F	None	Cocaine, cannabis, and other substances were studied	Catatonia as described by the Bush-Francis catatonia rating scale	Cocaine and other stimulants caused acute onset catatonia

Reference	Age /Sex	Comorbidities	Cocaine route, mixture of drugs	Clinical manifestations	Notes
Srichawla et al. (2023)	51/M	None	Intranasal cocaine, alcohol	Rigidity in bilateral upper and lower extremities, high blood pressure, high fever suggestive of malignant catatonia	–
Mixture of movement disorders and different types of studies					
Dhopesh et al. (1997)	57 (mean) /M (50 individuals)	None	Cocaine, unknown route	UPDRS 0 to 1 in cocaine users. UPDRS scores range from 0 to 3 among controls	This study suggested chronic heavy use of cocaine did not result in parkinsonism. Fifty age-matched cases and controls were enrolled
Maat et al. (2008)	Age unspecified /M (106 individuals)	None	Cocaine, multiple routes	Dyskinesias, parkinsonism, and akathisia	UPDRS, Barnes Akathisia rating scale, and AIMS rating scales were used in the assessment of extrapyramidal symptoms
Kim et al. (2023)	40 (mean) /16 M and 5 F	None	Cocaine	Parkinsonism, dystonias, dyskinesias, and akathisias	Cocaine use was associated with increased risk of movement disorders with antipsychotic use

AIMS – abnormal involuntary movement scale; F – female; M – male; NA – not available/not applicable; UPDRS – unified Parkinson's disease rating scale

"crack dancing" even among users of cocaine. Cocaine-induced moderate to severe involuntary choreiform movements have also been reported, which were transient and improved after a short hospital stay. While phenotypically, the movements are indistinguishable from other movement disorders, the pathogenesis in cocaine-induced movement disorders involves excess dopamine in the synaptic cleft secondary to cocaine (Narula et al., 2017), and sensitization of the basal ganglia and change in the dopaminergic activity are hypotheses that explain the mechanism of these abnormal movements (Bartzokis et al., 1999).

Dystonia

Binge use of cocaine has resulted in acute dystonic reactions in patients who have not taken other drugs. However, individuals who are already on antidopaminergic

agents had worsened dystonic symptoms after cocaine use (Catalano et al., 1997). Cocaine withdrawal has been reported to cause generalized dystonia, vocalization, and posturing in young women who were treated with diphenhydramine (Millichap, 1989). Also, long-term use of cocaine can cause structural changes in the dopaminergic receptors in the basal ganglia, leading to persistent and severe spasmodic torticollis. Noteworthy, family history and other secondary causes of cervical dystonia should be revised before the diagnosis of cocaine-induced dystonia (Vinkers et al., 2010). Case reports describing orofacial dystonia involving the lips, jaw, tongue, and extrapyramidal motor tract dysfunction impacting speech secondary to cocaine use have been reported.

Tics

Cocaine-induced tics have been described in individuals who used cocaine chronically without pre-existing conditions or a family history of movement disorders. Case reports describe individuals who used cocaine and presented with grunting, head jerks, and flaring of the nostrils. Cocaine worsens pre-existing tics in individuals with Tourette syndrome, and new-onset tics were reported after high-dose cocaine use. The tics were complex and included vocal and motor components. In one of these cases, cerebrospinal fluid homovanillic acid levels were low which was a finding previously reported in similar cases. While abnormalities of cerebral blood flow were possibly confounding the findings, the absence of lateralization of tics favoured the hypothesis that cocaine was responsible (Pascual-Leone and Dhuna, 1990; Attig et al., 1994).

Dyskinesia

"Crack dancing" consists of self-limiting, choreoathetoid movements involving orofacial and limb musculature that may be associated with akathisia and can last up to several days. Prolonged cocaine use, even after abstinence, results in movement disorders such as dyskinesias. A case report describes a young female with twisting movements of her trunk, which emerged during periods of cocaine withdrawal and eventually became persistent. Rocking of the body, painful muscular spasms of the abdominal region, along with persistent truncal flexion were reported by the patient. She did not have pre-existing conditions, did not use neuroleptics, and denied family history, but reported polysubstance use. Interestingly, cocaine abusers had decreased cerebral blood flow in the frontal lobes in functional studies that were persistent even after a 90-day interval. Computed tomography also demonstrated cerebral atrophy in chronic cocaine users with a positive dose-response relationship. A characteristic stereotypical motor movement called "punding" has been described among cocaine users which involves the examination of objects or parts of the body with fascination, resembling obsessive-compulsive disorder patterns (Weiner et al., 2001).

Possibly one of the most visually dramatic movement disorders induced by cocaine is transient chorea and buccolingual dyskinesias, known in street slang as "crack dancing" or "boca torcida" by Hispanic addicts.

Parkinsonism

A case report of long-term intranasal and intravenous cocaine use resulting in parkinsonism has been described in the literature (Domingo and Martínez, 1997). A case report suggested genetic susceptibility to developing Parkinsonian features in individuals with chronic cocaine use. After 18 months of cocaine use, the individual described developed features of parkinsonism, and the dopamine transporter study was asymmetric, consistent with phenotypic findings. His genetic makeup revealed leucine-rich repeat kinase-2 gene homozygosity. The phenotypic and genotypic features were no longer present after the individual was abstinent from cocaine (Illés et al., 2019).

Alpha-synuclein overexpression in dopaminergic neurons has been described in cocaine users. Hyperechogenicity of the substantia nigra on ultrasound has been found in individuals with Parkinson's disease and also among chronic cocaine users indicating similar underlying pathology (Cenci et al., 2022). Although cocaine and Parkinson's disease have depleted dopamine, chronic use of cocaine was not found to result in Parkinsonian features in other studies. Interestingly, cocaine users had excess iron accumulation in their globus pallidus, indicating iron dysregulation resulting in free radical-mediated damage (Dhopesh et al., 1997; Ball et al., 2019).

Parkinsonism is rarely described as a result of cocaine use, and, in fact, inhaled cocaine has been reported to ameliorate Parkinsonian "off" periods in self-medicating patients without triggering dyskinesias (Di Rocco et al., 2006).

Opsoclonus-myoclonus

Popularly known as "dancing eye-dancing feet", opsoclonus-myoclonus secondary to cocaine use has been reported in the literature. Continuous intermittent nystagmus beats in a circumductive fashion were noted on physical examination, along with myoclonic jerks and ataxia. Elkardoudi-Pijnenburg and Van Vliet (1996) reported a case where after a few weeks of hospital stay, the opsoclonus improved, and his symptoms were completely resolved after four months. Previous reports have demonstrated similar findings with intranasal cocaine use. Opsoclonus is generally thought to occur secondary to loss of inhibition of ocular saccades. Several differential diagnoses should be excluded, including viral illness, tumours, toxins, poisons, and autoimmune etiologies, and the exact pathogenesis remains unclear (Scharf, 1989).

Tremors

Cocaine is reported to cause hand tremors, among other movement disorders. The nigrostriatal and mesolimbic tracts are the primary dopaminergic systems that are downregulated, resulting in tremors. Interestingly, individuals who were abstinent from

cocaine displayed resting tremors and slow reaction time in the study. Confounding factors such as anxiety, alcohol, and nicotine were studied, but no significant relationship was established. Cocaine is hypothesized to dysregulate the metabolism of glucose in the basal ganglia and alter receptor binding in the striatum in controlled studies demonstrating a link between cocaine and Parkinsonian features such as tremors (Bauer, 1996).

Stuttering

Linazasoro and Van Blercom (2007) reported an interesting observation on cocaine and stuttering. They describe a case report of a 30-year-old male with developmental stuttering and mild facial dyskinesias whose symptoms resolved for a few hours without re-emergence when he used cocaine. This finding was surprising because multiple case reports indicate that cocaine can induce new tics or worsen existing tics. It was conjectured that this phenomenon is secondary to a relatively low dopamine state due to a complex interaction between the neurotransmitters.

Future studies

Reporting cocaine use in a standardized format by healthcare professionals can prove useful in understanding the impact on society, and thereby, the need for allocation of budget by policymakers. Risks of developing movement disorders in particular conditions can be studied, and this knowledge can be implemented as a preventative care measure for affected populations. Studying the effects of cocaine on the dopaminergic system can provide insights into the neurobiology of stimulant use in general. Moreover, it can provide reliable information on targeting future therapeutics against addiction.

Understanding the intricacies of movement disorders and their response to substances can be useful in developing strategies to reduce movement disorder disease burden. Imaging modalities and biomarkers are essential for supporting understanding of neurological pathologies and research is needed to identify imaging findings and biomarkers that can support diagnosis and thereby initiation of treatment promptly. Longitudinal studies, while complicated because of the nature of the study, should be undertaken to improve understanding of the long-term use of cocaine.

Experiences of patients and their families of movement disorders secondary to cocaine should be recorded and reported so information is available to discuss prognostication and encourage abstinence among subjects. Studies assessing the understanding of drug use and associated complications among the general population can help guide resources toward educating the community as a whole. Animal models can help enhance our understanding of interactions of the brain and chemicals.

Limitations

Cocaine use disorder is underreported due to perceived social stigma and legal consequences, which limits the data gathered to perform a thorough analysis of the literature. Cocaine use disorder commonly occurs in conjunction with opioid use disorder and alcohol use disorder, among others, and even contaminants, which results in confounding data.

Case reports and case series, which lack control groups and randomization, are core data sources for this review. The quality of individual reports and studies will vary significantly, which translates to the quality of the literature review as concrete conclusions cannot be drawn. As a case in point, multiple case reports omit the route and quantity of cocaine use, which is important information to assess a dose-response relationship. Timelines of case reports and series are varied, and updates in research could have been missed. Ethical concerns arise in experimenting with substances to study their effects in animal and human subjects, which results in relying on data obtained from illicit consumption.

Conlusion

Cocaine use, acutely or chronically, can result in a wide array of movement disorders. This literature review provides insights into our understanding of mechanisms underlying cocaine-induced movement disorders. Also, it highlights the knowledge gaps that need to be filled through dedicated research, paving the way to potential therapeutic modalities in the hope of reducing the disease burden. Studying the effects of a widely used substance on the dopaminergic system will result in an enhanced understanding of neurobiology, which can be used in understanding, preventing, and developing therapeutic strategies for other movement disorders. It will add another reason to restrict the use of substances in medical care and research.

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