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Review Article

Phenytoin-associated movement disorder: A literature review

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Abstract

Phenytoin (PHT) was first synthesized as a barbiturate derivative and was approved in 1953 by the Food and Drug Administration. This work aimed to review the pathophysiology, epidemiology, clinical presentation, and treatment of PHT-associated movement disorders (MDs). Studies were searched in relevant databases (ScienceDirect, Google Scholar, Excerpta Medica, Latin American and Caribbean Health Sciences Literature, Medline, and Scientific Electronic Library Online) and were selected by two reviewers irrespective of language between 1963 and 2021. Papers of PHT-induced ataxia alone or tremor were excluded. In total, 127 reports with 219 individuals who developed MDs associated with PHT were encountered. MDs found: 126 dyskinesias, 49 myoclonus, 19 dystonia, 14 parkinsonism, 6 tics, 3 stuttering, and 2 restless legs syndrome. The mean age was 35 years (standard deviation [SD]: 23.5) and the predominant sex was male (53.4%). The mean PHT dose when the MD took place was 370.4 mg (SD: 117.5). A serum PHT concentration was reported in 103 cases, ranging from 4 to 110 μg/mL (median: 27.7 μg/mL). No significant relationship was found between PHT dose and age or PHT level. The mean onset time of PHT-associated MD was 23.4 months (SD: 4.4). The mean recovery time after MD management was 3.7 weeks (SD: 1.1). Regarding management, the most common form was PHT withdrawal in 90.4%. 86.3% of the individuals recovered fully. PHT-induced MD was extensively reported in the literature. Only general terms were used in the majority of the reports. The mechanisms underlying the adverse events caused by PHT probably depend on the presence of predisposing factors.

Keywords: *Dilantin, Drug-induced, Movement Disorder, Phenytoin, Review*

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Introduction

Phenytoin (PHT), also known as 5,5-diphenylhydantoin, was first synthesized as a barbiturate derivative in 1908 by German chemist Heinrich Biltz. Two decades later, animal model studies showed that PHT had the property of electroshock convulsion suppression [1]. In 1938, Tracy Putnam and H. Houston Merritt found out that PHT was useful as an antiepileptic. In addition, it had the advantage of almost no sedative effects when compared to phenobarbital, which was the mainstay of treatment at the time [2]. Subsequently, PHT was tested in a large number of patients in clinical trials. In the early 1950s, Food and Drug Administration approved PHT under the brand name Dilantin. It is noteworthy that no patent on the use of PHT in epilepsy was filed by the inventors. In the first reports, the PHT's dose varied between 200 and 600 mg/day, which was rapidly associated with a large number of severe side effects [3]. Ten years later, many clinical reports about PHT demonstrated the neurological spectrum of adverse events including abnormal movements and pseudodementia [4].

The clinical indications of PHT are generalized tonic–clonic seizure, focal seizure, as well as prophylaxis, or management of seizures occurring during or following neurosurgery [5]. Two common off-label uses of this drug are the management of trigeminal neuralgia and psychiatric disorders such as mania in bipolar disorder [6]. PHT is believed to block voltage-dependent sodium channels causing an enhancement of steady-state inactivation and reduction of the sodium-dependent action potential amplitude [7]. It is believed that the main site of PHT's action is the motor cortex and that this drug mitigates the spread of seizure activity.

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Interestingly, the structure of PHT has two phenyl rings that seem to be responsible for its activity as a nonsedative anticonvulsant [8].

Common side effects related to PHT are fatigue, allergic reactions in the form of rashes, gastrointestinal symptoms, hirsutism, coarsening of the facies, and gingival hyperplasia. There is a black box warning about the cardiovascular risk associated with rapid infusion rates of this antiepileptic drug [9]. In this context, abnormal involuntary movements related to PHT such as ataxia and tremor are frequently seen in clinical practice. They are mainly associated with cerebellar atrophy and dysfunction related to PHT [10]. In the past, the diagnosis of adverse drug reactions secondary to PHT only occurred with intoxication due to the unavailable measure of PHT serum concentrations. Furthermore, the fact that PHT follows zero-order kinetics at therapeutic concentrations was not understood initially, which contributed to many patients experiencing serious adverse events even with conventional or previously tolerated dosages [11].

Movement disorders (MDs) secondary to PHT are not always easily diagnosed and treated. In addition, the individuals reported with PHT use had a coexisting neurological disease, which could alter the manifestations of toxicity or impair their recognition [5]. Thus, this work aims to review the pathophysiology, epidemiology, clinical presentation, and treatment of PHT-associated movement disorders (MDs).

Methods

Database research strategy

We performed a search on six research directories to find all the existing reports on MDs related to PHT published electronically from 1963 until 2021. Latin American and Caribbean Health Sciences Literature, Excerpta Medica, ScienceDirect, Google Scholar, Scientific Electronic Library Online, and Medline were inspected. Keywords researched were "movement disorders, restless legs syndrome, bradykinesia, tics, chorea, dystonia, myoclonus, akathisia, tremor, restlessness, stuttering, ataxia, parkinsonism, ballism, hyperkinetic, dyskinesia, hypokinetic." To these words was added the term "phenytoin" [Supplementary Table 1].

Selection criteria

To ensure a thorough review, original articles, case reports, letters to the editor, case series, poster presentations, and bulletins published from 1963 to 2021, without language exclusion criteria, were included. Google Translate services were used when non-English literature was beyond the authors' proficiency (Portuguese, English, Spanish, French, and German) or when the abstract in English was not able to provide enough information [12].

Reports of patients who developed ataxia alone or tremor following PHT use were excluded since details on the neurological examination and clarity in symptom description were lacking. In addition, both disorders were mainly reported in clinical trials that used questionnaires to assess adverse effects, and this could have led to a higher incidence in their reported diagnoses [13].

Abstracts and titles found at the beginning of the study were analyzed independently by each author and then discussed in cases of inconsistencies. Studies were excluded when it was evident that the etiology of the MD was known, or PHT was not related to the motor symptoms. Naranjo algorithm was implemented to analyze the factors contributing to the MD. Whenever the authors were unable to access an article due to unavailability in the electronic form or unresponsiveness after a formal e-mail request of the paper, the studies were excluded [14].

Data extraction

We found a total of 3817 articles about PHT; 3216 articles were inadequate, and 474 had exclusion criteria [Figure 1]. When available, we extracted country, author, the number of patients affected, department, PHT indication including off-label uses, year of publication, time from first PHT dose until MD onset, time from PHT withdrawal to recovery, neuroimaging features, patient's status at follow-up, and medical history and treatment. Two independent authors extracted the data, double-checked to eliminate errors, and structured it accordingly when the MD was a side effect of the PHT use.

Statistical analysis

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

Definitions

The scientific work by Jankovic and Tolosa was the basis for the use of clinical and pathological definitions in our study, as well as for the identification of MDs such as dystonia (DTN), ballism, akathisia, dyskinesia (DKN), tics,

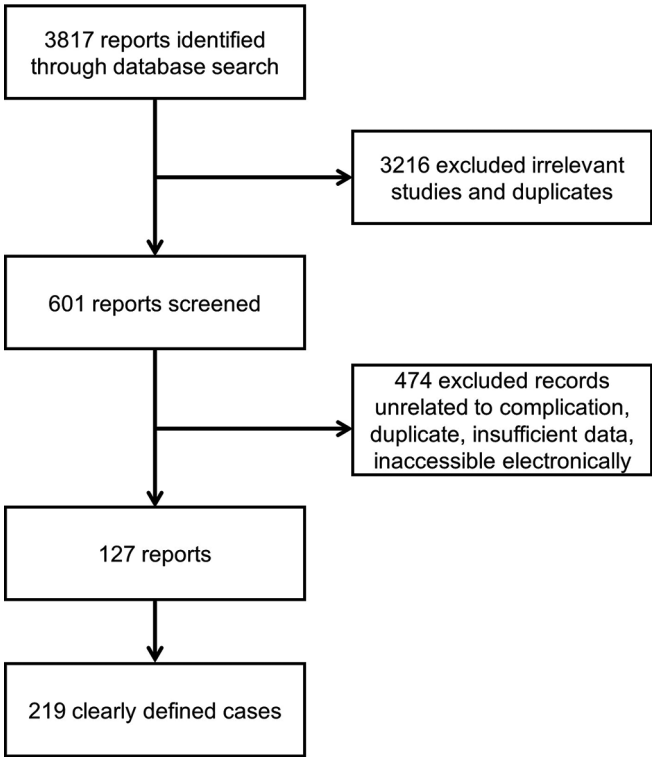

Figure 1: Flowchart of the screening process

stuttering, restless legs syndrome (RLS), myoclonus (MCL), chorea, tremor, ataxia, and parkinsonism (PKN) [15]. To determine the likelihood that an adverse drug reaction was directly correlated to a drug and not a result of other confounding factors, the Naranjo algorithm was used [14].

Results

We found 127 reports with 219 cases of individuals who developed PHT-related MDs from 26 countries were reported [Supplementary Table 2]. The origin of the individuals reported was North American in 108, European in 57, Asian in 41, South American in 9, African in 3, and Australian in 1. The MDs associated with PHT found were 126 DKN, 49 MCL, 19 DTN, 14 PKN, 6 tics, 3 stuttering, and 2 RLS. Figure 2 shows the articles published about MDs and PHT over time.

The general data about PHT-associated MD are provided in Table 1. Here, we provide an overview of the data we encountered on established PHT-MD cases.

The mean and median age was 35 (SD: 23.56) and 28 years (age range: 1 month to 88 years). The predominant sex was male in 53.4% (78/146) of the cases. The most common indication of PHT was epilepsy. Other indications for PHT were eclampsia [16] and thalamic pain [17]. The clinical comorbidities reported besides PHT indication included traumatic brain injury [18], intellectual disability [19], encephalopathy [20], diabetes mellitus, hypertension, psychiatric disorders, atrial fibrillation, congestive heart failure [21], meningioma, CHARGE syndrome [22], and Lennox–Gastaut syndrome [23].

The mean and median dose of PHT associated with the occurrence of MD was 370.4 (SD: 117.5) and 300 mg (PHT dose range: 70–900 mg). No significant relationship was found between PHT dose and age (r: −0.05) [Figure 3]. A serum PHT concentration was reported in 103 cases, ranging from 4 to 110 μg/mL (median 27.7 μg/mL; mean: 31.7 μg/mL). In addition, no significant relationship was found between PHT dose and serum concentration (r: 0.21) [Figure 3]. Figure 4 shows box and whisker plots of the distributions of MDs and PHT dose and serum PHT concentration.

The mean and median time of onset of PHT-associated MD was 23.4 months (SD: 4.46) and 2 weeks (MD onset range: 2 h to 40 years). The mean and median recovery time after MD treatment was 3.7 (SD: 1.15) and 1 week (MD recovery range: 1 day to 6 months). Figure 5 shows a contrast between the percentage of MD patients since the PHT onset and the percentage of MD patients who recovered after drug withdrawal. Remission was reached within 6 months after drug withdrawal in almost all of the cases (92%).

The most widely chosen treatment was PHT discontinuation in 90.4% of the cases. Other therapeutic measures found were the continuation of the offending drug [24], dose

Table 1: Resume of phenytoin-associated movement disorder

MD	DKN	DTN	MCL	PKN	RLS	Stutter	Tics	General data
Cases (%)	126 (57.5)	19 (8.6)	49 (22.3)	14 (6.3)	2 (0.9)	3 (1.3)	6 (2.7)	219 (100)
Continent (%)								
Africa	2 (1.5)	1 (5.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (1.3)
Australia	0 (0)	1 (5.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.4)
Asia	26 (20.6)	7 (36.8)	4 (8.1)	3 (21.4)	0 (0)	1 (33.3)	0 (0)	41 (18.7)
Europe	39 (30.9)	4 (21.0)	9 (18.3)	4 (28.5)	0 (0)	1 (33.3)	0 (0)	57 (26.0)
North America	52 (41.2)	6 (31.5)	36 (73.4)	6 (42.8)	2 (100)	1 (33.3)	5 (83.3)	108 (49.3)
South America	7 (5.55)	0 (0)	0 (0)	1 (7.1)	0 (0)	0 (0)	1 (16.6)	9 (4.1)
Sex (%)								
Female	51 (40.4)	3 (15.7)	9 (18.3)	3 (21.4)	1 (50)	0	1 (16.6)	68 (31.0)
Male	39 (30.9)	10 (52.6)	9 (18.3)	11 (78.5)	1 (50)	3 (100)	5 (83.3)	78 (35.6)
Unknown	36 (28.5)	6 (31.5)	31 (63.2)	0 (0)	0 (0)	0 (0)	0 (0)	73 (33.3)
Age (years)								
Rg	9 months-88 years	2.5 years-65 years	1 month-84 years	9 years-71 years	43 years	3 years-60 years	13 years-57 years	1 month-88 years (Md: 28 years)
Mn	30.1	24.5	70.7	51	43	35	28.6	35 (SD: 23.5)
PHT dose (Mn mg)	328.4	837.5	356.2	337.5	NA	250	200	370.4 (SD: 117.5; Rg: 70-900; Md: 300)
PHT level (μg/mL)	36.5	39.6	22.8	42.6	19	5.1	NA	31.7 (SD: 11.3; Rg: 4-110; Md: 27.7)
MD onset								
Range	1 day-40 years	2 h-8 weeks	1 day-1 month	7 day-20 years	NA	10 days	1 week	2 h-40 years (Md: 2 weeks)
Mean	27.7 months	8.5 days	2.3 week	5.1 years	NA	10 days	1 week	23.4 months (SD: 4.4)
MD recovery								
Range	1 day-14 months	1 day-2 months	2 days-6 months	2 week-6 months	NA	10 days	1 week	1 day-14 months (Md: 1 week)
Mean	1.1 months	13 days	3.2 weeks	2.8 months	NA	10 days	1 week	3.7 weeks (SD: 1.1)
Follow-up - Percentage CR (number of reports)	88.4 (61/69)	60 (3/5)	90 (9/10)	100 (5/5)	0 (0/1)	100 (2/2)	66.6 (2/3)	86.3 (82/95)

CR: Complete recovery, DKN: Dyskinesia, DTN: Dystonia, MCL: Myoclonus, MD: Movement disorder, Md: Median, Mn: Mean, NA: Not available, PKN: Parkinsonism, Rg: Range (minimum-maximum), RLS: Restless legs syndrome, SD: Standard deviation, PHT: Phenytoin

augmentation [25], dose decrease [26], or even the addition of drugs such as carbamazepine, oxcarbazepine, phenobarbital, and valproate. Some authors described PHT rechallenges, and they demonstrated the reoccurrence of the MD [27]. Only 33.3% of the reports described electrodiagnostic studies and neuroimaging findings. After management, 86.3% of the individuals had a full recovery.

Discussion

General

PHT is on the World Health Organization's List of Essential Medicines due to its effectiveness and safety profile [28]. In 2019, it was the 271st most commonly prescribed medication in the United States with more than one and half million prescriptions [29]. Furthermore, PHT is available in the majority of the countries and is on the market for more than 80 years [30]. These facts combined could explain the large number of adverse events observed with this anticonvulsant.

PHT intoxication was only reported many years later after its commercialization. Pharmacodynamic studies were performed solely after the occurrence of numerous publications on PHT intoxication [31]. The studies showed that rapid metabolizers of PHT have a greater capacity to increase the output of para-hydroxy diphenyl hydantoin in urine, which is the major metabolite of this drug [27,32]. Some individuals who developed severe neurological side effects were rechallenged more than three times with the inclusion of liver biopsy studies due to poor understanding of the PHT's nonlinear kinetics [27,33].

Based on the data available in our literature review, we can illustrate a hypothetic case. A middle-aged North American male with poorly controlled seizures searches his neurologist. PHT 100 mg three tablets a day is prescribed. Over 6 months, the patient notices involuntary, random muscle movements in the distal limbs associated with involuntary repetitive movements of the mouth and face. Neurological examination reveals hyperkinetic movements, and a diagnosis of choreoathetosis and orofacial DKN secondary to PHT is done. PHT is discontinued and carbamazepine, oxcarbazepine, or phenobarbital is started. In the follow-up after 1 month, the individual has a full recovery and can walk without assistance and the hyperkinetic movements ceased.

Most of the abnormal movements related to PHT are underreported in the literature [34]. Table 2 provides an overview of the incidence of MDs secondary to PHT [16,35-37]. Clinical trials and population-based studies that provided enough data were used in this analysis. It is worthy mentioning that the literature about PHT's profile of side effects is mainly focused on acute intoxication [38].

In the subsequent sections, we further discuss some of the PHT-MDs in greater detail for a better comprehension of these clinical presentations.

Dyskinesia – The first and most common movement disorder

In 1963, Hoaken and Kane probably described the first case of PHT-induced DKN in the *American Journal of Psychiatry* [39]. Some authors believe that the first study was done by Peters *et al*., but he only published his first work in 1966 in the *Diseases of the Nervous System Journal* [40]. Hoaken and Kane reported a young adult female showing writhing motor movements of the extremities associated with stiffening after a single dose of PHT [39].

PHT-induced DKN was the first and most commonly described abnormal movement. More than half of the

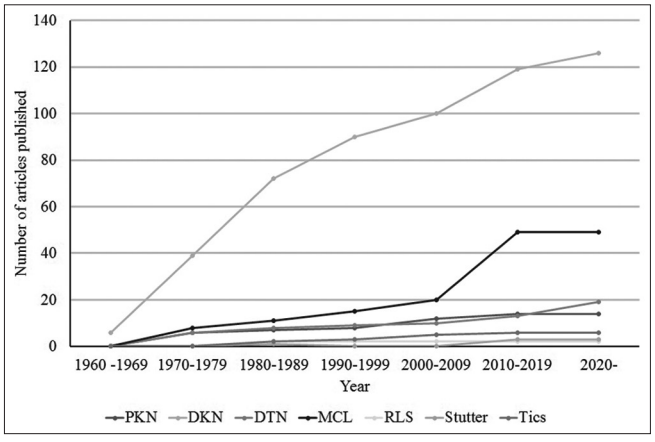

Figure 2: Line graph showing the cumulative number of publications regarding movement disorders and phenytoin throughout the decades. DKN: Dyskinesia, DTN: Dystonia, MCL: Myoclonus, No: Cumulative number, PKN: Parkinsonism, RLS: Restless legs syndrome

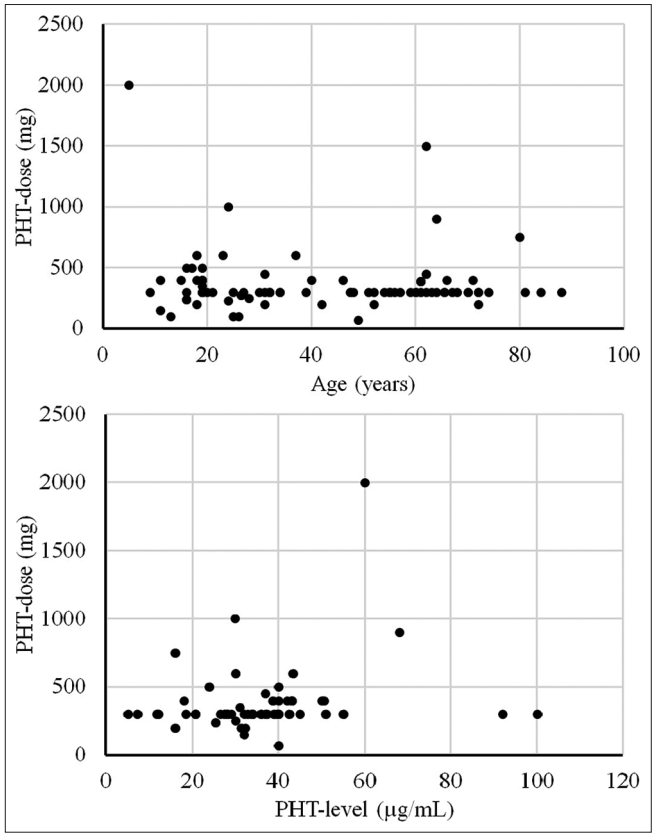

Figure 3: Scatterplot figures of PHT dose (mg) versus age (years) (above) and serum PHT concentration (µg/mL) and PHT dose (mg) (below). PHT: Phenytoin

individuals affected are female, which is a different finding when we compare with the other abnormal movements associated with PHT. Interestingly, this feature was already observed with other drugs such as carbamazepine-induced DKN [41]. High levels and doses of PHT were noted in DKN individuals. This could partly be explained by chronic higher doses of PHT and acute PHT intoxications [42].

The spectrum of abnormal movements related to PHT included chorea [43], choreoathetosis [44], ballism [45], athetosis [46], and orofacial DKN [47]. Cases of PHT worsening chorea in individuals with Huntington's disease were reported [48]. In addition, PHT was noted to aggravate orofacial DKN and tardive DKN symptoms by antipsychotic medications [47,49,50].

DKN secondary to PHT more commonly affects individuals with intellectual disabilities [51]. In this context, epileptic individuals with cognitive impairment or persistent neurologic signs are more likely to have DKN MDs. However, these neurological features could be explained by the long-term PHT intoxication, leading to permanent brain damage in susceptible subjects [52].

The majority of the individuals were in the use of PHT for months before the occurrence of this hyperkinetic movement. Drug cessation was the most common therapeutic measure, and the majority of the individuals had a full recovery within 1 month.

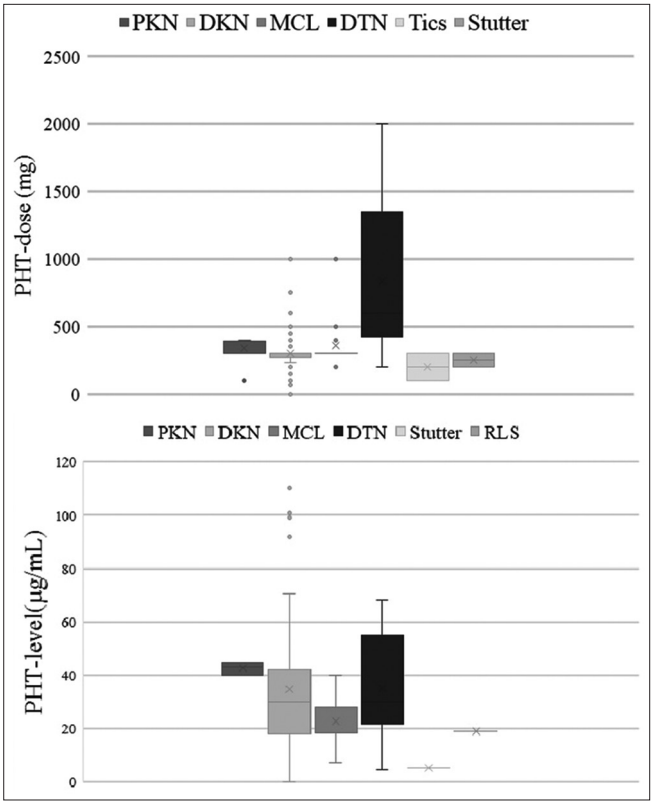

Figure 4: Box and whisker plots of the distributions of movement disorders and PHT dose (mg) (above) and serum PHT concentration (μg/mL) (below). The length of the box represents the IQR, the horizontal line in the box interior represents the median, the whiskers represent the 1.5 IQR of the 25th quartile or 1.5 IQR of the 75th quartile, and the dots represent outliers. In addition, the average values have been indicated by "x" in the boxplot. DKN: Dyskinesia, DTN: Dystonia, MCL: Myoclonus, PKN: Parkinsonism, RLS: Restless legs syndrome, PHT: Phenytoin, IQR: Interquartile range

Table 2: Incidence of some abnormal movements associated with phenytoin in the literature

MD	Incidence (%)	NR	*n*	Reference	Notes
Choreoathetosis	0.72	1	139	Cranford *et al*. (1978)	Intravenous PHT
ATX	62.96	17	27	Mellick *et al*. (1989)	Acute PHT intoxication
Horizontal nystagmus	37.04	10	27		
Wide-base/ staggering gait	22.22	6	27		
Vertical nystagmus	18.52	5	27		
Tremor	11.11	3	27		
Status dystonicus	11.11	3	27		
Intention tremor	7.41	2	27		
Tongue fasciculations	3.70	1	27		
Nystagmus	3.85	4	104	Ryan *et al*. (1989)	PHT use in preeclampsia
Choreoathetosis	2.88	3	104		
Incoordination	2.88	3	104		
Nystagmus	95.29	81	85	Murphy *et al*. (1991)	Acute PHT intoxication
ATX	88.24	75	85		
Asterixis	1.18	1	85		

ATX: Ataxia, MD: Movement disorder, *n*: Number of individuals in the study using PHT, NR: Number of reports with the movement disorder, PHT: Phenytoin

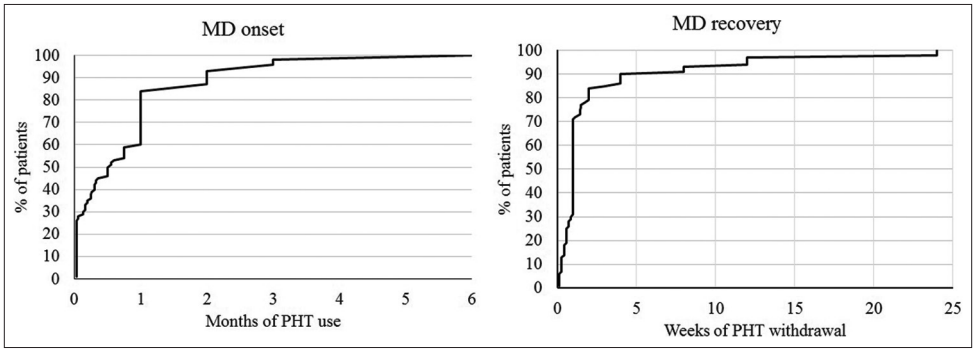

Figure 5: Comparison between the percentage of patients developing MDs since the beginning of the PHT and the percentage of patients recovering after PHT discontinuation. PHT: Phenytoin, MD: Movement disorder

Neuroleptics and PHT have a similar spectrum of movement disorders, but they probably do not have the same pathophysiological mechanism. Nausieda *et al*. reported three facts about PHT-induced MDs to support this hypothesis [53]. First, the majority of individuals affected by PHT-induced DKN have a structural or functional abnormality in the central nervous system [54]. Second, PHT-induced chorea is rare and seems unrelated to cumulative dosage or duration of therapy. Third, PHT-induced DKN is pleomorphic in presentation and lateralized, which differs from the symmetric and predominantly orofacial involvement of neuroleptics [55]. However, PHT administration can induce alterations in monoamine levels in specific brain regions [56]. Thus, a hypothesis for the mechanism of drug-induced DKN consists of the overactivation of the direct pathway as a result of an abnormal adaptation of the striatal organization [57].

Myoclonus - Asterixis

There is no sex preference for the development of this abnormal movement. However, the majority of the studies of PHT-induced MCL did not report the sex of the individual, which may impact the data distribution [58]. Interestingly, this MD most commonly affected the elderly population. It is worthy of mentioning that the subgroup PHT-induced MCL mean age was two times higher than that of the general data about PHT-associated MD.

Subcortical was the most common source followed by cortical origin [59]. 87% of the individuals presented with asterixis. This finding could be explained by the age group affected and chronic hepatic damage [60]. According to our review, the majority of the studies did not provide information about electrodiagnostic studies and laboratory examinations. Therefore, the relationship between MCL and PHT may be misleading due to the unavailability of a satisfactory methodological approach.

The pathophysiological mechanisms of MCL are unclear, but probably, serotonin and cerebellar dysfunction play an important role [61]. Long-term use of PHT is associated with atrophy of cerebellar vermis, loss of Purkinje cells, and cerebellar dysfunction [25]. In addition, Baets *et al*. showed loss of cerebellar granular cell and Purkinje layers in autopsy studies of patients with MCL [62]. This abnormal movement has been already related to deficiency and increase of serotonin [63,64]. In Wistar rats, it was demonstrated that PHT can increase 5-HT levels in the motor cortex but decrease in the cerebellum [56,65].

Dystonia – The toxic

The time from PHT start to DTN onset was the lowest among PHT-associated MDs. This is a characteristic feature of drug-induced DTN and was reported with antiepileptic drugs and tricyclic antidepressants [66]. An interesting fact is that DTN only occurred with the highest doses of PHT, which is a distinctive finding compared to the published literature. It is believed that DTN is the most sensitive movement disorder to occur as a side effect of medications. On a decrescent scale of mean PHT dose and MD occurrence, the following abnormal movements would be reported: DTN (837.5 mg), MCL (356.2 mg), PKN (337.5 mg), DKN (328.4 mg), stuttering (250 mg), and tics (200 mg), respectively.

DTN presented with focal [67], segmental [68], multifocal, and generalized [69]. Rajkumar *et al*. reported a case of status dystonicus following accidental massive ingestion of PHT [70]. The most common presentation was upper limb DTN. Four cases of tardive DTN were reported in a study with almost 100 individuals with drug-induced MDs [50]. PHT has been reported to induce DTN at normal and toxic serum levels but more commonly occurs at toxic levels. The mean PHT serum concentration reported in DTN individuals was 39.6 μg/mL.

The exact mechanism by which PHT induces DTN is poorly understood. In addition to its sodium channel blocking mechanism, PHT has an anticholinergic and a central serotonergic effect [71]. One of the possible explanations of the drug-induced DTN lies in GABAergic effects. We hypothesize that the increased concentrations of PHT could lead to a disruption of the direct and indirect pathways involving the thalamus. In this context, the under-activation of the indirect pathway could predominate, leading to an increase in the thalamocortical input and eventually resulting in DTN [72]. However, there are also recent studies suggesting that, at serum concentrations and in clinical practice, PHT does not appear to modify the GABAergic neurotransmission [73]. In this way, another explanation could be related to dopamine abnormal concentrations in the striatum, resulting in MDs [56].

Parkinsonism – Full recovery

78.5% of the individuals with PHT-induced PKN were males. The PHT serum concentration was the highest among other MDs associated with PHT. In addition, the time from the PHT prescription to the MD onset was the longest. Hence, PKN could occur due to long-term use of PHT, leading to a disturbance in the direct and indirect pathways of the basal ganglia [74].

Shin and Youn. reported an interesting case of a neuroleptic malignant syndrome (NMS) induced by PHT, in which the patient had akinetic-rigid PKN for months [75]. This sequence of MDs may reveal the clinical course of PHT intoxication. NMS spectrum-related symptoms can be categorized as stages I–V. It is noteworthy that antipsychotic-induced PKN is considered stage I of NMS spectrum-related symptoms [76].

At supratherapeutic concentration, PHT has been known to cause inhibition of calcium influx and interaction with neurotransmitters, including acetylcholine and dopamine [77,78]. PHT-induced PKN results from its interaction with the central dopaminergic system, although the exact mechanism is yet to be elucidated [79]. Experimental studies theorize that PHT may affect dopamine metabolism and dopaminergic synapses [48].

The management was PHT withdrawal in the majority of the cases. However, dose adjustment was also attempted with good outcomes. In the follow-up, all the PKN individuals had a full recovery within 6 months.

Tics – Phonic and motors

PHT was reported to cause or exacerbate tics and Tourette syndrome [80]. The individuals with tics secondary to PHT presented with phonic and motor tics including excessive eye blinking [81] and oral intermittent movements [82]. For example, the tics presented were grunting, throat-clearing, sniffing, tongue-clacking, habitual scratching of their nose, fidgeting, shoulder-shrugging, and echolalia [83]. Approximately, half of the PHT-induced tics patients had intellectual disabilities. This finding was also observed with DKN related to PHT [51].

Zadikoff *et al*. assessed the occurrence of MDs with anticonvulsants in 201 epileptic individuals [81]. They observed that tics were usually related to PHT, but valproate and carbamazepine were more commonly associated with tremors.

The management was the discontinuation of PHT. One report suggested the maintenance of the offending drug and the individual had a full recovery, but temporal characterization from the management until resolution of the MD was not specified [84].

Restless legs syndrome and stuttering

RLS, stuttering, and tics secondary to PHT were rarely reported in the literature. To be more specific, these three disorders together accounted for 4.9% of the MDs associated with PHT. On the other hand, DKN, DTN, and MCL represent almost 90% of the abnormal involuntary movements.

Drake *et al.* reported two epileptic individuals who developed RLS symptoms after taking PHT [83]. The management was the PHT discontinuation. Both patients had improvement in their symptoms, but they remained with occasional discomfort and restless sleep. One of the individuals had RLS symptoms with a combination of antiepileptics. The other developed RLS with PHT monotherapy. There are two possible hypotheses to explain drug-induced RLS, which are prolonged use of dopamine antagonists and increased concentrations of serotonin in the brainstem [85]. The serotonin pathway is probably the main mechanism responsible for the development of RLS by PHT and was already hypothesized to occur with some atypical antidepressants such as mirtazapine [86].

Stuttering associated with PHT was one of the most well-described abnormal movements. McClean *et al.* provided an extensive speech analysis with dysfluency graphs and fine motor control assessment [87]. In addition, the motor performance of speech and nonspeech muscle systems was evaluated during changes in anticonvulsant medications. Sudo *et al.* reported a probable case of PHT-induced stuttering [88]. The authors explain that due to the standard therapeutic range of PHT and dose maintenance, the patient's symptoms were unlikely a side effect of PHT. However, other MDs secondary to PHT were already reported with normal PHT serum concentration [89]. Moreover, some authors reported improvement of symptoms with the maintenance of the PHT dose [90].

Conclusion

In sum, the MDs associated with PHT are, in order of frequency, DKN, MCL, DTN, PKN, tics, stuttering, and RLS. The abnormal movements were poorly reported in the majority of the studies and lacked detailing of the follow-up. Moreover, frequently, only general terms were used to describe abnormal movements. Future studies need to further describe the clinical picture and the outcomes of each MD to improve the management of patients affected by these conditions. The mechanisms underlying the adverse events caused by PHT probably depend on the presence of predisposing factors such as epilepsy type and structural brain changes, although MDs have been reported in patients without any preexisting brain disorders.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Material

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

Category	Search terms	Results
Parkinsonism	(“phenytoin”[MeSH Terms] OR “phenytoin”[All Fields] OR “phenytoine”[All Fields] OR “phenytoin s”[All Fields] OR “phenytoins”[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])	51
Tics	(“phenytoin”[MeSH Terms] OR “phenytoin”[All Fields] OR “phenytoine”[All Fields] OR “phenytoin s”[All Fields] OR “phenytoins”[All Fields]) AND (“tics”[MeSH Terms] OR “tics”[All Fields])	4
Dyskinesia	(“phenytoin”[MeSH Terms] OR “phenytoin”[All Fields] OR “phenytoine”[All Fields] OR “phenytoin s”[All Fields] OR “phenytoins”[All Fields]) AND (“dyskinesiae”[All Fields] OR “dyskinesias”[MeSH Terms] OR “dyskinesias”[All Fields] OR “dyskinesia”[All Fields])	410
Dystonia	(“phenytoin”[MeSH Terms] OR “phenytoin”[All Fields] OR “phenytoine”[All Fields] OR “phenytoin s”[All Fields] OR “phenytoins”[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])	45
Stuttering	(“phenytoin”[MeSH Terms] OR “phenytoin”[All Fields] OR “phenytoine”[All Fields] OR “phenytoin s”[All Fields] OR “phenytoins”[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])	8
Myoclonus	(“phenytoin”[MeSH Terms] OR “phenytoin”[All Fields] OR “phenytoine”[All Fields] OR “phenytoin s”[All Fields] OR “phenytoins”[All Fields]) AND (“myoclonus”[MeSH Terms] OR “myoclonus”[All Fields])	120
Restless legs syndrome	(“phenytoin”[MeSH Terms] OR “phenytoin”[All Fields] OR “phenytoine”[All Fields] OR “phenytoin s”[All Fields] OR “phenytoins”[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])	5
Akathisia	(“phenytoin”[MeSH Terms] OR “phenytoin”[All Fields] OR “phenytoine”[All Fields] OR “phenytoin s”[All Fields] OR “phenytoins”[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])	12
Tremor	(“phenytoin”[MeSH Terms] OR “phenytoin”[All Fields] OR “phenytoine”[All Fields] OR “phenytoin s”[All Fields] OR “phenytoins”[All Fields]) AND (“tremor”[MeSH Terms] OR “tremor”[All Fields] OR “tremors”[All Fields] OR “tremoring”[All Fields] OR “tremorous”[All Fields])	95
Chorea	(“phenytoin”[MeSH Terms] OR “phenytoin”[All Fields] OR “phenytoine”[All Fields] OR “phenytoin s”[All Fields] OR “phenytoins”[All Fields]) AND (“chorea”[MeSH Terms] OR “chorea”[All Fields] OR “choreas”[All Fields])	83
Restlessness	(“phenytoin”[MeSH Terms] OR “phenytoin”[All Fields] OR “phenytoine”[All Fields] OR “phenytoin s”[All Fields] OR “phenytoins”[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])	24
Ataxia	(“phenytoin”[MeSH Terms] OR “phenytoin”[All Fields] OR “phenytoine”[All Fields] OR “phenytoin s”[All Fields] OR “phenytoins”[All Fields]) AND (“ataxia”[MeSH Terms] OR “ataxia”[All Fields] OR “ataxias”[All Fields])	290
Ballism	(“phenytoin”[MeSH Terms] OR “phenytoin”[All Fields] OR “phenytoine”[All Fields] OR “phenytoin s”[All Fields] OR “phenytoins”[All Fields]) AND (“dyskinesias”[MeSH Terms] OR “dyskinesias”[All Fields] OR “ballism”[All Fields])	397
Hyperkinetic	(“phenytoin”[MeSH Terms] OR “phenytoin”[All Fields] OR “phenytoine”[All Fields] OR “phenytoin s”[All Fields] OR “phenytoins”[All Fields]) AND (“hyperkinetic”[All Fields] OR “hyperkinetics”[All Fields])	9
Hypokinetic	(“phenytoin”[MeSH Terms] OR “phenytoin”[All Fields] OR “phenytoine”[All Fields] OR “phenytoin s”[All Fields] OR “phenytoins”[All Fields]) AND (“hypokinesia”[MeSH Terms] OR “hypokinesia”[All Fields] OR “hypokinetic”[All Fields])	1
Bradykinesia	(“phenytoin”[MeSH Terms] OR “phenytoin”[All Fields] OR “phenytoine”[All Fields] OR “phenytoin s”[All Fields] OR “phenytoins”[All Fields]) AND (“hypokinesia”[MeSH Terms] OR “hypokinesia”[All Fields] OR “bradykinesia”[All Fields])	1
Movement disorder	(“phenytoin”[MeSH Terms] OR “phenytoin”[All Fields] OR “phenytoine”[All Fields] OR “phenytoin s”[All Fields] OR “phenytoins”[All Fields]) AND (“movement disorders”[MeSH Terms] OR (“movement”[All Fields] AND “disorders”[All Fields]) OR “movement disorders”[All Fields] OR (“movement”[All Fields] AND “disorder”[All Fields]) OR “movement disorder”[All Fields])	262
Total		1817