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Substances of abuse and movement disorders: complex interactions and comorbidities

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Abstract

The relationship between movement disorders and substance abuse which we previously reviewed are updated. We examine these relationships bidirectionally with focus on drugs of abuse which cause movement disorders, as well as primary movement disorders that are associated with use and abuse of alcohol and dopaminergic medications. First, we review the movement disorders that may develop from the acute use or withdrawal of frequent drugs of abuse, including alcohol, cocaine, heroin, amphetamine and methcathinone. We then comment on the interaction between alcoholism and alcohol-responsive movement disorders, such as essential tremor and myoclonus-dystonia. Lastly, we discuss the potential for abuse of antiparkinsonian dopaminergic agents in patients with Parkinson's disease (PD).

Keywords

Movement disorders; Parkinsonism; dystonia; chorea; drugs; tremor; tics; alcohol

ADDITIONAL KEY WORDS

Cocaine; amphetamines; Methcathinone; opioids; Heroin; cannabinoids; Marijuana; dopamine dysregulation syndrome; essential tremor; myoclonus-dystonia

1- MOVEMENT DISORDERS ASSOCIATED WITH ACUTE USE OR WITHDRAWAL OF DRUGS OF ABUSE

Movement disorders may be classified according to their primary phenomenology as either hyperkinetic or hypokinetic. Hyperkinetic disorders are characterized by an excess of movement, including tremor, dystonia, chorea, myoclonus, tics and akathisia. In hypokinetic disorders there is absence or paucity of movement that is unrelated to weakness or paralysis, and this suggests parkinsonism. These terms are defined in the prior version of this review [1].

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Although many movement disorders may develop either in isolation or as part of primary neurologic disease, they may also emerge from the acute use or withdrawal of medications. As an example, beta agonists, lithium and the chronic use of some anticonvulsants may lead to the development of action and postural tremors [2–4], and dopamine-blocking neuroleptic and antiemetic medications may trigger acute dystonic reactions and tardive syndromes [5]. Similarly, acute alcohol withdrawal may precipitate action tremors involving the hands or other body parts, along with other neuropsychiatric and autonomic disturbances.

The description of disorders associated with drugs of abuse, however, is more challenging. Toxicity data is derived primarily from individual case reports and small observational case series. In addition, adulterants in drugs of abuse added for the purpose of increasing bulk, enhancing or mimicking a pharmacological effect, or to facilitate drug delivery [6] may themselves cause movement disorders. For example, heroin has been found to be mixed with the synthetic potent opioid fentanyl hydrochloride; cocaine with diltiazem; and methylephedrine and ecstasy with pseudoephedrine, dextromethorphan and caffeine [7]. Caffeine [8] and pseudoephedrine [9] are known to cause postural and action tremors that closely resemble essential tremor. Finally, performing studies on patients struggling with substance abuse and addiction may be particularly challenging due to the frequent psychosocial issues that either precede or result from drug use. Indeed, even within the medical community the terms of drug “addiction” and “dependence” have historically had an implicit moralistic connotation that is fortunately transitioning to a less judgmental one as our understanding of the neurobiology of these conditions continues to expand [10].

We will review the impact of these and other drugs of abuse in the genesis of some movement disorders, and will also describe those substances of abuse that have treatment-like effects on particular movement disorders. Each section will be introduced and illustrated with clinical vignettes, and will finalize with a brief conclusion.

Cocaine

> Clinical Vignette #1: “*A 34-year-old homeless man with a history of frequent crack cocaine use for the last seven years presented to the emergency room with agitation several hours after smoking crack cocaine. The neurology service was consulted after he developed dance-like movements of his head and extremities. The patient acknowledged to similar symptoms in the past that resolved spontaneously within days of abstinence from crack cocaine.*”

Cocaine use remains a significant problem in the United States since its peak in the 1980s, and it affects millions of people worldwide [11], [12]. Cocaine blocks the dopamine transporter (DAT), preventing the reuptake of dopamine and other catecholamines at the presynaptic terminal and hence increasing extracellular dopamine levels. It also exhibits local anesthetic properties, presumably via inhibition of fast sodium channels in peripheral nerve endings [13].

The dopaminergic system is linked to many processes controlling reward, movement control and cognition [14], [15] and the increased extracellular levels of dopamine are thought to be involved with the euphoric effects of cocaine as well as explain its motoric side effects. With chronic use, dopamine depletion may occur from overstimulated dopaminergic terminals and excessive metabolism of the neurotransmitter, as suggested by neuropathologic studies. Chronic cocaine abusers have been found to have decreased levels of dopamine in the caudate nucleus and frontal cortex that is not paralleled by an increase of dopamine D1 and D2 receptor gene expression; they also have marked reductions in the vesicular monoamine transporter-2 [16]. Dopamine depletion may explain the dysphoric aspects and parkinsonism seen during cocaine abstinence and cocaine urges[17], [18], as

lingering rest tremor has been described in former abusers, which is suggested to be proportional to the degree of use and inversely related to the length of time since the last use, [17] perhaps implying an enduring toxic effect of cocaine on basal ganglia function. A reduction of dopamine receptors accompanied by a diminished release of endogenous dopamine in the ventral striatum has been demonstrated in human imaging studies of cocaine, heroin, and alcohol-dependent subjects [19].

The medical and neurological complications of cocaine use are well known. Among the neurological complications, cocaine is known to cause cerebrovascular events (both ischemic and hemorrhagic) via diverse mechanisms including induced hypertension, vasospasm, cerebral vasculitis and impaired vascular autoregulation [11], [20]. It can also precipitate generalized seizures and worsen pre-existing seizure disorders [21], [22]. Cerebral atrophy may result from chronic use [23].

A variety of movement disorders may be associated with cocaine use. While movement disorders from cocaine use may be independent of structural neurological damage such as stroke, preexisting brain disease and previous or concomitant neuroleptic use appear to be predisposing factors for their development [24], [25]. The proposed mechanism leading to abnormal movements after cocaine exposure is locomotor sensitization, the augmented motor-stimulant response that occurs with repeated, intermittent exposure to cocaine [26]. Locomotor sensitization has been hypothesized to result from a decrease in inhibitory modulation of excitatory transmission from the medial prefrontal cortex to the ventral tegmental area and nucleus accumbens [27]. Recent animal data suggests that cocaine-induced activation of cAMP-element binding protein and generation of new silent synapses may serve as key cellular events mediating cocaine-induced locomotor sensitization [28]. Sensitization is considered a model for some aspects of drug addiction in humans, particularly drug craving during abstinence [26].

Cocaine has been associated with de novo motor and vocal tics as well as with exacerbations of Guilles de la Tourette's syndrome in first time and chronic users [25]. Adults presenting with tics in the absence of a childhood history should be inquired about cocaine use. Cocaine has also been described as a predisposing risk factor for acute dystonia in patients using neuroleptic agents [29], although there are reports of dystonia affecting different body regions resulting directly from cocaine use independent of neuroleptic use [30], [31, 32]. Opsoclonus-myoclonus has also been described following the intranasal usage of this drug [33].

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, and is depicted in our first clinical vignette. Of note, "crack" or smoked cocaine allows much higher doses than are possible with sniffed or snorted cocaine [34]. "Crack dancing" consists on self-limiting, choreoathetoid movements involving orofacial and limb musculature that may be associated with akathisia, and can last for up to several days [24], [35]. Prior neuroleptic use or preexisting organic brain disease have been reported as potential risk factors for the development of this disorder [24], [36]. However, antistreptolysin and anti-cardiolipin antibody titers are typically not elevated, structural lesions are not identified on brain imaging and, in at least one reported case, genetic screening for Huntington's disease and dentatorubralpallidoluysian atrophy was negative [36]. Because the movements are self-limited, not life-threatening and may be unapparent to the substance users themselves, affected individuals are not likely to seek medical care, and it is difficult to estimate the actual prevalence of this phenomenon. Impaired self-awareness is a recognized feature of other choreas, such as Huntington's disease, regardless of their cognitive status [37].

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 [38]. However, chronic use has been reported to cause subtle parkinsonian features (such as tremor at rest) that may persist after drug withdrawal [17]. The pathological hallmark of PD is the Lewy body, an intracellular inclusion body composed of pathological aggregations of the presynaptic protein alpha-synuclein [39]. Overexpressed alpha-synuclein has been observed in midbrain dopaminergic neurons from cocaine abusers, possibly representing a neuroadaptive response to the exposure and potentially exposing them at risk for degenerative changes in dopaminergic neurons [40]. In addition, alpha-synuclein protein levels are increased in serum from recently abstinent cocaine abusers [41]. However, unlike methamphetamine or other amphetamine-type drugs, the available evidence suggests it is unlikely that cocaine confers increased risk of PD [42].

Amphetamines

> Clinical Vignette #2: "*A 19-year-old previously healthy woman, ingested several "ecstasy" tablets at a rave party and presented the morning after to the emergency room with inability to fully open her mouth. On examination, there was visible forceful mouth closure with prominence of bilateral masseter muscles, which improved with the administration of IV diphenhydramine. After continuous anticholinergic therapy for five days, her symptoms resolved.*"

Acute amphetamine intoxication frequently warrants presentation to emergency departments [43]. Similar to cocaine, the effects of amphetamine and methamphetamine are mainly attributed to their binding and reversal of the dopamine transporter (DAT) function, resulting in both reuptake inhibition and release of dopamine at the mesocorticolimbic dopaminergic nerve terminals [14]. The central nervous system stimulation can cause agitation, tremor and ataxia in extreme cases, and can induce seizures, coma and intracranial hemorrhages [8], [43].

3,4-Methyenedioxymethanphetamine (MDMA), commonly known as "ecstasy", causes the release and inhibition of reuptake of serotonin, dopamine and norepinephrine in the central nervous system, leading to an acute increase in the intra-synaptic concentration of these neurotransmitters. In addition, MDMA has a slight monoamino oxidase (MAO) inhibiting activity. The main effects of euphoria and emotional closeness are thought to be secondary to the release of serotonin [44].

In mice, administration of MDMA causes the formation of ubiquitinated inclusions in the substantia nigra and striatum, and several cases of parkinsonism have been reported in MDMA users [45–47]. However, the true occurrence of neurotoxic effects of MDMA in the dopaminergic system of primates and humans is debatable [48–50], since, unlike other amphetamines, MDMA has been shown to selectively destroy serotonergic axon terminals [34].

Tremor has been described in MDMA users and it is thought to be related to sympathetic arousal [51], [52]. Trismus, bruxism, restless legs [52], [53] and acute dystonic reactions [54], [55], such as the one depicted in the clinical vignette have also been reported.

Although not strictly a movement disorder, one of the signs of methamphetamine abuse is the development of punding [56], which is defined as non-goal directed repetitive activity. Punding, however, is not exclusive to amphetamine abusers, as it has also been reported in cocaine users, and more recently in patients with Parkinson's disease receiving dopamine replacement therapy [56]. This so-called dopamine dysregulation syndrome will be described in greater detail in a subsequent section.

Overlapping symptoms of neuroleptic malignant syndrome and serotonin syndrome were described in a 19 year old woman after a single exposure to MDMA [57]. Recent concern has been raised in Australia by reports of cases of fatal serotonin toxicity caused by the combination of MDMA and moclobemide, a reversible MAO-A inhibitor with potent serotonergic activity [58].

Methcathinone (Ephedrone)

> Clinical Vignette #3: "*A 45 year-old man who recently emigrated from Russia presented to the Movement Disorders Center clinic with a three year history of gait difficulties and frequent falls. Neurologic examination was remarkable for parkinsonian signs including hypomimia, hypophonia, symmetric bilateral bradykinesia and axial rigidity without rest tremor. He was diagnosed with an atypical parkinsonian syndrome and prescribed levodopa, which was titrated up to 1000 mg/day without any noticeable improvement in his condition. A brain MRI revealed bilateral T1 pallidal hyperintensities. When asked, the patient admitted to intermittent use of self-prepared injectable methcathinone for the past five years.*"

A new form of manganese poisoning has been reported mainly from the Ukraine, Estonia, Latvia and Russia in drug abusers chronically injecting self-prepared methcathinone (ephedrone, 'ephedrone encephalopathy'). Ephedrone is synthesized from the oxidation of pseudoephedrine hydrochloride with potassium permanganate [59], [60]. It appears that in addition to the potential manganese toxicity associated with its use, ephedrone has an affinity for the monoaminergic transporters similar to that of methamphetamine. Its abuse results in a syndrome of levodopa-resistant, akinetic, rigid parkinsonism with myoclonus, speech dysfunction, bradyphrenia, gait and postural instability that very closely resembles a syndrome previously reported with manganese poisoning [59], [61].

Different imaging modalities have been used to study this phenomenon. Brain MRI imaging may show symmetrical hyperintensity on T1-weighted images in the globus pallidus and substantia nigra pars reticulata [61], [60, 62]. Less frequently reported involved structures are the subthalamic nucleus, substantia innominata, putamen, caudate, anterior midbrain, pontine tegmentum, and dentate nucleus [62]. Diffusion tensor imaging has demonstrated widespread white matter abnormalities, particularly in central white matter and areas underlying the right ventral premotor cortex and medial prefrontal premotor cortex [62]. Positron emission tomography (PET) studies have shown decreased density of striatal DAT sites in abstinent users of these substances in a similar fashion as in PD, possibly indicating permanent damage of striatal dopamine axon and axon terminals [63].

Opioids

> Clinical Vignette #4: "*A 43 year old Filipino man presented to the Movement Disorders center with a ten year history of a "creepy-crawly" feeling of his legs that was relieved by voluntary movement and was consistent with restless legs syndrome. He had been treated with pramipexole at the time of evaluation. Fifty milligrams of Tramadol were added as adjunctive treatment, which caused a significant reduction in his discomfort. Symptoms resolved completely upon titrating up to 100 mg a day, but he developed mutifocal, asynchronous, fast jerks of his arms and legs, consistent with myoclonus. The abnormal movements abated after Tramadol was titrated back to 50 mg daily.*"

Opioids, like some other addictive substances, elevate forebrain dopamine levels by blocking the inhibitory gamma aminobutyric acid (GABA) interneurons near the ventral tegmental area (VTA), which in turn activates the mesocorticolimbic dopaminergic neurons [14, 64].

Myoclonus has been frequently reported in association to opiate use, and opiate-induced myoclonus is recognized as a syndrome. It is often generalized, tends to respond to naloxone or benzodiazepines and patients concurrently using dopamine blockers (including antipsychotics and antiemetics), nonsteroidal-antiinflammatories and antidepressants seem to be at a higher risk [65]. Opioids such as morphine [66], hydrocodone [65] and parenteral tramadol [67] have been reported to precipitate myoclonus. Interestingly, methadone-induced acute chorea resolving after switching to a different opioid has been reported and suggests non-opioid mechanisms in its genesis [68], [69].

Meperidine use can lead to a full-blown neurotoxic syndrome characterized by recurrent convulsions, myoclonus, and asterixis [70]. Normeperidine, its metabolite, is thought to mediate this syndrome and symptoms are especially severe (and potentially fatal) when taken in combination with a monoamine oxidase inhibitor [71].

The spongiform leukoencephalopathy resulting from "*chasing the dragon*" (inhaling the vapors of heroin pyrolysate, black-market heroin heated on aluminum foil, as opposed to "pure" pharmaceutical diamorphine) may manifest with choreoathetoid movements, tremors and ataxia as part of the clinical spectrum, although obtundation and corticospinal tract signs usually dominate the clinical picture [72], [73]. Parkinsonism and bradykinesia may also occur [74]. Pallidal abnormalities in imaging have been reported in addition to the classical symmetric posterior fossa and supratentorial deep white matter changes [75], and cerebrospinal fluid studies in these patients have shown a marked acute reduction of the dopamine metabolite homovanillic acid (HVA) as well as the co-factor necessary for dopamine synthesis, tetrahydrobiopterin (BH4) [72], [74]. The mortality of "*chasing the dragon*" has been reported to be as high as 23% [73].

Clandestine laboratory attempts to produce analogs of the synthetic opioid meperidine in the 1980s resulted in the production of 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) as a toxic by-product. Heroin-addicts that injected MPTP-containing "new heroin" developed acute, levodopa-responsive parkinsonism [76]. Interestingly, this serendipitous discovery led to the use of MPTP-induced parkinsonism in primates as the one of the most widely used animal models of PD. Its toxic metabolite 1-methyl-4-phenylpyridium (MPP+) is synthesized by the enzyme MAO-B (monoamine oxidase type B) and transported into dopaminergic cells via the dopamine transporter (DAT), were it is thought to act as a mitochondrial complex I inhibitor [77]. Recently, MPTP has also been found to activate the death-signaling pathway mediator apoptosis signal-regulating kinase 1 (ASK1) in midbrains of mice [78].

Levodopa-responsive parkinsonism developing within two weeks after snorting heroin has been reported, [79] but, in general, parkinsonian syndromes with encephalopathy after heroin abuse are rare. MRI revealed bilateral basal ganglia and occipitopolar cortex hyperintensities on fluid-attenuated inversion recovery, T1-weighted hyperintensities to this cortical area and the globus pallidus internus, and T2-weighted hyperintensities of the substantia nigra. It is unclear whether these changes were caused directly by heroin or due to an additive in the snorted substance

While opioid medications have been associated with development of movement disorders as described earlier, it is important to recognize their effectiveness in the management of restless legs syndrome (RLS). In fact, the results of a pilot, post-mortem study suggests that there may be altered central processing of pain in RLS, implicating the endogenous opioid system in its pathogenesis [80].

Cannabinoids

> Clinical Vignette #5: "*A 24 year old young man admitted to a rehabilitation facility for heavy marijuana use started pacing around his room one week after his last use. When asked, he insisted that he "didn't know what was wrong with him, but couldn't seem to be able to stay still". He seemed anxious and diaphoretic. Vitals signs were within normal limits, except for mild tachycardia. He was given an oral benzodiazepine, after which his symptoms resolved and he fell asleep. His symptoms recurred, albeit in a milder fashion, for the following 2 days*".

In general, apart from jitteriness, restlessness and shakiness resulting from withdrawal of heavy marijuana use [81], movement disorders are not typically associated with the use of cannabinoids. A single report is published on propriospinal myoclonus after cannabis use, [82] defined by the authors of this paper as a brisk wave of muscle contractions originating in the mid-thoracic cord and propagating both proximally and distally at a rate of 3 to 11 m/second by means of propriospinal pathways. Interestingly, cannabinoids have been studied in the management of different neurologic conditions, with varying degrees of success: they have been approved in Germany for the treatment of spasticity in multiple sclerosis, [83] have been found not to be different than placebo in the management of chorea in Huntington's disease [84], and have been suggested to be effective (although larger confirmatory trials are warranted) in the treatment of tics in Guilles de la Tourette's syndrome [85, 86] and symptoms in antipsychotic-induced tardive dystonia [87]. The potentially neuroprotective effects of cannabinoids in PD and possibly other neurodegenerative disorders is provocative but remains to be proven [88].

Alcohol (Ethanol)

> Clinical Vignette #6: "*A 62 year old homeless, alcoholic woman was hospitalized for profuse hematemesis. An esophagogastroduodenoscopy revealed bleeding esophageal varices, which were banded and cauterized. Three days after admission, the patient became acutely delirious. On neurological examination, a flapping movement was seen affecting both palms when these were held in extension (asterixis). The abnormal movements and confusion improved with the use of oral lactulose*".

Acute ethanol (ethyl alcohol) exposure is thought to increase GABAergic transmission at the synapse between the cerebellar molecular layer interneurons and Purkinje cells, which in turns leads to a decrease in glutamatergic transmission at granule cell-Purkinje cell synapses [89]. Whereas alcohol may ameliorate some movement disorders (see next section), both its abuse and withdrawal are associated frequently with tremor. The most frequent tremor seen is a postural tremor (present when sustaining a position against gravity, such as holding both arms outstretched [90]), which may both be seen in the late stage of alcohol dependence or during early alcohol withdrawal [91]. With prolonged exposure to alcohol, cerebellar degeneration may also ensue, which is clinically characterized by cerebellar ataxia preferentially affecting the legs as compared to the arms. Macroscopically, there is severe vermian degeneration (mainly involving the anterior and superior portions of the vermis), which translates microscopically in degeneration of all three layers of the cerebellar cortex: almost complete loss of Purkinje cells, apparent narrowing of the molecular layer, and definite tissue rarefaction of the granular cell layer. [92].

During abstinence from alcohol, patients may develop a tremor that closely mimics essential tremor (see below for a further description of this condition), but has a greater frequency, mainly involves the hands and responds exquisitely to propranolol [93].

Other than tremor, patients with alcoholic liver disease leading to hepatic encephalopathy frequently exhibit asterixis, like the patient depicted in Clinical Vignette #6. Asterixis is characterized by brief, arrhythmic interruptions of sustained voluntary muscle contraction due to brief lapse of posture. It manifests as a bilateral flapping tremor occurring at a rate of 3–5 Hz during active maintenance of posture [94].

A history of alcohol abuse or dependence is also associated with an increased risk of developing tardive orofacial dyskinesias in patients exposed to neuroleptic medications, and the severity of such dyskinesias appears to be correlated with greater alcohol consumption [95]

Table 1 summarizes the presumed pathophysiology and associated movement disorders of the drugs described thus far.

Miscellaneous

The withdrawal syndrome from benzodiazepines may result in tremor and myoclonus [96]. Similar symptoms have also been associated with withdrawal from chronic gammahydroxybutyrate use [97] and zolpidem [98]. Inhalant exposure to solvents such as toluene, xylene and paint thinners may cause tremor, and, in chronic users, parkinsonism [99]. Myoclonus, chorea and ataxia among other symptoms are described after gasoline sniffing [100]. Tremor, rigidity, myoclonus and dystonia have been described with phencyclidine [PCP] intoxication [34, 101].

Pathophysiologic – Clinical correlation

In clinical practice, remembering the main pharmacodynamic mechanisms that each of these drugs possesses can useful in identifying the offending agent when faced with a presumed drug-induced movement disorders. In general, it can be conceptualized that drugs that enhance monoaminergic transmission, either by inhibition of their reuptake (like in the case of cocaine), promoting their release from presynaptic terminals (as amphetamines can) or by inhibition of inhibitory interneurons projecting to the dopaminergic system (in the case of heroin) will likely provoke hyperkinetic movements, while substances stimulating inhibitory neurotransmission, (as alcohol is believed to do), will likely counteract the magnitude of hyperkinetic movements and will only favor the development of hyperkinetic movements in the setting of withdrawal.

These markedly oversimplified concepts, can, of course, be subject to error, and can never replace a thorough history and physical examination, especially looking for associated comorbidities or other stigmata that may point towards a particular offending agent (such as track marks or a perforated nasal septum). In particular, it is important to be mindful that substance abuse can have medical complications leading to other movement disorders (as is the case of chronic alcoholics developing asterixis as a result of marked liver disease, or IV drug users contracting HIV, with all of its known deleterious consequences).

Finally, as mentioned above, parkinsonism can be a consequence of drug use, and may be seen in Ephedrone abusers or in heroin users, the latter causing hypokinesis by the active component or as a catastrophic consequence of unfortunate contamination.

2- ALCOHOL USE IN PATIENTS WITH MOVEMENT DISORDERS: ESSENTIAL TREMOR AND MYOCLONUS- DYSTONIA

Clinical Vignette #7: *“A 65 year old man presented with complaints of tremor to the neurology clinic. He first noticed bilateral hand tremor when reaching out to*

> *grab objects more than ten years ago, and that it had progressed to the point that he had severe difficulty writing and feeding himself, which was additionally a source of social embarrassment. The tremor increased with stress or after drinking coffee, but improved significantly after two glasses of wine. Neurological examination was significant for a low amplitude, 10 Hertz postural tremor that increased in amplitude on action, without dysmetria, bradykinesia or rigidity, consistent with essential tremor. The patient was prescribed the beta blocker propranolol, with significant symptomatic benefit.*"

Essential tremor is one the most common movement disorders [102]. It is characterized by slowly progressive, bilateral postural and action tremors of the hands and forearms with an otherwise normal neurological examination, although unilaterality or asymmetry and involvement of the head, tongue, lower limbs and voice may be present [103]. While considered a "benign" condition, it can be a source of great disability for some patients [104]. It is presumed to be secondary to dysfunction of the olivocerebellothalamic pathways [105], [106]. Although debated, relatively recent neuropathologic studies point towards Purkinje cell axonal swellings ("torpedoes") in the cerebellar hemispheres and vermis as potential markers of disease [107].

Alcohol is perhaps the most efficacious pharmacological agent to ameliorate the symptoms of this condition, providing a 50–90% of improvement in many patients [108], [109]. Alcohol ingestion decreases the amplitude, although typically not the frequency of postural tremors; its effect is however frequently short-lived and may cause rebound worsening upon wearing off [110]. The mechanism of action by which alcohol exerts its effects is unclear, but a direct effect on the inferior olivary nuclei and/or effects on GABA transmission are suspected [111], [112]. Studies have shown that ethanol activates GABA-A, glycine, and nicotinic acetylcholine receptors, and that it inhibits N-methyl-D-aspartate (NMDA) glutamate receptors [113]. Other post synaptic ligand-gated ion-channels have been proposed as potential ethanol targets [114].

Because of its efficacy but short-term duration, concerns about increased alcoholism rates in the essential tremor population have been raised. The literature is however conflicting in this matter. Although a retrospective case-control study showed marked higher rates of alcoholism and alcohol abuse in essential tremor cases as compared to age-matched controls in veterans (66% vs. 25%) [115], two prospective studies showed no significant difference between the two groups [116], [117] suggesting that there is no increased risk of alcoholism in patients with essential tremor. Furthermore, a recent Czech study on the prevalence of laboratory parameters reflecting chronic alcohol abuse (including liver function tests and erythrocyte mean corpuscular volume) in subjects with essential tremor when compared to controls did not detect a higher incidence of alcoholism in these patients. This study suggested their alcohol intake was well controlled and did not exceed the limits of healthy social drinking [118]. Interestingly, a negative association between wine drinking and essential tremor has been recently suggested, perhaps due to the long-term neuroprotective effect of its antioxidant components [119]. Despite these findings, essential tremor patients should nonetheless be inquired about alcohol use and counseled about potential abuse and the negative effects of alcohol on sleep and mood (among others) when appropriate.

Myoclonus-dystonia (M-D) is an uncommon inherited disease characterized by early onset myoclonus in the first or second decades of life, followed by the development of dystonia in some individuals [120]. Infrequently, family members may present with dystonia as an isolated feature. This syndrome has been associated to mutations in the Epsilon-sarcoglycan gene (*SGCE*, DYT11), mapped to 7q21 [121], [122]. It is typical for alcohol to improve myoclonus in the majority of patients, [123] but the dystonia may also improve in a lesser

degree. Myoclonus in M-D has been reported to respond to benzodiazepines [124], sodium oxybate (gammahydroxybutyric acid) [125], valproic acid [126], levetiracetam [127] and l-5-hydroxy-tryptophan [128]. The response of dystonia to anticholinergic medications, however, has been far less than satisfactory [129]. A report on deep brain stimulation (DBS) of the ventral intermediate thalamic nucleus has reported isolated improvement in myoclonus in a patient with M-D [130]; however, targeting the globus pallidus internus has shown improvement in both myoclonus and dystonia in small case series 1, [131], [132].

There is a higher frequency of alcohol abuse in M-D, presumably due to the ameliorative effects of alcohol in this condition, leading to misuse in an attempt to self-medicate [109]. Prior to gene identification, in a study of three families with myoclonus-dystonia demonstrating linkage to the DYT11 locus, 44% of manifesting carriers met criteria for alcohol dependence, versus 13% of non-manifesting carriers. The rates of alcohol dependence between all carriers and non carriers did not differ, suggesting a palliative effect of alcohol in the motor symptoms rather than a result of the gene expression [133]. These results were further replicated in a larger cohort of patients with identified epsilon sarcoglycan mutations [134]. Because of the exquisite response of M-D to alcohol, this raises questions about the pathophysiologic mechanism of alcohol on M-D, and the sites at which alcohol is exerting its effects. A recent review further discusses the relation of alcohol and M-D [109].

Despite the differences in phenomenology between ET and M-D, their alcohol responsiveness sets them apart from other movement disorders and brings up the potential for abuse, which may be challenging to diagnose and manage. The sensitivity of both these conditions to alcohol points perhaps towards shared pathophysiologic mechanisms, especially given the growing support for a role of the cerebellum in the etiology of dystonia [135]. Furthermore, a knock-out mouse model of M-D has identified nuclear envelope abnormalities in cerebellar Purkinje cells [136]; this, however, has not yet been shown in humans.

In regards to the putative neuroprotective effects of wine and grapes that is presumably mediated mainly by Resveratrol, recent data suggest that the beneficial effects of this compound, if any, may be present only at lower concentrations [137]. Thus, as with essential tremor patients, a conservative approach in M-D patients is encouraged, by counseling them on their increased potential for alcohol abuse, and to advice them to drink only in moderation, if at all. Increased awareness is of course key in identifying patients who may start exhibiting signs of addiction, and obtaining collateral information may be necessary when patients have poor insight into their problem.

3- ABUSE OF DOPAMINERGIC AGENTS AND THE “DOPAMINE DYSREGULATION SYNDROME”

Clinical Vignette #8: “*A 62 year old woman with a 6 year history of PD was hospitalized due to confusion, agitation and chorea involving her neck, arms and legs, which made it difficult for her to sit in a chair without falling out. On admission, the patient was found to be dyskinetic and emaciated. As per the family, she had lost 20 lbs over the previous three months, presumably due to levodopa-induced dyskinesias, which were present most of the day. They also acknowledge that she was taking frequent “rescue” doses of levodopa, and over the last 6 months had increased her daily levodopa dose from 800 mg a day to 1300 mg a day, or more at times. During the preceding week, she had also become suspicious and confused. She was diagnosed with dopamine dysregulation syndrome and a slow levodopa taper was started towards her prior outpatient levodopa dose, along*

with escalating doses of clozapine. Two months after discharge she was seen at follow up. She had regained 10 lbs and was no longer dyskinetic, confused or paranoid."

The "dopamine dysregulation syndrome" (or DDS, formerly known as "hedonistic homeostatic dysregulation syndrome") is a neuropsychiatric behavioral syndrome first described in 2000 by Giovannoni [138] and thought to occur in ~4% of treated PD patients [139]. It is an uncommon [140], [141] but very disabling neuropsychiatric complication of dopaminergic therapy in PD. In this syndrome, usually relatively young patients (frequently men), with longstanding idiopathic, levodopa-responsive PD [142] develop what some consider to be an addiction to their dopaminergic therapies, although whether DDS indeed fulfills criteria to be considered a form of addiction remains controversial [143]. Interestingly, some patients with DDS may have a previous mood disorder, as well as history of heavy alcohol consumption and illegal drug use [144]. These patients consume excessive amounts of the antiparkinsonian medications far beyond the amount needed to treat their motor symptoms. The use of intermittent subcutaneous injections of apomorphine, a very potent D1 and D2 dopamine receptor agonist [145], intended for the treatment of prolonged "off" periods in advanced PD [146], [147] may unmask or trigger this syndrome [138], [148], [149], [150]. Compulsive levodopa intake frequently extends into the night hours, and patients may seek multiple, simultaneous sources of medication, including obtaining redundant prescriptions from different physicians and ordering medications online [142].

Deleterious effects resulting from DDS include hypomania, psychosis, and violent levodopa-induced dyskinesias and often have a profound impact on social and occupational functioning [138], [151], [148]. In fact, early and severe dyskinesias (within the first 12–24 months) might be a warning sign for developing DDS [139]. Altered appetite, hypersexuality, pathological gambling and shopping, heightened aggression, euphoria and hypomania leading on occasion to florid psychosis may be associated with DDS [138], [140], [148]. Not all patients with DDS necessarily develop impulse control disorders, but most of them tend to exhibit punding behaviors [152].

Effects of levodopa, apomorphine and other dopaminergic medications in the reward dopaminergic mesolimbic pathways projecting to nucleus accumbens are postulated to underlie the disorder [138], [148]. There is evidence of sensitization of the ventral striatum (including the accumbens) reward system by PET imaging with [11C]-raclopride in PD patients with DDS who had enhanced levodopa-induced ventral striatal dopamine release compared with levodopa-treated patients with no compulsive drug use [153]. Thus, PD patients with more pronounced mesolimbic dopaminergic denervation (which can be related to the presence of non-motor fluctuations and has been shown by PET studies to affect the connectivity with the orbitofrontal, dorsolateral prefrontal, posterior cingulate and temporal cortices, left striatum and right amygdale [154]), may be prone to develop compulsive behaviors after dopaminergic treatment [153, 155]. In terms of behavior, habituation [142] and negative reinforcement by unpleasant off symptoms [139] (including dysphoria, pain and reemergence of parkinsonism, among others) tend to perpetuate this syndrome.

Although there are no controlled trials that address the management of this syndrome, a reduction in the total daily levodopa dose and discontinuation of rescue medication is key [142]. This task may be challenging, however, as patients may lack insight and may experience frank craving for medicine and display withdrawal symptoms [142], similar to the syndrome that has been described for dopamine agonist withdrawal [156].

Indeed, the dopamine agonist (DA) withdrawal syndrome (DAWS) is defined as a severe, stereotyped cluster of physical and psychological symptoms that correlate with DA

withdrawal in a dose-dependent manner. DAWS may cause clinically significant distress and/or social/occupational dysfunction, is refractory to levodopa and other antiparkinsonian medications and cannot be accounted for by other clinical factors [156]. Although there is no established medication that can be useful for DDS, anecdotal evidence has shown that atypical neuroleptics may be helpful [144, 157], and naltrexone is currently under investigation [142]. Hospitalization and supervised medication titration should be considered on a case by case basis. Anti-depressants and psychotherapy may aid in treating mood disorders, while positive reinforcement (on–off diaries) may keep patients aware of their daily medication requirements [144].

The relationship between deep brain stimulation (DBS), a recognized surgical treatment for the motor symptoms of PD, and DDS remains controversial. DBS may improve, worsen, or have no effect on the syndrome and the syndrome itself may manifest for the first time after DBS surgery [158]. This latter scenario has been reported to have a poor prognosis [159].

Impulse control disorders (including, but not limited to, DDS) in PD are often under recognized, although they are thought to occur in 15% to 20% of PD patients [160]. In response, increasing awareness in the medical community has been raised recently in regards to behavioral complications of dopaminergic therapy. In fact, the Movement Disorders Society - Unified Parkinson Disease Rating Scale (MDS-UPDRS), a widely used rating scale for PD, now includes a question screening for these disorders [161]. However, rating scales designed to measure severity of symptoms and support a diagnosis of impulse control disorders and related disorders in PD still require further validation [160].

In sum, DDS is a phenomenon that is being increasingly recognized in the PD population and that, similar to other impulse control disorders, can be very distressing to the patient and his or her family. Increased awareness is thus required, and prompt reduction in the total daily dose of dopaminergic treatment can reduce the incidence of potentially life threatening complications, such as florid psychosis. Dose reduction, however, may not be an easy goal to achieve, and is hindered by lack of insight from the patient and the development of symptoms reminiscent of drug withdrawal. Hence, prevention, perhaps by avoidance of high-dose dopaminergic therapy in those patients at highest risk, may be a valid treatment strategy in selected patients at the expense of suboptimal control of their symptoms. The clinical application of functional imaging as a screening tool of such a population remains to be established, and may become a practical resource in the future.

4- CONCLUSION

Multiple drugs of abuse may cause a myriad of movement disorders through their interaction with different neurotransmitter systems, including the dopaminergic, noradrenergic, serotonergic and GABAergic systems. Depending on the specific agent, these abnormal movements may be transient or permanent, and may appear as a direct consequence of their sporadic use, abuse and/or withdrawal.

Our understanding on their exact mechanisms of action continues to expand with the advent of sophisticated neuroimaging and neuropathologic techniques, but there still remains much to learn. The use of some of these compounds in the management of movement disorders has helped to provide insight into the pathophysiology of some of these diseases, and thus continued research in the action of these substances may shed light into the pathophysiology of other movement disorders.

Unfortunately, substance abuse is not limited to illegal drugs, as the abuse of prescription medications is on the rise. The dopamine dysregulation syndrome is a reminder of the narrow window that may exist between the therapeutic use of a medication and its abuse,

and should urge the clinician to exercise caution when prescribing other medications, such as opiates and benzodiazepines. In the future, our better understanding of the mechanisms of addiction will hopefully enable us to improve treatment practice, and minimize risks in vulnerable populations.

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KEY LEARNING OBJECTIVES

1. To describe the drugs of abuse which are associated with movement disorders, and the types of movements that may result from their use. Substances of abuse may precipitate the onset of a myriad of transient or permanent movement disorders, which vary depending on the individual agent.
2. To understand the relationship between two movement disorders, myoclonus-dystonia and essential tremor, and alcohol use and abuse. Although alcohol may provide temporary symptomatic improvement in essential tremor and myoclonus-dystonia, it may be also associated with abuse in patients who self-medicate for these disorders.
3. To describe the emerging literature on dopaminergic medication abuse in Parkinson's disease (PD) patients. A proportion of PD patients meet criteria for dependence and addiction to either levodopa or apomorphine; they exhibit an array of behavioral symptoms referred to as the dopamine dysregulation syndrome.

FUTURE RESEARCH QUESTIONS

The exact neuropathologic mechanisms through which drugs of abuse exert an effect on movement disorders is incompletely understood, and neuroimaging, biochemical and pharmacologic studies will lend further insight into these mechanisms. Further, the relationship between the genetic predisposition to certain movement disorders and alcohol abuse is still not well elucidated; additional genotype-phenotype correlation may assist in dissecting this issue. Finally, the further development and validation of screening tools for compulsive disorders in Parkinson's disease (including the dopamine dysregulation syndrome) will lead to improved recognition of this entity. These tools will also facilitate the standardization needed in the design of clinical trials.

Table 1

Movement disorders associated with substances of abuse

Drug	Associated movement disorders	Presumed pathophysiology
Cocaine	Tics, dystonia, chorea	Locomotor sensitization resulting from decrease in inhibitory modulation of excitatory transmission from the medial prefrontal cortex to the ventral tegmental area and nucleus accumbens
Amphetamines	Tremor, ataxia (with acute intoxication)	Binding and reversal of DAT function, causing reuptake inhibition and release of dopamine at the mesocorticolimbic dopaminergic nerve terminals
MDMA	Tremor, serotonin syndrome	Release and inhibition of reuptake of serotonin, dopamine and norepinephrine
Methcathinone	Parkinsonism (as part of the syndrome of manganese poisoning)	Affinity for the monoaminergic transporters similar to that of methamphetamine
Opioids	Myoclonus, hiccups, parkinsonism, chorea	Elevation of forebrain dopamine levels by blocking GABA interneurons near the VTA, leading to activation of the mesocorticolimbic dopaminergic neurons
Alcohol	Tremor, worsening of tardive dyskinesia	Increased GABAergic transmission