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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,

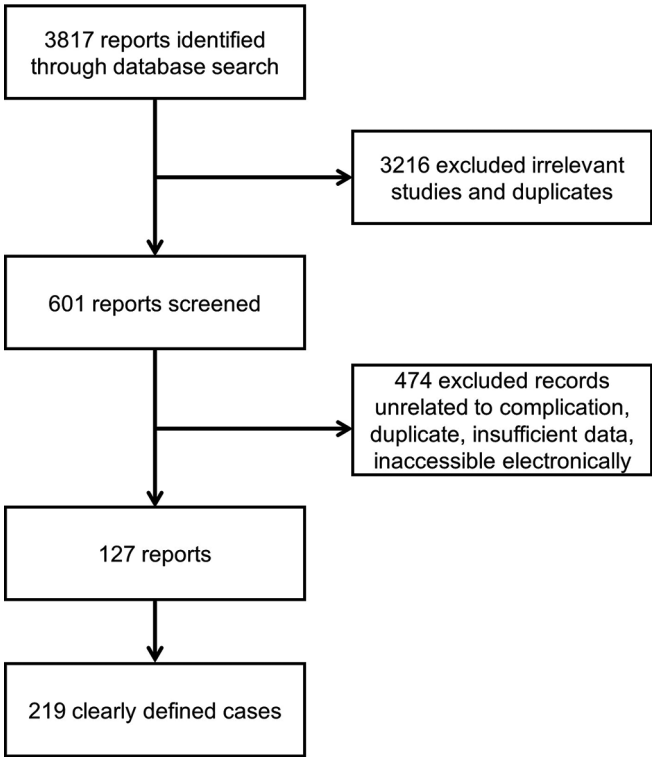

Figure 1: Flowchart of the screening process

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.

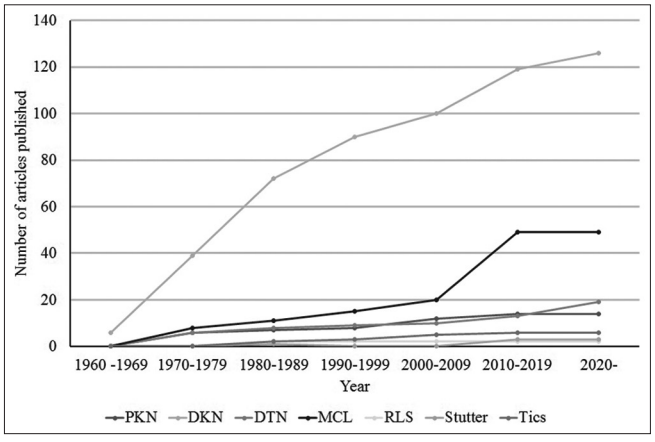

Figure 2: Line graph showing the cumulative number of publications regarding movement disorders and phenytoin throughout the decades. DKN: Dyskinesia, DTN: Dystonia, MCL: Myoclonus, No: Cumulative number, PKN: Parkinsonism, RLS: Restless legs syndrome

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

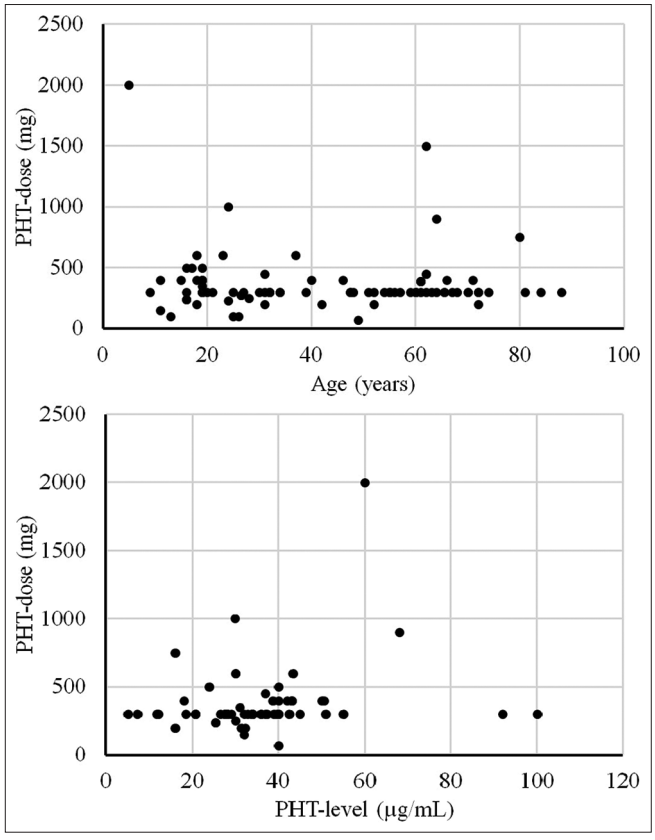

Figure 3: Scatterplot figures of PHT dose (mg) versus age (years) (above) and serum PHT concentration (µg/mL) and PHT dose (mg) (below). PHT: Phenytoin

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.

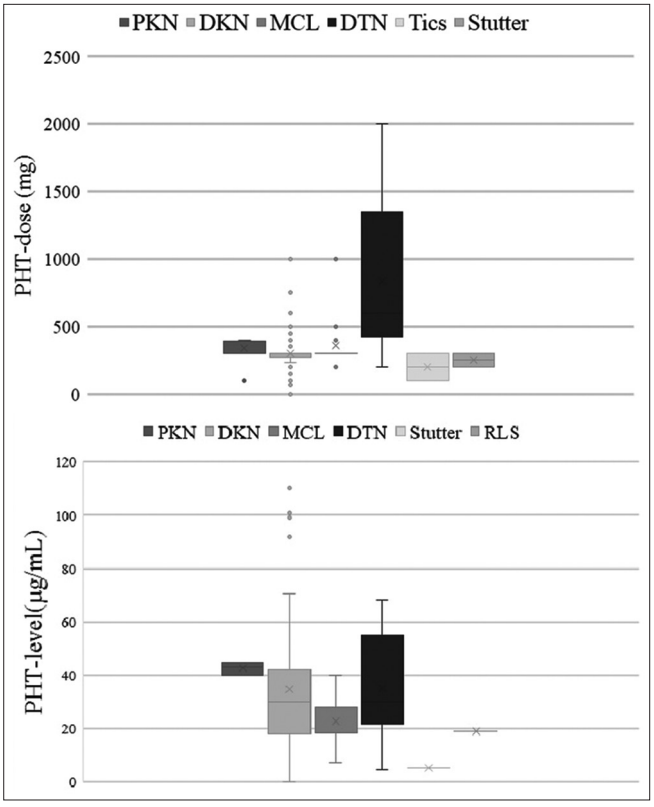

Figure 4: Box and whisker plots of the distributions of movement disorders and PHT dose (mg) (above) and serum PHT concentration (µg/mL) (below). The length of the box represents the IQR, the horizontal line in the box interior represents the median, the whiskers represent the 1.5 IQR of the 25th quartile 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

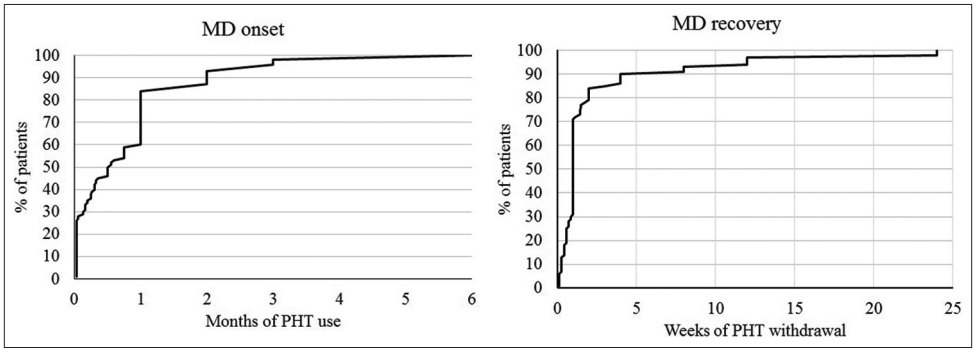

Figure 5: Comparison between the percentage of patients developing MDs since the beginning of the PHT and the percentage of patients recovering after PHT discontinuation. PHT: Phenytoin, MD: Movement disorder

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

Supplementary Table 2: Clinical reports of PHT-associated MD

Author	Reference	Country	Year	Number of patients reported	Type	Age (y)	Sex	Comorbidities besides PHT-indication	PHT-indication
Parkinsonism (PKN)									
Prensky *et al*	Prensky AL, DeVivo DC, Palkes H. Severe bradykinesia as a manifestation of toxicity to antiepileptic medications. J Pediatr. 1971 Apr;78(4):700-4. DOI: 10.1016/s0022-3476(71)80481-x. PMID: 5547831.	USA	1971	1	PKN	9	M	-	Epilepsy
Mendez *et al*	Mendez JS, Cotzias GC, Mena I, Papavasiliou PS. Diphenylhydantoin. Blocking of levodopa effects. Arch Neurol. 1975 Jan;32(1):44-6. DOI: 10.1001/archneur.1975.00490430066011. PMID: 123156.	USA	1975	5	PKN	61 (mean)	3M + 2F	-	Epilepsy
Goñi *et al*	Goñi M, Jimenez M, Feijoo M. Parkinsonism induced by phenytoin. Clin Neuropharmacol. 1985;8(4):383-4. DOI: 10.1097/00002826-198512000-00012. PMID: 4075309.	Spain	1985	1	PKN	68	M	Cranial injury	Epilepsy
Benvenuti	Benvenuti F, Bandinelli S, Mencarelli MA, Lunardelli ML, Campostrini R, Zaccara G, Pantaleo T. Alterations of ballistic movements in epileptic patients with phenytoin intoxication. Epilepsia. 1992 Mar-Apr;33(2):376-88. DOI: 10.1111/j.1528-1157.1992.tb02331.x. PMID: 1547770.	Italy	1992	1	PKN	40	F	-	Epilepsy
Türkdogan *et al*	Türkdogan D, Onat F, Türe U, Pamir N. Phenytoin toxicity with mandibular tremor secondary to intravenous administration. Int J Clin Pharmacol Ther. 2002 Jan;40(1):18-9. DOI: 10.5414/cpp40018. PMID: 11837377.	Turkey	2002	1	PKN - Possible	52	M	-	Epilepsy
Ertan *et al*	Ertan S, Ulu MO, Hanimoglu H, Tanriverdi T, Kafadar AM, Acar ZU, Kiziltan G. Phenytoin-induced parkinsonism. Singapore Med J. 2006 Nov;47(11):981-3. PMID: 17075669.	Turkey	2006	1	PKN - PKN, Ataxia	30	M	Traumatic brain injury	Epilepsy
Kim *et al*	Kim SH, Shin DJ. Parkinsonism Caused by Phenytoin Intoxication-A Case Report. Journal of Korean Epilepsy Society. 2009;13:31-4.	Korea	2009	1	PKN	71	M	-	Epilepsy
Ponte *et al*	Ponte M, Wachs A, Noel A. . Drug induced–Parkinsonism in hospitalized patients. Mov Disord 2009;24:66.	Argentina	2009	1	PKN	-	M	-	-
Shin *et al*	Shin HW, Youn YC. Neuroleptic malignant syndrome induced by phenytoin in a patient with drug-induced Parkinsonism. Neurol Sci. 2014 Oct;35(10):1641-3. DOI: 10.1007/s10072-014-1826-1. Epub 2014 May 29. PMID: 24870221.	Korea	2014	1	PKN	62	M	-	Epilepsy
Shaik *et al*	Shaik Kareemulla CT, Kavyasree AV, Prashanth M. PHENYTOIN INDUCED PARKINSONISM: A RARE CASE REPORT. European Journal of Biomedical. 2019;6(1):615-7.	India	2019	1	PKN	26	M	-	Epilepsy
Dyskinesia (DKN)									
Hoaken *et al*	Hoaken PC, Kane FJ. Unusual brain syndrome seen with diphenylhydantoin and pentobarbital. Am J Psychiatry 1963;120:282-3.	USA	1963	1	DKN - Chorea distal, DTN axial	25	F	None	Epilepsy

Contd...

Supplementary Table 2: Contd...

Author	Reference	Country	Year	Number of patients reported	Type	Age (y)	Sex	Comorbidities besides PHT-indication	PHT-indication
Peters *et al*	Peters HA, Eichman PL, Price JM, Kozelka FL, Reese HH. Abnormal copper and tryptophan metabolism and chelation therapy in anticonvulsant drug intolerance. Dis Nerv Syst 1966;27:97-107.	Germany	1966	1	DKN - Choreoathetosis	-	-	-	-
Reimer *et al*	Reimer F, Christiani K. Motorische Reizerscheinungen nach Diphenylhydantoinintoxikation. Nervenarrz 1967;38:509-615.	Germany	1967	2	DKN - Ballism, athetosis	23	M	-	Epilepsy
					DKN - Rhythmic movements	22	M	-	Epilepsy
Diehl *et al*	Diehl L. Nil nocere! Unusual hyperkinetic syndromes following diphenylhydantoin administration. Munchen Med Wochenschr 1969;3:1679-1681.	Germany	1969	1	DKN - Choreoathetosis	-	-	-	Epilepsy
Logan *et al*	Logan WJ, Freeman JM. Pseudodegenerative disease due to diphenylhydantoin intoxication. Arch Neurol 1969;21:631-7.	USA	1969	1	DKN - Choreoathetosis	19	M	Mental retardation	Epilepsy
Gerber *et al*	Gerber N, Lynn R, Oates J. Acute intoxication with 5,5-diphenylhydantoin (Dilantin) associated with impairment of biotransformation. Plasma levels and urinary metabolites; and studies in healthy volunteers. Ann Intern Med. 1972 Nov;77(5):765-71. DOI: 10.7326/0003-4819-77-5-765. PMID: 4628215.	USA	1972	1	DKN - Choreoathetosis	34	F	None	Epilepsy
Bellman *et al*	Bellman MH, Haas L. Letter: Toxic reaction to phenytoin. Br Med J. 1974 Jul 27;3(5925):256-7. DOI: 10.1136/bmj.3.5925.256-a. PMID: 4846140; PMCID: PMC1612009.	UK	1974	1	DKN - Choreoathetosis	11	F	Mental retardation	Epilepsy
Jan *et al*	Jan JE, Kliman MR. Extrapyramidal disturbance and vascular changes during diphenylhydantoin intoxication. Can Med Assoc J. 1974 Oct 5;111(7):636, 641. PMID: 4413402; PMCID: PMC1947857.	Canada	1974	1	DKN - Choreoathetosis	10 months	F	-	Epilepsy
Kooiker *et al*	Kooiker JC, Sumi SM. Movement disorder as a manifestation of diphenylhydantoin intoxication. Neurology. 1974 Jan;24(1):68-71. DOI: 10.1212/wnl.24.1.68. PMID: 4855667.	USA	1974	2	DKN - Choreoathetosis	-	-	-	-
					DKN - Orofacial DKN	-	-	-	-
Mclellan *et al*	McLellan DL, Swash M. Choreo-athetosis and encephalopathy induced by phenytoin. Br Med J. 1974 Apr 27;2(5912):204-5. DOI: 10.1136/bmj.2.5912.204. PMID: 4151655; PMCID: PMC1610848.	UK	1974	2	DKN - Choreoathetosis	31	M	-	Epilepsy
					DKN - Choreoathetosis, DTN	15	M	-	Epilepsy
Rosenblum *et al*	Rosenblum E, Rodichok L, Hanson PA. Movement disorder as a manifestation of diphenylhydantoin toxicity. Pediatrics. 1974 Sep;54(3):364-6. PMID: 4414729.	USA	1974	1	DKN - Choreiform	-	-	-	-

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Supplementary Table 2: Contd...

Author	Reference	Country	Year	Number of patients reported	Type	Age (y)	Sex	Comorbidities besides PHT-indication	PHT-indication
Shuttleworth *et al*	Shuttleworth E, Wise G, Paulson G. Choreoathetosis and diphenylhydantoin intoxication. JAMA. 1974 Nov 25;230(8):1170-1. PMID: 4479423.	USA	1974	3	DKN - Choreoathetosis	18	M	Mental retardation	Epilepsy
					DKN - Choreoathetosis	39	F	-	Epilepsy
					DKN - Choreoathetosis	37	M	Mental retardation	Epilepsy
Ahmad *et al*	Ahmad S, Laidlaw J, Houghton GW, Richens A. Involuntary movements caused by phenytoin intoxication in epileptic patients. J Neurol Neurosurg Psychiatry. 1975 Mar;38(3):225-31. DOI: 10.1136/jnnp.38.3.225. PMID: 239101; PMCID: PMC491900.	UK	1975	4	DKN - Choreiform	19	M	-	Epilepsy
					DKN - Choreoathetosis	34	F	-	Epilepsy
					DKN - Athetosis	28	F	-	Epilepsy
					DKN - Choreoathetosis, PKN	61	F	Cognitive impairment	Epilepsy
Mendez *et al*	Mendez JS, Cotzias GC, Mena I, Papavasiliou PS. Diphenylhydantoin. Blocking of levodopa effects. Arch Neurol. 1975 Jan;32(1):44-6. DOI: 10.1001/archneur.1975.00490430066011. PMID: 123156.	USA	1975	2	DKN - Huntington chorea worsening	62 (mean)	2F	-	Epilepsy
Chalhub *et al*	Chalhub EG, DeVivo DC. Letter: Phenytoin-induced choreoathetosis. J Pediatr. 1976 Jul;89(1):153-4. DOI: 10.1016/s0022-3476(76)80956-0. PMID: 932884.	USA	1976	1	DKN - Choreoathetosis	3.5	M	-	Epilepsy
Chalhub *et al*	Chalhub EG, Devivo DC, Volpe JJ. Phenytoin-induced dystonia and choreoathetosis in two retarded epileptic children. Neurology. 1976 May;26(5):494-8. DOI: 10.1212/wnl.26.5.494. PMID: 944401.	USA	1976	1	DKN - Choreoathetosis	8	-	Encephalopathy	-
Zinsmeister *et al*	Zinsmeister S, Marks RE. Acute athetosis as a result of phenytoin toxicity in a child. Am J Dis Child. 1976 Jan;130(1):75-6. DOI: 10.1001/archpedi.1976.02120020077015. PMID: 1247004.	USA	1976	1	DKN - Choreoathetosis	3.6	M	-	Epilepsy
Buchanan *et al*	Buchanan N, Rosen E, Rabinowitz L. Athetosis and phenytoin toxicity. Am J Dis Child. 1977 Jan;131(1):105. DOI: 10.1001/archpedi.1977.02120140107020. PMID: 835515.	South Africa	1977	1	DKN - Athetosis	1.8	-	Mental retardation	Epilepsy
Lühdorf *et al*	Lühdorf K, Lund M. Phenytoin-induced hyperkinesia. Epilepsia. 1977 Sep;18(3):409-15. DOI: 10.1111/j.1528-1157.1977.tb04984.x. PMID: 891495.	Denmark	1977	3	DKN - Choreoathetosis	18	F	Mental retardation	Epilepsy
					DKN - Choreoathetosis	19	F	-	Epilepsy
					DKN - Choreoathetosis	19	F	-	Epilepsy
Rasmussen *et al*	Rasmussen S, Kristensen M. Choreoathetosis during phenytoin treatment. Acta Med Scand. 1977;201(3):239-41. DOI: 10.1111/j.0954-6820.1977.tb15691.x. PMID: 403743.	Denmark	1977	1	DKN - Choreoathetosis, orofacial DKN	66	F	Myocardial infarction	-

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Author	Reference	Country	Year	Number of patients reported	Type	Age (y)	Sex	Comorbidities besides PHT-indication	PHT-indication
Strandjord *et al*	Strandjord RE. Involuntary movements in patients with organic brain lesions treated with antiepileptic drugs. Antiepileptic drug monitoring. Pitman medical publishing: London, UK; 1977:298-303.	-	1977	1	DKN - Choreoathetosis	-	-	-	-
Cranford *et al*	Cranford RE, Leppik IE, Patrick B, Anderson CB, Kostick B. Intravenous phenytoin: clinical and pharmacokinetic aspects. Neurology. 1978 Sep;28(9 Pt 1):874-80. DOI: 10.1212/wnl.28.9.874. PMID: 567761.	USA	1978	1	DKN - Choreoathetosis	37	-	Chronic subdural hematoma	Epilepsy
DeVeaugh-Geiss *et al*	DeVeaugh-Geiss J. Aggravation of tardive dyskinesia by phenytoin. N Engl J Med. 1978 Feb 23;298(8):457-8. DOI: 10.1056/nejm197802232980817. PMID: 622127.	USA	1978	1	DKN - Aggravation of orofacial DKN	55	M	Psychiatric disorder	Epilepsy
Fanø *et al*	Fanø N. Koreoatetose og orofaciale dyskinesier ved fenytoinbehandling [Choreoathetosis and orofacial dyskinesia during phenytoin treatment]. Ugeskr Laeger. 1978 Nov 20;140(47):2929-31. Danish. PMID: 568838.	Denmark	1978	1	DKN - Choreoathetosis	-	-	-	-
Opida *et al*	Opida CL, Korthals JK, Somasundaram M. Bilateral ballismus in phenytoin intoxication. Ann Neurol. 1978 Feb;3(2):186. DOI: 10.1002/ana.410030219. PMID: 655669.	USA	1978	1	DKN - Ballism	28	M	Alcoholism	Epilepsy
Mauguiere *et al*	Mauguière F, Dalery J, de Villard R, Courjon J. Transient hyperkinesia after a single intravenous perfusion of diphenylhydantoin. Report of a case associated with nontoxic plasma levels of diphenylhydantoin. Eur Neurol. 1979;18(2):116-23. DOI: 10.1159/000115065. PMID: 456389.	France	1979	1	DKN - Choreoathetosis	17	M	-	Epilepsy
Nausieda *et al*	Nausieda PA, Koller WC, Weiner WJ, Klawans HL. Clinical and experimental studies of phenytoin-induced hyperkinesias. J Neural Transm. 1979;45(4):291-305. DOI: 10.1007/BF01247146. PMID: 490152.	USA	1979	2	DKN - Chorea, orofacial DKN	72	F	Sydenham's chorea, chorea gravidarum	Epilepsy
					DKN - Orofacial DKN	52	M	Diabetes Mellitus, congestive heart failure, hypertension, and atrial fibrillation	Epilepsy
Dravet *et al*	Dravet C, Dalla Bernardina B, Mesdjian E, Galland MC, Roger J. Dyskinésies paroxystiques au cours des traitements par la diphénylhydantoïne [Paroxysmal dyskinesia during treatment with diphenylhydantoin]. Rev Neurol (Paris). 1980;136(1):1-14. French. PMID: 7394437.	France	1980	10	DKN - Choreoathetosis, orofacial DKN	-	-	Encephalopathy, mental retardation	Epilepsy
Vincent *et al*	Vincent FM. Phenothiazine-induced phenytoin intoxication. Ann Intern Med. 1980 Jul;93(1):56-7. DOI: 10.7326/0003-4819-93-1-56. PMID: 7396317.	USA	1980	2	DKN - Tardive DKN	-	-	Meningioma	Epilepsy
Sandyk *et al*	Sandyk R. Choreo-athetosis induced by phenytoin in an epileptic child. A case report. S Afr Med J. 1981 Oct 17;60(16):627-8. PMID: 7292204.	South Africa	1981	1	DKN - Choreoathetosis	5	M	-	Epilepsy
Krishnamoorthy *et al*	Krishnamoorthy KS, Zalneraitis EL, Young RS, Bernad PG. Phenytoin-induced choreoathetosis in infancy: case reports and a review. Pediatrics. 1983 Dec;72(6):831-4. PMID: 6646926.	USA	1983	3	DKN - Choreoathetosis	2	-	-	Epilepsy

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Author	Reference	Country	Year	Number of patients reported	Type	Age (y)	Sex	Comorbidities besides PHT-indication	PHT-indication
Todt *et al*	Todt H, Vock K, Eysold R. Beitrag zur phenytoininduzierten paroxysmalen Choreoathetose [Phenytoin-induced paroxysmal choreoathetosis]. Padiatr Grenzgeb. 1984;23(6):467-70. German. PMID: 6442766.	Germany	1984	1	DKN - Choreoathetosis	-	-	-	-
Howrie *et al*	Howrie DL, Crumrine PK. Phenytoin-induced movement disorder associated with intravenous administration for status epilepticus. Clin Pediatr (Phila). 1985 Aug;24(8):467-9. DOI: 10.1177/000992288502400902. PMID: 4006358.	USA	1985	2	DKN - Choreoathetosis, orofacial DKN, DTN	8	F	Mild development delay	Epilepsy
					DKN - Choreoathetosis	1.6	M	Severe psychomotor delay	Epilepsy
Yoshida *et al*	Yoshida M, Yamada S, Ozaki Y, Nakanishi T. Phenytoin-induced orofacial dyskinesia. A case report. J Neurol. 1985;231(6):340-2. DOI: 10.1007/BF00313713. PMID: 2983034.	Japan	1985	1	DKN - Orofacial DKN	56	M	Glioblastoma multiforme	Epilepsy
Filloux *et al*	Filloux F, Thompson JA. Transient chorea induced by phenytoin. J Pediatr. 1987 Apr;110(4):639-41. DOI: 10.1016/s0022-3476(87)80570-x. Erratum in: J Pediatr 1987 Jun;110(6):1000. PMID: 3559817.	USA	1987	4	DKN - Choreoathetosis	1.45	3M + 1F	1 Mental retardation, 1 developmental delay	Epilepsy
Maiti *et al*	Maiti B, Saha P. Phenytoin intoxication with activated seizure and dyskinesia. J Assoc Physicians India. 1987 Aug;35(8):598-9. PMID: 3693316.	India	1987	1	DKN	-	-	-	-
Roullet *et al*	Roullet E, Koskas P, Mahieux F, Marteau R. Dyskinésies aigues récidivantes seules manifestations d'un surdosage en phénytoine [Recurrent acute dyskinesia as the sole manifestation of phenytoin poisoning]. Rev Neurol (Paris). 1987;143(12):836-8. French. PMID: 3438640.	France	1987	1	DKN	20	F	-	Epilepsy
Szczechowski *et al*	Szczechowski L, Rościszewska D. Wystepowanie ruchów plasawiczo-atetotycznych u chorego na padaczke w nastepstwie leczenia difenylhydantoina [Choreoathetotic movements in a patient with epilepsy after treatment with diphenylhydantoin]. Neurol Neurochir Pol. 1987 May-Jun;21(3):255-7. Polish. PMID: 3118226.	Poland	1987	1	DKN - Choreoathetosis	-	-	-	Epilepsy
Kurata *et al*	Kurata K, Kido H, Kobayashi K, Yamaguchi N. Long-lasting movement disorder induced by intravenous phenytoin administration for status epilepticus. A case report. Clin Neuropharmacol. 1988 Oct;11(5):467-71. DOI: 10.1097/00002826-198810000-00008. PMID: 3219679.	Japan	1988	1	DKN - Choreoathetosis, orofacial DKN, ballism, DTN	24	F	Meningoencephalitis	Seizures
Tomson *et al*	Tomson T. Choreoathetosis induced by ordinary phenytoin levels, explained by high free fraction?--A case report. Ther Drug Monit. 1988;10(2):239-41. DOI: 10.1097/00007691-198802000-00022. PMID: 3381246.	Sweden	1988	1	DKN - Choreoathetosis, ataxia, orofacial DKN	81	F		Seizures

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Author	Reference	Country	Year	Number of patients reported	Type	Age (y)	Sex	Comorbidities besides PHT-indication	PHT-indication
Mellick *et al*	Mellick LB, Morgan JA, Mellick GA. Presentations of acute phenytoin overdose. Am J Emerg Med. 1989 Jan;7(1):61-7. DOI: 10.1016/0735-6757(89)90088-0. PMID: 2643962.	USA	1989	1	DKN - Choreoathetosis, DTN	15	M	Schizophrenia and multiple suicide threats	-
Ryan *et al*	Ryan G, Lange IR, Naugler MA. Clinical experience with phenytoin prophylaxis in severe preeclampsia. Am J Obstet Gynecol. 1989 Nov;161(5):1297-304. DOI: 10.1016/0002-9378(89)90687-x. PMID: 2589455.	Canada	1989	3	DKN - Choreoathetosis	26 (mean)	F	Eclampsia, preeclampsia	Eclampsia, preeclampsia
Haider *et al*	Haider Y, Abbott RJ. Phenytoin-induced choreoathetosis. Postgrad Med J. 1990 Dec;66(782):1089. DOI: 10.1136/pgmj.66.782.1089. PMID: 2084667; PMCID: PMC2429770.	UK	1990	1	DKN - Choreoathetosis	54	F	Glioma, parathyroid adenoma	Epilepsy
Martínez Orgado *et al*	Martínez Orgado J, García Aparicio J, Cabanillas Vilaplana L, Sáez Pérez E. Coreoatetosis inducida por difenilhidantoina en un lactante con síndrome CHARGE [Choreoathetosis induced by diphenylhydantoin in and infant with CHARGE syndrome]. An Esp Pediatr. 1990 Oct;33(4):384-6. Spanish. PMID: 2278444.	Spain	1990	1	DKN - Choreoathetosis	-	M	CHARGE syndrome	Epilepsy
Martiñón Sánchez *et al*	Martiñón Sánchez F, Viso Lorenzo JA. Una observación pediátrica de coreoatetosis por difenilhidantoina [A case of childhood choreoathetosis induced by diphenylhydantoin]. An Esp Pediatr. 1990 Jun;32(6):554-5. Spanish. PMID: 2221636.	Spain	1990	1	DKN - Choreoathetosis	-	-	-	Epilepsy
Yamamoto *et al*	Yamamoto K, Noda S, Itou H, Umezaki H, Morimatsu M. [A case of involuntary movements probably produced by low doses of phenytoin intoxication]. Rinsho Shinkeigaku. 1990 May;30(5):571-3. Japanese. PMID: 2401119.	Japan	1990	1	DKN - Choreoathetosis, orofacial DKN	49	F	Hypothyroidism, migraine	Epilepsy
Murphy *et al*	Murphy JM, Motiwala R, Devinsky O. Phenytoin intoxication. South Med J. 1991 Oct;84(10):1199-204. DOI: 10.1097/00007611-199110000-00010. PMID: 1925719.	USA	1991	1	DKN - Orofacial DKN	43 (mean)	-	-	Intoxication
Heo *et al*	Heo JH, Lee MS, Kim JS. A Case of Orofacial Dyskinesia Induced by Diphenylhydantioin. Journal of the Korean Neurological Association. 1992;10:248-51.	Korea	1992	1	DKN - Orofacial DKN	-	-	-	Epilepsy
Harrison *et al*	Harrison MB, Lyons GR, Landow ER. Phenytoin and dyskinesias: a report of two cases and review of the literature. Mov Disord. 1993;8(1):19-27. DOI: 10.1002/mds.870080104. PMID: 8419804.	USA	1993	2	DKN - Choreoathetosis, DTN	65.5 (mean)	1M + 1F	Hypertension	Epilepsy
Micheli *et al*	Micheli F, Lehkuniec E, Gatto M, Pelli M, Asconape J. Hemiballism in a patient with partial motor status epilepticus treated with phenytoin. Funct Neurol. 1993 Mar-Apr;8(2):103-7. PMID: 8330755.	Argentina	1993	1	DKN - Hemiballism, DTN	13	F	-	Epilepsy
Lancman *et al*	Lancman ME, Asconapé JJ, Penry JK. Choreiform movements are associated with the use of valproate. Arch Neurol. 1994 Jul;51(7):702-4. DOI: 10.1001/archneur.1994.00540190086020. PMID: 8018044.	USA	1994	2	DKN - Chorea	26.5 (mean)	1F + 1M	Traumatic brain injury, mental retardation	Epilepsy

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Supplementary Table 2: Contd...

Author	Reference	Country	Year	Number of patients reported	Type	Age (y)	Sex	Comorbidities besides PHT-indication	PHT-indication
Koukkari *et al*	Koukkari MW, Vanefsky MA, Steinberg GK, Hahn JS. Phenytoin-related chorea in children with deep hemispheric vascular malformations. J Child Neurol. 1996 Nov;11(6):490-1. DOI: 10.1177/088307389601100617. PMID: 9120230.	USA	1996	2	DKN - Choreoathetosis, ballism	12	2F	Hemispheric malformations	Epilepsy
Shulman *et al*	Shulman LM, Singer C, Weiner WJ. Phenytoin-induced focal chorea. Mov Disord. 1996 Jan;11(1):111-4. DOI: 10.1002/mds.870110128. PMID: 8771085.	USA	1996	1	DKN - Choreoathetosis (focal)	74	M	Anxiety	Epilepsy
Chaudhary *et al*	Chaudhary N, Ravat SH, Shah PU. Phenytoin induced dyskinesia. Indian Pediatr. 1998 Mar;35(3):274-6. PMID: 9707885.	India	1998	1	DKN - Choreoathetosis, ballism	11	M	-	Epilepsy
Montenegro *et al*	Montenegro MA, Scotoni AE, Cendes F. Dyskinesia induced by phenytoin. Arq Neuropsiquiatr. 1999 Jun;57(2B):356-60. doi: 10.1590/s0004-282x1999000300002. PMID: 10450338.	Brazil	1999	3	DKN - Choreoathetosis, orofacial DKN	19 (mean)	2F + 1M	-	Epilepsy
Brandolese *et al*	Brandolese R, Scordo MG, Spina E, Gusella M, Padrini R. Severe phenytoin intoxication in a subject homozygous for CYP2C9*3. Clin Pharmacol Ther. 2001 Oct;70(4):391-4. PMID: 11673755.	Italy	2001	1	DKN - Orofacial DKN	31	F	Traumatic brain injury	Epilepsy
Saito *et al*	Saito Y, Oguni H, Awaya Y, Hayashi K, Osawa M. Phenytoin-induced choreoathetosis in patients with severe myoclonic epilepsy in infancy. Neuropediatrics. 2001 Oct;32(5):231-5. DOI: 10.1055/s-2001-19116. PMID: 11748493.	Japan	2001	3	DKN - Choreoathetosis	16 (mean)	1F + 2M	Myoclonic Epilepsy	Epilepsy
Zaatreh *et al*	Zaatreh M, Tennison M, D'Cruz O, Beach RL. Anticonvulsants-induced chorea: a role for pharmacodynamic drug interaction? Seizure. 2001 Dec;10(8):596-9. DOI: 10.1053/seiz.2001.0555. PMID: 11792164.	USA	2001	3	DKN - Choreoathetosis	32 (mean)	2F + 1M	Lennox–Gastaut syndrome	Epilepsy
Girija *et al*	Girija AS. Paroxysmal dyskinesia in phenytoin toxicity. J Assoc Physicians India. 2002 Nov;50:1449-50. PMID: 12583484.	India	2002	1	DKN	-	-	-	-
Caksen *et al*	Caksen H, Odabaş D, Anlar O. Use of biperiden hydrochloride in a child with severe dyskinesia induced by phenytoin. J Child Neurol. 2003 Jul;18(7):494-6. DOI: 10.1177/08830738030180070101. PMID: 12940655.	Turkey	2003	1	DKN - Orofacial DKN	5	F	-	Epilepsy
Lee *et al*	Lee CH, Li JY. Phenytoin intoxication and upper facial dyskinesia: an unusual presentation. Mov Disord. 2008 Jun 15;23(8):1188-9. DOI: 10.1002/mds.22004. PMID: 18361472.	Taiwan	2008	1	DKN - Orofacial DKN	52	F	-	-
Barvaliya *et al*	Barvaliya M, Sanmukhani J, Patel TK, Tripathi CB. Phenytoin induced chorea in a pediatric patient: An interaction between phenytoin, phenobarbital and clobazam. Indian J Pharmacol. 2011 Nov;43(6):731-2. DOI: 10.4103/0253-7613.89839. PMID: 22144787; PMCID: PMC3229798.	India	2011	1	DKN - Choreoathetosis	3	F	-	Epilepsy

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Author	Reference	Country	Year	Number of patients reported	Type	Age (y)	Sex	Comorbidities besides PHT-indication	PHT-indication
Lucey *et al*	Lucey BP. Teaching Video NeuroImages: phenytoin-induced orofacial dyskinesias. Neurology. 2012 Nov 6;79(19):e177. DOI: 10.1212/WNL.0b013e3182735eac. PMID: 23128448.	USA	2012	1	DKN - Orofacial DKN	55	M	-	Epilepsy
Nunez *et al*	Nunez Y, De la Cruz W, Rafael S, Cosentino C, Torres L. Acute phenytoin-induced dyskinesia. Mov Disord 2012;27:434.	Peru	2012	2	DKN - Chorea, orofacial DKN	-	2F	-	Epilepsy
García-Ramos *et al*	García-Ramos R, Moreno Ramos T, Villarejo Galende A, Porta Etessam J. Phenytoin-induced acute orofacial dyskinesia. Neurologia. 2013 Apr;28(3):193-4. English, Spanish. doi: 10.1016/j.nrl.2012.02.005. Epub 2012 May 15. PMID: 22595500.	Spain	2013	1	DKN - Orofacial DKN	80	M	Hypertension, atrial fibrillation	Epilepsy
Gunduz *et al*	Gunduz T, Kocasoy-Orhan E, Hanagasi HA. Orolingual dyskinesia and involuntary neck movements caused by phenytoin intoxication. J Neuropsychiatry Clin Neurosci. 2013 Fall;25(4):E51. DOI: 10.1176/appi.neuropsych.12120396. PMID: 24247892.	Turkey	2013	1	DKN - Orofacial DKN, DTN	88	F	Chronic subdural hematoma	Epilepsy
Gupta *et al*	Gupta M, Patidar Y, Khwaja GA, Chowdhury D, Batra A, Dasgupta A. Persistent cerebellar ataxia with cerebellar cognitive affective syndrome due to acute phenytoin intoxication: A case report. Neurol Asia. 2013 Mar 1;18(1):107-1.	India	2013	1	DKN - Orofacial DKN, chorea	20	F	-	Epilepsy
Rajasekharan *et al*	Rajasekharan C, Tina AM, Renjith SW. Orofaciolingual dyskinesia due to diphenylhydantoin sodium. BMJ Case Rep. 2013 May 23;2013:bcr2013009246. DOI: 10.1136/bcr-2013-009246. PMID: 23709146; PMCID: PMC3669996.	India	2013	1	DKN - Orofacial DKN	60	F	Subarachnoid hemorrhage	Epilepsy
Venkatarathnamma *et al*	Venkatarathnamma PN, Shekara MC, Srinivasa SV. Jagadish basavaih (2013) Phenytoin Induced Cerebellar Ataxia and Orofacial Dyskinesia in a Case of Disseminated Cysticercosis: A Case Report. Int J Clin Pharmacol Toxicol. 2013 Oct 7;2(702):102-5.	India	2013	1	DKN - Orofacial DKN, chorea	25	M	-	Epilepsy
Anand *et al*	Anand NN, Alam KR, Padma V. A rare case of phenytoin induced chorea & phenytoin hypersensitivity syndrome. Int J Pharma Bio Sci. 2014;5(4):596-600.	India	2014	1	DKN - Orofacial DKN, chorea	57	F	-	Epilepsy
González *et al*	González Otárula KA, Ugarnes G, Rossi M, Ballesteros D, D'Giano C. Phenytoin-Induced Chorea: Drug Interaction or Genetic Predisposition? Clin Neuropharmacol. 2016 Mar-Apr;39(2):120. doi: 10.1097/WNF.0000000000000140. PMID: 26818047.	Argentina	2016	1	DKN - Chorea	27	M	Isodicentric chromosome 15 syndrome	Epilepsy
Kaur *et al*	Kaur U, Chakrabarti SS, Gambhir IS. Orofacial dyskinesias by phenytoin in an elderly female: The dangers of poor therapeutic monitoring. Epilepsy Behav. 2016 Jun;59:155-6. DOI: 10.1016/j.yebeh.2016.03.010. Epub 2016 Apr 8. PMID: 27068813.	India	2016	1	DKN - Orofacial DKN	70	F	-	Epilepsy
Shuyi *et al*	Shuyi S, Liyong W, Na Y, Jia L, Jianping J. Ataxia and orofacial involuntary movement due to compound phenytoin sodium. Adverse Drug Reactions Journal 2016;18: 211-212.	China	2016	1	DKN - Orofacial DKN	63	F	Chronic obstructive pulmonary diseases	Epilepsy

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Supplementary Table 2: Contd...

Author	Reference	Country	Year	Number of patients reported	Type	Age (y)	Sex	Comorbidities besides PHT-indication	PHT-indication
Thodeson *et al*	Thodeson DM, Reiber DC, Dolce AM, Sirsi D. Fosphenytoin-induced dyskinesias in an infant with Sturge-Weber syndrome. Neurology. 2016 Apr 19;86(16):1561-2. DOI: 10.1212/WNL.0000000000002595. PMID: 27164450.	USA	2016	1	DKN - Hemi-DKN	11 months	F	Sturge-Weber syndrome	Epilepsy
Gill *et al*	Gill D, Lyons M, Allam F. Phenytoin Induced Chorea: A Case Report. Am J Ther. 2018 May/Jun;25(3):e390. DOI: 10.1097/MJT.0000000000000562. PMID: 28166164.	USA	2017	1	DKN - Chorea	66	M	Coronary artery disease, diabetes mellitus type 2, and osteomyelitis	Epilepsy
Finsterer *et al*	Finsterer J, Keller H, Reining-Festa A, Enzelsberger B, Weidinger F. Phenytoin-induced choreoathetosis after serial seizures due to traumatic brain injury and chronic alcoholism. Clin Case Rep. 2018 Oct 17;6(12):2316-2318. DOI: 10.1002/ccr3.1870. PMID: 30564320; PMCID: PMC6293133.	Austria	2018	1	DKN - Choreoathetosis	70	M	Cerebral palsy, bilateral hip dysplasia since birth, chronic alcoholism, arterial hypertension, inguinal hernia, reflux esophagitis	Epilepsy
Panachiyil *et al*	PANACHIYIL G, BABU T, SEBASTIAN J, RAVI MD. A Case Report of Fosphenytoin Induced Orofacial Dyskinesia in an 11-month-old Baby with Post-encephalitic Sequelae. J Clin Diagn Res 2019;13:7-8.	India	2019	1	DKN - Orofacial DKN	11 months	F	-	Epilepsy
Patel *et al*	Patel DM, Gurumukhani JK, Patel MV, Patel GR. Phenytoin Induced Chorea: A Rare Adverse Effect of the Drug. Curr Drug Saf. 2019;14(1):51-52. DOI: 10.2174/1574886313666181031161215. PMID: 30381086.	India	2019	1	DKN - Chorea	-	M	-	Epilepsy
Salim *et al*	Salim EJ , Suwarba IM, Mahalini DS, Windiyanto R. Phenytoin Induced Transient Chorea in a 9-Month-Old Baby Boy with Japanese Encephalitis. IJSR 2019;8: 1859-62	Indonesia	2019	1	DKN - Chorea	9 months	M	-	Epilepsy
Chouksey *et al*	Chouksey A, Pandey S. Clinical Spectrum of Drug-Induced Movement Disorders: A Study of 97 Patients. Tremor Other Hyperkinet Mov (N Y). 2020 Oct 26;10:48. DOI: 10.5334/tohm.554. PMID: 33178486; PMCID: PMC7597587.	India	2020	4	DKN - Tardive DKN	-	-	-	-
Keerty *et al*	Keerty D MD FACP, Kessler R MD, Koverzhenko V APRN, Peguero E MD. Dyskinesia during concomitant usage of phenytoin and capecitabine. Postgrad Med J. 2021 Oct;97(1152):629. DOI: 10.1136/postgradmedj-2020-138063. Epub 2020 Aug 7. PMID: 32769104.	USA	2020	1	DKN - Chorea	52	F	Breast cancer, lumpectomy	Epilepsy
Nagireddy *et al*	Nagireddy R, Joshi D, Patil S, Kumar A. Phenytoin induced Chorea: commonly used antiepileptic drug causing a rare movement disorder. Asia Pacific Journal of Medical Toxicology. 2020 Nov 1;9(4):163-4.	India	2020	1	DKN - Chorea	21	F	-	Epilepsy

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Supplementary Table 2: Contd...

Author	Reference	Country	Year	Number of patients reported	Type	Age (y)	Sex	Comorbidities besides PHT-indication	PHT-indication
Marefi *et al*	Marefi A, Srour M. The epilepsy-movement disorder phenotypic spectrum and phenytoin-induced dyskinesia associated with GABRB3 pathogenic variants. Epileptic Disord. 2021 Dec 1;23(6):947-950. DOI: 10.1684/epd.2021.1343. PMID: 34668866.	Canada	2021	1	DKN - Chorea	7	M	Autism spectrum disorder, intellectual disability	Epilepsy
Myoclonus (MCL)									
Engel *et al*	Engel J, Cruz ME, Shapiro B. Phenytoin encephalopathy? Lancet. 1971 Oct 9;2(7728):824-5. DOI: 10.1016/s0140-6736(71)92787-5. PMID: 4106649.	USA	1971	1	MCL - Asterixis	48	M	Alcoholic cirrhosis	Epilepsy
Murphy *et al*	Murphy MJ, Goldstein MN. Diphenylhydantoin-induced asterixis. A clinical study. JAMA. 1974 Jul 29;229(5):538-40. PMID: 4406897.	USA	1974	2	MCL - Asterixis	60	M	Hypertension, alcoholism	Epilepsy
					MCL - Asterixis	46	F	Glioblastoma multiforme	Epilepsy
Chadwick *et al*	Chadwick D, Reynolds EH, Marsden CD. Anticonvulsant-induced dyskinesias: a comparison with dyskinesias induced by neuroleptics. J Neurol Neurosurg Psychiatry. 1976 Dec;39(12):1210-8. DOI: 10.1136/jnnp.39.12.1210. PMID: 1011032; PMCID: PMC492567.	UK	1976	4	MCL - Asterixis	51	F	Mental retardation	Epilepsy
					MCL - Asterixis	67	M	-	Epilepsy
					MCL - Asterixis, DKN	59	F	-	Epilepsy
					MCL - Asterixis, DTN, DKN	72	M	-	Epilepsy
Gitlin *et al*	Gitlin N, Morris HB. Flapping tremor associated with administration of diphenylhydantoin sodium. S Afr Med J. 1976 Aug 28;50(3F):1427. PMID: 973155.	USA	1976	1	MCL - Asterixis	-	-	-	-
Trauner *et al*	Trauner DA. Stimulus-induced myoclonus and burst suppression on EEG: effects of phenytoin toxicity. Ann Neurol. 1985 Mar;17(3):312-3. DOI: 10.1002/ana.410170319. PMID: 3994321.	USA	1985	1	MCL - Cortical?	0.08	F	-	-
Sandford *et al*	Sandford NL, Murray N, Keyser AJ, Reynolds TB. Phenytoin toxicity and hepatic encephalopathy: simulation or stimulation? J Clin Gastroenterol. 1987 Jun;9(3):337-41. DOI: 10.1097/00004836-198706000-00019. PMID: 3611689.	USA	1987	2	MCL - Asterixis	55 (mean)	1F + 1M	Alcohol abuse	Epilepsy
Murphy *et al*	Murphy JM, Motiwala R, Devinsky O. Phenytoin intoxication. South Med J. 1991 Oct;84(10):1199-204. DOI: 10.1097/00007611-199110000-00010. PMID: 1925719.	USA	1991	2	MCL - Asterixis, Cortical	43 (mean)	-	-	Intoxication
Duarte *et al*	Duarte J, Sempere AP, Cabezas MC, Marcos J, Clavería LE. Postural myoclonus induced by phenytoin. Clin Neuropharmacol. 1996 Dec;19(6):536-8. doi: 10.1097/00002826-199619060-00009. PMID: 8937794.	Spain	1996	1	MCL - Generalized (postural)	72	M	-	Epilepsy
Vogt *et al*	Vogt H, Mothersill I. Asterixis: An adverse event also with new anti-epileptic drugs. Mov Disord 1996;11:345.	Switzerland	1996	1	MCL - Asterixis	58	F	Mental retardation, obstructive sleep-apnea-syndrome	Epilepsy

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Author	Reference	Country	Year	Number of patients reported	Type	Age (y)	Sex	Comorbidities besides PHT-indication	PHT-indication
Chi *et al*	Chi WM, Chua KS, Kong KH. Phenytoin-induced asterixis--uncommon or under-diagnosed? Brain Inj. 2000 Sep;14(9):847-50. DOI: 10.1080/026990500421949. PMID: 11030457.	Singapore	2000	1	MCL - Asterixis	84	M	Stroke	Epilepsy
Miralles *et al*	Miralles A, Vivancos F, Iváñez V, Arpa J, Barreiro P. Encefalopatía aguda con mioclonías por fenitoína. A propósito de un caso [Acute encephalopathy with myoclonus caused by phenytoin. Apropos of a case]. Rev Neurol. 2001 Feb 1-15;32(3):298-9. Spanish. PMID: 11310291.	Spain	2001	1	MCL - Asterixis	-	-	-	-
Yoo *et al*	Yoo BG, Park YH, Kim KS, Yoo KM. Asymmetric Asterixis Induced by Phenytoin in a Patient with Thalamic Infarction. Journal of the Korean Neurological Association. 2002;20:86-8.	Korean	2002	1	MCL - Asterixis	64	F	Thalamic infarction	Thalamic pain
Kemper *et al*	Kemper EM, van Kan HJ, Speelman P, de Gans K, Beijnen JH, Schellens JH. Ernstige fenytoïne-intoxicatie bij patiënten met hypoalbuminemie [Severe phenytoin intoxication in patients with hypoalbuminaemia]. Ned Tijdschr Geneeskd. 2007 Jan 13;151(2):138-41. Dutch. PMID: 17315493.	Netherlands	2007	2	MCL	47.5 (mean)	1F + 1M	Spina bifida, hydrocephalus, recurrent urinary tract infection, diabetes	Epilepsy
Nair *et al*	Nair PP, Wadwekar V, Murgai A, Narayan SK. Refractory status epilepticus is complicated by drug-induced involuntary movements. BMJ Case Rep. 2014 Feb 11;2014:bcr2013202691. DOI: 10.1136/bcr-2013-202691. PMID: 24518529; PMCID: PMC3926348.	India	2014	1	MCL - Generalized	24	F	-	Epilepsy
Pal *et al*	Pal G, Lin MM, Laureno R. Asterixis: a study of 103 patients. Metab Brain Dis. 2014 Sep;29(3):813-24. DOI: 10.1007/s11011-014-9514-7. Epub 2014 Mar 7. PMID: 24599759.	USA	2014	27	MCL - Asterixis	-	-	-	-
Verma *et al*	Verma R, Kumar S, Biyani S, Singh A. Opsoclonus - Myoclonus syndrome induced by phenytoin intoxication. J Neurosci Rural Pract. 2014 Nov;5(Suppl 1):S109-10. DOI: 10.4103/0976-3147.145254. PMID: 25540528; PMCID: PMC4271371.	India	2014	1	MCL	19	M	Tuberculous meningitis, hydrocephalus, and generalized tonic-clonic seizures	Epilepsy
Dystonia (DTN)									
Chadwick	Chadwick D, Reynolds EH, Marsden CD. Anticonvulsant-induced dyskinesias: a comparison with dyskinesias induced by neuroleptics. J Neurol Neurosurg Psychiatry. 1976 Dec;39(12):1210-8. DOI: 10.1136/jnnp.39.12.1210. PMID: 1011032; PMCID: PMC492567.	UK	1976	3	DTN - Limb DTN	18	M	Mental retardation, behavioral problems	Epilepsy
					DTN - Limb DTN	31	M	Lefr frontal abscess	Epilepsy
					DTN - Limb DTN	16	F	Mental retardation	Epilepsy
Chalhub *et al*	Chalhub EG, Devivo DC, Volpe JJ. Phenytoin-induced dystonia and choreoathetosis in two retarded epileptic children. Neurology. 1976 May;26(5):494-8. DOI: 10.1212/wnl.26.5.494. PMID: 944401.	USA	1976	1	DTN	8	-	Encephalopathy	-

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Author	Reference	Country	Year	Number of patients reported	Type	Age (y)	Sex	Comorbidities besides PHT-indication	PHT-indication
Crosley *et al*	Crosley C, Swender P. Dystonia associated with carbamazepine use. Pediatr Res 1978;12:550.DOI: 10.1203/00006450-197804001-01125	USA	1979	1	DTN	-	-	-	-
Stark *et al*	Stark RJ. Spasticity due to phenytoin toxicity. Med J Aust. 1979 Mar 10;1(5):156. DOI: 10.5694/j.1326-5377.1979.tb128955.x. PMID: 109744.	Australia	1979	1	DTN - Limb DTN	19	M	-	Epilepsy
Corey *et al*	Corey A, Koller W. Phenytoin-induced dystonia. Ann Neurol. 1983 Jul;14(1):92-3. DOI: 10.1002/ana.410140119. PMID: 6614878.	USA	1983	1	DTN - Limb DTN	23	M	-	Epilepsy
Choonara *et al*	Choonara IA, Rosenbloom L. Focal dystonic reaction to phenytoin. Dev Med Child Neurol. 1984 Oct;26(5):677-8. DOI: 10.1111/j.1469-8749.1984.tb04510.x. PMID: 6439583.	UK	1984	1	DTN - Segmental DTN	16	M	-	Epilepsy
Moss *et al*	Moss W, Ojukwu C, Chiriboga CA. Phenytoin-induced movement disorder. Unilateral presentation in a child and response to diphenhydramine. Clin Pediatr (Phila). 1994 Oct;33(10):634-8. DOI: 10.1177/000992289403301012. PMID: 7813146.	USA	1994	1	DTN - Limb DTN, orofacial DKN	5	F	-	Epilepsy
Pillai *et al*	Pillai LV, Ambike DP, Hussainy SM, Vishwasrao S, Pataskar S, Gaikwad MM. Hypersensitivity and dose-related side effects of phenytoin mimicking critical illness. Indian Journal of Critical Care Medicine 2005;9:22-7.	India	2005	1	DTN - Limb DTN	65	M	Hypertension, diabetes, hepatic encephalopathy	Epilepsy
Digby *et al*	Digby G, Jalini S, Taylor S. Medication-induced acute dystonic reaction: the challenge of diagnosing movement disorders in the intensive care unit. BMJ Case Rep 2015;2015:bcr2014207215. DOI: 10.1136/bcr-2014-207215. PMID: 26392457; PMCID: PMC4577690.	Canada	2015	1	DTN - Generalized	62	M	-	Epilepsy
Gupta *et al*	Gupta A, Yek C, Hendler RS. Phenytoin Toxicity. JAMA. 2017 Jun 20;317(23):2445-2446. DOI: 10.1001/jama.2017.6881. PMID: 28632869.	USA	2017	1	DTN	64	M	Chronic obstructive pulmonary disease	Epilepsy
Acar *et al*	Acar T, Alkan G, Çaksen H, Ertekin B, Ergin M, Koçak S, Cander B. Phenytoin induced dystonia. Turk J Pediatr. 2018;60(1):111-112. DOI: 10.24953/turkjped.2018.01.019. PMID: 30102491.	Turkey	2018	1	DTN - Generalized	2.5	M	-	Epilepsy
Chouksey *et al*	Chouksey A, Pandey S. Clinical Spectrum of Drug-Induced Movement Disorders: A Study of 97 Patients. Tremor Other Hyperkinet Mov (N Y). 2020 Oct 26;10:48. DOI: 10.5334/tohm.554. PMID: 33178486; PMCID: PMC7597587.	India	2020	4	DTN - Tardive DTN	-	-	-	-
Rajkumar *et al*	Rajkumar D, Manokaran RK, Shubha S, Shruthi TK. Phenytoin Induced Status Dystonicus: A Rare Manifestation of Phenytoin Toxicity in a Child with Autism Spectrum Disorder. Indian J Pediatr. 2021 Jan;88(1):85-86. DOI: 10.1007/s12098-020-03392-y. Epub 2020 Jun 12. PMID: 32529400.	India	2021	1	DTN - Generalized	5	M	Autism spectrum disorder	Epilepsy

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Author	Reference	Country	Year	Number of patients reported	Type	Age (y)	Sex	Comorbidities besides PHT-indication	PHT-indication
Mteshana *et al*	Mteshana P Z, Naidoo K D, Rowjee V, Hauptfleisch M P K, Dangor Z. Choreoathetosis and dystonia in a child with COVID-19 and multisystem inflammatory syndrome. S. Afr. j. child health [Internet]. 2021 Dec [cited 2022 Mar 17] ; 15(4): 229-231. Available from: http://www.scielo.org.za/scielo.php?script=sci_arttext&pid=S1999-76712021000400012&lng=en. http://dx.doi.org/10.7196/SAJCH.2021.v15i4.1859.	South Africa	2021	1	DTN - DTN, choreoathetosis	9	F	-	Epilepsy
Tics									
Drake *et al*	Drake ME. Tourette syndrome was precipitated by phenytoin. Clin Pediatr. 1985;24:323.	USA	1985	1	Tourette's Syndrome-induced	16	M	-	Epilepsy
Kurlan *et al*	Kurlan R, Kersun J, Behr J, Leibovici A, Tariot P, Lichter D, Shoulson I. Carbamazepine-induced tics. Clin Neuropharmacol. 1989 Aug;12(4):298-302. DOI: 10.1097/00002826-198908000-00007. PMID: 2529963.	USA	1989	1	Tourette's Syndrome - worsening	13	M	Tourette's Syndrome	Epilepsy
Parraga *et al*	Parraga HC, Cochran MK. Emergence of motor and vocal tics during imipramine administration in two children. J Child Adolesc Psychopharmacol. 1992 Fall;2(3):227-34. DOI: 10.1089/cap.1992.2.227. PMID: 19630634.	USA	1992	1	Tourette's Syndrome-induced	13	M	Depression, cognitive impairment	Epilepsy
Zadikoff *et al*	Zadikoff C, Munhoz RP, Asante AN, Politzer N, Wennberg R, Carlen P, Lang A. Movement disorders in patients taking anticonvulsants. J Neurol Neurosurg Psychiatry. 2007 Feb;78(2):147-51. DOI: 10.1136/jnnp.2006.100222. Epub 2006 Sep 29. PMID: 17012337; PMCID: PMC2077655.	Canada	2007	2	Excessive eye blinking	57	M	-	Epilepsy
Guilhoto *et al*	Guilhoto LM, Loddenkemper T, Gooty VD, Rotenberg A, Takeoka M, Duffy FH, Coulter D, Urion D, Bourgeois BF, Kothare SV. Experience with lacosamide in a series of children with drug-resistant focal epilepsy. Pediatr Neurol. 2011 Jun;44(6):414-9. DOI: 10.1016/j.pediatrneurol.2010.12.003. PMID: 21555051.	Brazil	2011	1	Oral tics	15.6	F	Cognitive impairment	Epilepsy
Stuttering									
McClean *et al*	McClean MD, McLean Jr A. Case report of stuttering acquired in association with phenytoin use for post-head-injury seizures. Journal of Fluency Disorders. 1985 Dec 1;10(4):241-55.	USA	1985	1	Dysfluency	42	M	Traumatic brain injury	Epilepsy
Ekici *et al*	Ekici MA, Ekici A, Ozdemir O. Phenytoin-induced stuttering: an extremely rare association. Pediatr Neurol. 2013 Aug;49(2):e5. DOI: 10.1016/j.pediatrneurol.2013.03.011. PMID: 23859866.	Turkey	2013	1	-	3	M	Traumatic brain injury	Epilepsy

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Supplementary Table 2: Contd...

Author	Reference	Country	Year	Number of patients reported	Type	Age (y)	Sex	Comorbidities besides PHT-indication	PHT-indication
Sudo *et al*	Sudo D, Doutake Y, Yokota H, Watanabe E. Recovery of brain abscess-induced stuttering after neurosurgical intervention. BMJ Case Rep. 2018 May 12;2018:bcr2017223259. DOI: 10.1136/bcr-2017-223259. PMID: 29754132; PMCID: PMC5950552.	Japan	2018	1	Dysfluency	60	M	Brain abscess	Epilepsy
Restless Legs Syndrome (RLS)									
Drake *et al*	Drake ME. Restless legs with antiepileptic drug therapy. Clin Neurol Neurosurg. 1988;90(2):151-4. DOI: 10.1016/s0303-8467(88)80037-4. PMID: 3145164.	USA	1988	2	RLS	43 (mean)	1F + 1M	Traumatic brain injury, subarachnoid hemorrhage	Epilepsy

Author	PHT-dose (mg)	PHT levels	Time from PHT-start to symptoms	Time from management to recovery	Management	Follow-up	Important clinical history (CH) and clinical management (CM)	Neurological symptoms	Neuroimaging - Computed tomography or Magnetic resonance imaging	Notes
Parkinsonism (PKN)										
Prensky *et al*	300 mg	44.9 ug/ml	3 years	2 months	PHT-dose reduced	Complete recovery	A summary of the clinical course of the patient is provided in the case report.	Lethargy, ataxia, nystagmus, and bradykinesia.	EEG: diffusely slow.	The individual was investigated for possible degenerative disease.
Mendez *et al*	390 mg (mean)	-	-	-	-	-	PHT diminished the therapeutic effects of levodopa both in patients with PKN, as well as the levodopa-dependent DKN.	-	-	-
Goñi *et al*	300 mg	Normal	1 month	-	PHT withdrawal	Complete recovery	Nasopalpebral reflex persisted after other symptoms of parkinsonism improved. Phenytoin was changed by carbamazepine.	-	-	-
Benvenuti	400 mg	43 ug/ml	8 years	-	PHT-dose reduced	Complete recovery	-	Drowsiness, moderate gait ataxia, slowness of movement	-	EMG patterns.

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Supplementary Table 2: Contd...

Author	PHT-dose (mg)	PHT levels	Time from PHT-start to symptoms	Time from management to recovery	Management	Follow-up	Important clinical history (CH) and clinical management (CM)	Neurological symptoms	Neuroimaging - Computed tomography or Magnetic resonance imaging	Notes
Türkdogan *et al*	-	-	7 days	-	-	-	Possible PKN. Presence of jaw tremor with the rigidity of limbs. However, the abnormal movement was poorly described. Hypoalbuminemia.	Mandibular tremor + rigidity	-	-
Ertan *et al*	300 mg	40 ug/ml	2 weeks	6 months	PHT withdrawal	Complete recovery	PHT was changed by carbamazepine.	He experienced an intentional tremor of his hands and bradykinesia with the stiffness of his arms and legs. Subsequently, gait ataxia, diplopia, and bradymimia were added to the clinical picture.	EEG, Brain MRI: not significant changes.	-
Kim *et al*	400 mg	-	20 years	-	PHT-dose reduced	Complete recovery	He was in the use of PHT and oxcarbazepine. PHT dose was reduced from 400 mg to 300 mg with complete recovery of PKN.	Progressive cognitive decline, postural tremor, bradykinesia, and gait disturbance.	Brain MRI and PET: normal, not significant. EEG: diffusely slow.	-
Ponte *et al*	-	-	-	-	-	-	-	-	-	7,200 hospital admissions; 528 adverse drug reactions; 6 drug-induced PKN. One of these individuals was in the use of PHT.
Shin *et al*	300 mg	-	2 weeks	-	PHT withdrawal	-	Neuroleptic malignant syndrome	Severe akinetic-rigid PKN	EEG high-voltage irregular delta slowing in the frontal areas and frequent high-voltage sharp waves in the right frontal area, suggesting focal seizure disorder with diffuse cerebral dysfunction.	-

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Supplementary Table 2: Contd...

Author	PHT-dose (mg)	PHT levels	Time from PHT-start to symptoms	Time from management to recovery	Management	Follow-up	Important clinical history (CH) and clinical management (CM)	Neurological symptoms	Neuroimaging - Computed tomography or Magnetic resonance imaging	Notes
Shaik *et al*	100 mg	-	10 years	2 weeks	PHT withdrawal	-	PHT was changed by valproate.	Stiffening of fingers, jerk-like movements of upper and lower limbs, and slowness of his movements.	-	-
Dyskinesia (DKN)										
Hoaken *et al*	100 mg	-	6 days	3 months	PHT withdrawal	Complete recovery	She has been treated with pentobarbital 100 mg and diphenylhydantoin 100 mg.	Periods of restless agitated writhing muscular movement, complaints of diplopia, inability to see, and sensations of worms on the skin of her face and inside her head.	EEG: symmetrical with a dominant rhythm of 4-6 c/s theta and a rare delta of 3 c/s. consistent with an acute brain syndrome.	The first diagnosis was of psychiatric disease. The patient recovered after PHT withdrawal. An EEG showed signs of acute brain syndrome.
Peters *et al*	-	-	-	-	-	-	-	-	-	-
Reimer *et al*	-	-	-	-	-	-	-	Cerebellar signs	-	-
	-	-	-	-	-	-	-	Cerebellar signs	-	-
Diehl *et al*	-	-	-	-	-	-	-	-	-	-
Logan *et al*	400 mg	40 ug/ml	3 weeks	6 months	PHT-dose reduced	Complete recovery	The patient showed complete recovery with PHT-dose reduction.	He had coarse nystagmus in both vertical and horizontal gaze and poor upward gaze. There were choreic and athetoid movements of his face and all extremities with dystonic posturing of his upper extremities.	EEG: diffusely slow.	The toxicity seemed to interact with the underlying disease.
Gerber *et al*	300 mg	92 ug/ml	1 month (6 years)	2 weeks	PHT withdrawal	Complete recovery	Four-time PHT rechallenged with the same clinical manifestation.	Abrupt, purposeless movements of all four extremities, frequent grimacing, marked horizontal nystagmus, intention tremor with impaired heel-knee and finger-nose test, and severe dysdiadochokinesia.	-	This study highlights the PHT metabolism. The data indicate that "rapid" metabolizers of diphenylhydantoin have a greater capacity to increase the output of p-HPPH in urine in response to an increased dose of diphenylhydantoin.

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Supplementary Table 2: Contd...

Author	PHT-dose (mg)	PHT levels	Time from PHT-start to symptoms	Time from management to recovery	Management	Follow-up	Important clinical history (CH) and clinical management (CM)	Neurological symptoms	Neuroimaging - Computed tomography or Magnetic resonance imaging	Notes
Bellman *et al*	400 mg	42 ug/ml	11 years	-	PHT-dose reduced	Complete recovery	She was in the use of PHT and primidone. PHT rechallenged showed the same clinical manifestation. PHT was changed by carbamazepine with complete recovery.	Choreoathetoid movements of all her limbs and jerking movements of her tongue and facial muscles.	-	-
Jan *et al*	4 mg/ Kg	110 ug/ ml	6 months	1 week	PHT withdrawal	Complete recovery	PHT was changed to phenobarbital.	She was stuporous and extremely irritable. The child's extremities were thrashing around and she was frequently in an opisthotonic position.	EEG: diffusely slow.	-
Kooiker *et al*	-	40 ug/ml	-	-	PHT-dose reduced	-	-	Nystagmus was absent in both patients initially although it appeared transiently in one.	-	-
	-	65 ug/ml	-	-	PHT-dose reduced	-	-	Nystagmus was absent in both patients initially although it appeared transiently in one.	-	-
Mclellan *et al*	450 mg	37 ug/ml	2 years	6 days	PHT-dose reduced	Complete recovery	The increased frequency of seizures and the encephalopathy with involuntary movements were first ascribed to a degenerative or infective disorder associated with the Hodgkin's disease.	Chorea, ataxia, and nystagmus.	EEG: diffusely slow. The generalized atypical spike-and-wave activity was prominent.	Misdiagnosed at first presentation.
	400 mg	50 ug/ml	2 weeks (2 years)	10 days	PHT withdrawal	Complete recovery of DKN	The first PHT was withdrawn. After 7 days, it was reintroduced in a low dose without adverse effects.	There was pronounced dystonic rigidity in all four limbs with unsustained knee and ankle clonus. Nystagmus.	EEG: diffusely slow. The generalized atypical spike-and-wave activity was prominent.	Cognitive impairment by PHT.

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Author	PHT-dose (mg)	PHT levels	Time from PHT-start to symptoms	Time from management to recovery	Management	Follow-up	Important clinical history (CH) and clinical management (CM)	Neurological symptoms	Neuroimaging - Computed tomography or Magnetic resonance imaging	Notes
Rosenblum *et al*	-	Toxic range	-	1 week	-	-	-	-	-	-
Shuttleworth *et al*	400 mg	43 ug/ml	3 weeks	1 week	PHT-dose reduced	Complete recovery	-	Chorea, ataxia, and nystagmus.	-	-
	300 mg	29 ug/ml	-	1 week	PHT withdrawal	Complete recovery	-	Inappropriate silly behavior, drowsiness, diplopia, prominent choreoathetosis in the hands, and lateral and vertical nystagmus.	-	-
	600 mg	30 ug/ml	-	5 days	PHT withdrawal	Complete recovery	-	Chorea, ataxia, and nystagmus.	-	-
Ahmad *et al*	300 mg	51 ug/ml	3 weeks	1 week	PHT withdrawal	No	Multiples rechallenges.	A slight fine tremor of his hands and mild impairment of coordination	EEG: diffusely slow.	-
	300 mg	42.5 ug/ml	-	-	PHT withdrawal	No	Multiples rechallenges.	Ataxia, dysarthria, involuntary movements, and sleepiness	EEG: diffusely slow.	-
	250 mg	30 ug/ml	-	4 weeks	PHT withdrawal	-	-	-	-	-
	300 mg	26.5 ug/ml	-	-	-	-	-	She had coarse finger tremor, mild nystagmus on lateral gaze, and incoordination of upper and lower limbs.	-	-
Mendez *et al*	450 mg (mean)	-	-	-	-	-	-	PHT worsened chorea and mental psychosis in individuals with Huntington chorea.	-	-
Chalhub *et al*	10 mg/Kg	99 ug/ml	5 days	-	PHT withdrawal	Complete recovery	-	Choreoathetosis of the face and all extremities, truncal ataxia, and ataxia.	-	This case is interesting because the individual had normal intelligence, no demonstrable neurologic deficit, and had received phenytoin therapy for a short period.
Chalhub *et al*	-	Normal	2 hours	-	-	-	-	-	EEG: without new abnormalities.	Movement disorder secondary to PHT can occur at therapeutic serum concentrations of this drug.

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Zinsmeister *et al*	11 mg/ Kg	24.5 ug/ ml	1 month (3 years)	-	PHT withdrawal	Complete recovery	-	Choreoathetosis of the trunk and extremities, involuntary facial grimacing, and jerking of the head from side to side. The presence of ataxia was difficult to assess because of the severity of the movement disorder.	-	-
Buchanan *et al*	7 mg/ Kg	11.5 ug/ ml	(1.6 years)	5 days	PHT withdrawal	Complete recovery	-	-	-	-
Lühdorf *et al*	200 mg	16 ug/ml	-	-	PHT-dose reduced	-	Multiple times dose adjusts were tried without being effective. The individual always had a recurrence of the abnormal movement.	-	EEG: diffusely slow.	-
	350 mg	31 ug/ml	-	-	PHT withdrawal	No	A PHT rechallenged showed again DKN. Apparently, after PHT-induced DKN verbal tests showed low scores in performance tests, indicating a lesion in the dominant hemisphere	-	EEG: diffusely slow.	-
	400 mg	18 ug/ml	-	2 months	PHT withdrawal	-	-	-	EEG: diffusely slow.	Misdiagnosed at first presentation with a psychogenic movement disorder.
Rasmussen *et al*	400 mg	Normal	4 weeks	1 week	PHT withdrawal	Complete recovery	A PHT rechallenged showed again DKN.	-	-	Brain autopsy: Numerous small encephalomalacias are confined to the corpus striatum on both sides. The number of Purkinje cells in the cerebellum was estimated to be normal.

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Strandjord *et al*	-	-	-	-	-	-	-	-	-	-
Cranford *et al*	-	25-33 ug/ml	-	-	-	-	-	-	-	Study of intravenous PHT in 139 epileptic patients aged 17 to 94 years.
DeVeaugh-Geiss *et al*	300 mg	Normal	3.5 years	-	PHT withdrawal	No	Aggravation of DKN by PHT.	Severe orofacial DKN, with tongue-protrusion every 20 minutes, and severe choreoathetosis of the limbs.	-	-
Fanø *et al*	-	-	-	-	-	-	-	-	-	-
Opida *et al*	-	62.5 ug/ml	18 days	12 hours	PHT withdrawal	Complete recovery	He received an unknown amount of oral Dilantin and phenobarbital in three different hospitals.	When his legs were spread apart voluntarily or by the observer, quick flinging involuntary movements occurred that were asynchronous, nonrepetitive, and of large amplitude. The movements seen in this patient resembled the hemiballismus of subthalamic nuclear lesions but were bilateral and confined to the lower extremities.	EEG: normal.	-
Mauguiere *et al*	500 mg	Normal	3 hours	6 days	PHT withdrawal	Complete recovery	-	Slow flexion and extension movements of the fingers, the wrists, and the elbows, diversely associated with prosupination movements of the wrists, were the most frequent in the upper limbs; they occurred at rest and during voluntary movements as well.	-	A figure with the time course of status epilepticus and DPH-induced choreoathetosis is provided.

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Nausieda *et al*	300 mg	-	8 years	4 days	PHT withdrawal	Complete recovery	-	Continuous lingual-facial-buccal dyskinesias were present with the involuntary bobbing of the head. Fine choreatic movements were present in both outstretched hands. A mild intention tremor was noted bilaterally as well as a slightly wide-based gait.	-	An experimental study with guinea pigs.
	200 mg	Normal	2 days	-	PHT withdrawal	Complete recovery	Aggravation of orofacial DKN by PHT.	Involuntary movements of the face consisting of rolling tongue movements, and smacking and pursing of the lips.	-	-
Dravet *et al*	-	7 Normal 3 toxic	-	-	-	-	None of the patients showed neurological signs during the attacks, which could have suggested an overdose of PHT, and the EEG showed no alterations.	Abnormal movements were usually paroxysmal and were mainly athetotic or choreic affecting more particularly the facial region	-	-
Vincent *et al*	-	-	-	-	-	-	-	-	-	-
Sandyk *et al*	17.3 mg/Kg	57.8 ug/ml	-	4 weeks	PHT withdrawal	Complete recovery	-	Constant chewing motions were observed. There was generalized chorea at rest, enhanced by the movement of the limbs, all of which showed generalized hypotonicity.	-	-
Krishnamoorthy *et al*	-	Normal	-	1 week	PHT withdrawal	Complete recovery	-	The most striking clinical manifestations included the sudden onset of restlessness and agitation with superimposed choreoathetosis	-	-
Todt *et al*	-	-	-	-	-	-	-	-	-	-

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Howrie *et al*	15 mg/ Kg	7.6 ug/ml	Single-dose	3 days	PHT withdrawal	Complete recovery	Rechallenge without the reappearance of abnormal movements.	Rolling and thrusting of the tongue, choreoathetoid movements of the extremities, facial grimacing, dystonic posturing, and oral-buccal dyskinesias.	-	-
	20 mg/ Kg	15 ug/ml	Single-dose	several days	PHT withdrawal	Complete recovery	Rechallenge with the reappearance of abnormal movements.	Tongue thrusting and choreoathetoid movements.	-	-
Yoshida *et al*	300 mg	Normal	11 months	-	PHT withdrawal	Complete recovery	Rechallenge with the reappearance of abnormal movements.	Most noticeable were bizarre orofacial involuntary movements and a slight writhing movement of his hands. He exhibited incessant slow facial grimacing, frowned, raised his eyebrows, pursed his lips, and pulled the angles of his mouth. These involuntary movements could be stopped at will and disappeared during sleep.	EEG: epileptic activity. Cranial CT scan: normal.	-
Filloux *et al*	21 mg/ Kg	Normal	First dose	31.5 hours	PHT-dose maintained	Complete recovery	The PHT dose was maintained and the patients had a complete recovery.	The chorea consisted of buccofacial and appendicular involuntary DKN, with the most prominent activity noted in the upper extremities. Neither ballismus nor dystonic postures were observed.	-	This phenomenon has not been previously recognized and suggests that phenytoin-induced chorea does not necessarily imply toxicity or underlying brain damage.
Maiti *et al*	-	-	-	-	-	-	-	-	-	-
Roullet *et al*	-	42 ug/ml	3 months	-	-	-	She was receiving phenobarbital, PHT, and clonazepam	-	Cranial CT scan: normal	-

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Szczechowski *et al*	-	Toxic range	-	-	PHT-dose reduced	-	The DKN was reversible and disappeared after the reduction of drug dose and its serum concentration falling to the therapeutic range.	-	-	-
Kurata *et al*	230 mg	Normal	Single-dose	4 weeks	PHT withdrawal	No	The individual first developed choreoathetosis and orofacial DKN. After, she developed ballism and DTN. By last, PKN was observed and did not completely recover.	-	Cranial CT scan: normal	-
Tomson *et al*	300 mg	Normal	2 weeks (10 years)	-	PHT withdrawal	Complete recovery	Rechallenge showed abnormal movements. PHT was changed to carbamazepine.	-	-	These adverse events may be explained by a high free fraction (19%) of the phenytoin plasma concentration.
Mellick *et al*	-	100.8 ug/ml	Single-dose	-	-	-	He ingested 19.6 g of PHT. The patient presented DKN and DTN.	-	-	-
Ryan *et al*	15 mg/Kg	-	Single-dose	-	-	-	-	-	-	-
Haider *et al*	300 mg	-	Single-dose	24 hours	PHT withdrawal	Complete recovery	-	She developed sustained choreoathetoid movements affecting her mouth, neck, and limbs, disinhibited and bizarre speech, and mental confusion.	EEG and Cranial CT scan: no significant abnormality	-
Martínez Orgado *et al*	-	-	-	-	-	-	-	-	-	-
Martiñón Sánchez *et al*	-	-	-	-	-	-	-	-	-	-

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Yamamoto *et al*	70 mg	40 ug/ml	2 years	-	PHT withdrawal	Complete recovery	-	There was choreoathetosis of all extremities, orofacial dyskinesia, horizontal nystagmus, and dysdiadochokinesis with impaired heel-knee and finger-nose test.	EEG: 5 to 6 Hz moderate voltage theta waves	Acute PHT intoxication due to low dosages of phenytoin might be precipitated by upper respiratory infection and involuntary movements, in this case, might be related to hypothyroidism.
Murphy *et al*	-	-	-	-	-	-	-	-	-	-
Heo *et al*	-	-	-	-	PHT-dose reduced	Complete recovery	-	-	-	-
Harrison *et al*	300 mg	36 ug/ml	-	-	PHT-dose reduced	Complete recovery	PHT was changed to valproate.	-	-	Extended literature review about PHT-induced DKN.
Micheli *et al*	10 mg/ Kg	4 ug/ml	2 days	14 months	PHT withdrawal	Complete recovery	-	Left choreic-like flinging movements, consistent with hemiballism. Ataxia and nystagmus were observed.	EEG: Poorly organized rhythm without epileptiform activity.	-
Lancman *et al*	275 mg	Normal	-	-	PHT-dose maintained	Complete recovery	Possible interaction between valproate and PHT. The movement did not stop with PHT discontinuation but only occurred in the presence of PHT.	-	EEG: diffusely slow in one individual.	-

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Koukkari *et al*	-	17.45 ug/ml	-	Several months	PHT withdrawal	-	2 children with deep hemispheric malformations, seen after craniotomy procedures, received PHT postoperatively for seizure prophylaxis. They both had choreiform movements that appeared to be exacerbated by PHT and were relieved with the use of carbamazepine.	-	-	-
Shulman *et al*	300 mg	-	30 years	-	PHT withdrawal	No	-	Mild to moderate choreoathetotic movement disorder of the left upper extremity. These movements were more prominent distally than proximally and were more evident during ambulation.	Brain MRI: area of low signal in the right basal ganglia (posterior putamen) that extends into the right thalamus and corona radiata. EEG: normal.	Videotape
Chaudhary *et al*	150 mg	32 ug/ml	3 months	3 days	PHT-dose reduced	Complete recovery	PHT-dose was reduced as per the nomogram.	Bilateral gaze-evoked horizontal nystagmus, no papilledema, involuntary movements involving face, tongue, and upper extremities, depressed deep tendon reflexes, and flexor plantar response. The child had repeated twitching and grimacing movements of the face that changed constantly in character and location. He was unable to hold out his tongue for any length of time and when asked to protrude it he shot it out and then jerked it back.	-	-

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Montenegro *et al*	300 mg (6.3 mg/ KG)	20.6 ug/ ml	-	-	PHT withdrawal	Complete recovery	-	Besides DKN, they did not have other signs of phenytoin intoxication.	-	Interesting review.
Brandolese *et al*	300 mg	> 100 ug/ ml	10 days	4 weeks	PHT withdrawal	Complete recovery	Genotyping	Dysarthria, nystagmus, dysmetria, left hemifacial DKN, and alterations in mental status.	EEG: diffuse unspecific changes.	Genotyping revealed that the patient was homozygous for the CYP2C9*3 allele (CYP2C9*3/*3) and heterozygous for the CYP2C19*2 allele (CYP2C19*1/*2).
Saito *et al*	240 mg	25.25 ug/ ml	Weeks (years)	Weeks to months	PHT-dose reduced	Complete recovery	Choreoathetosis appeared 2 days to 6 months after increasing the PHT dose.	Individuals with severe myoclonic epilepsy in infancy who suffer from choreoathetosis due to PHT.	Ictal SPECT revealed decreased perfusion in the basal ganglia contralateral to the unilateral choreoathetosis	Patients with severe myoclonic epilepsy appear to be particularly vulnerable to this side effect of PHT, indicating the possible involvement of basal ganglia in the pathophysiology of this type of epilepsy.
Zaatreh *et al*	300 mg	-	9 days (mean)	4 days (mean)	PHT withdrawal	Complete recovery	All three patients were using PHT and lamotrigine in combination when the chorea started, chorea improved with tapering one of the medications. Possible drug interaction.	-	EEG, brain MRI	-
Girija *et al*	-	-	-	-	-	-	-	Paroxysmal DKN	-	-
Caksen *et al*	5 mg/ Kg	10 ug/ml	2 months	-	PHT withdrawal	Complete recovery	-	She had severe lingual facial-buccal extrapyramidal movements, slurred speech, and an ataxic gait.	EEG: diffusely slow. Brain MRI: normal.	Biperiden can be successfully used in the treatment of PHT-induced DKN.

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Lee *et al*	300 mg	37.34 ug/ml	30 years	-	PHT-dose reduced	Complete recovery	After discharge, oral PHT was prescribed and serum PHT concentration was within the therapeutic range. She has remained stable without recurrence of dyskinesia on follow-up evaluation.	Facial DKN with eyebrow elevation.	Brain MRI: normal.	Videotape: shows decreased facial expressions, the facial dyskinesia consisting of eyebrow elevation and unsteadiness on tandem gait at the next day of admission.
Barvaliya *et al*	5 mg/Kg	-	8 days	1 day	PHT withdrawal	Complete recovery	Possibly drug interaction: PHT, phenobarbital, and clobazam.	Involuntary, continuous, uncontrolled, jerky movements of the head and upper limbs.	Cranial CT scan: normal	-
Lucey *et al*	-	29.5 ug/ml	4 weeks	2 weeks	PHT withdrawal	Complete recovery	-	Eyebrow elevation and lip pursing.	-	Teaching Video NeuroImages
Nunez *et al*	300 mg	27.5 ug/ml (mean)	Single-dose, other -	-	PHT withdrawal	Complete recovery	-	Orolingual DKN movements, choreoathetosis in limbs, and visual hallucinations. They did not have other signs of phenytoin intoxication and had complete recovery after phenytoin withdrawal.	-	-
García-Ramos *et al*	750 mg	16 ug/ml	Single-dose	3 days	PHT withdrawal	Complete recovery	PHT was changed to valproate.	Choreic and dystonic movements of the mouth and tongue which caused mild dysarthria	Cranial CT scan: no significant.	-
Gunduz *et al*	300 mg	34 ug/ml	40 years	4 days	PHT withdrawal	Complete recovery	The patient was hydrated with intravenous fluids.	Continuous orolingual dyskinetic movements and paroxysmal backward neck movements were observed, and nystagmus was seen, with severe truncal and appendicular ataxia	Cranial CT scan: no significant.	-

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Gupta *et al*	300 mg	55 ug/ml	2 weeks	-	PHT withdrawal	No	PHT was given prophylactically due to the left basal ganglia bleeding.	Nystagmus, dysarthria, limb and truncal ataxia with orofacial DKN and chorea	PET scan: bilateral cerebellar hypometabolism. Brain MRI: diffuse cerebellar atrophy. EEG: normal.	Cerebellar hypometabolism and atrophy.
Rajasekharan *et al*	300 mg	34 ug/ml	17 days	3 weeks	PHT withdrawal	Complete recovery	PHT was withdrawn and she was started on trihexyphenidyl and clonazepam.	Abnormal dyskinetic movements of the face, perioral area, eyelids, nystagmus, and choreiform movement of the tongue.	Brain MRI: normal.	Videotape
Venkatarathnamma *et al*	300 mg	32.9 ug/ml	1 year	-	PHT withdrawal	-	PHT was changed to valproate.	Wide based ataxic gait, scanning dysarthria, horizontal gaze nystagmus, bilateral cerebellar signs, and occasional choreiform movements involving the left upper limb and orofacial dyskinesia.	Brain MRI: neurocysticercosis.	-
Anand *et al*	300 mg	32 ug/ml	1 month	3 days	PHT withdrawal	Complete recovery	Physical examination was notable for lymphadenopathy and a maculopapular, erythematous rash on her trunk, face, and ears.	Neurological examination was notable for the involuntary movements, namely repeated facial twitching and grimacing, abnormal vocalization and difficulty with the maintenance of phonation, and abrupt, rapid, forceful arm swinging at irregular intervals.	Brain MRI: normal.	-
González *et al*	300 mg	12 ug/ml	1 week	2 weeks	PHT withdrawal	-	-	Intermittent uncontrollable abnormal movements involving the trunk and upper extremities.	MRI, EEG: normal	Genetic predisposition?
Kaur *et al*	300 mg	>40 ug/ml	1 month	2 weeks	PHT withdrawal	No	Three days after stopping phenytoin, a significant decline in oral movements was seen, while almost complete disappearance of the same was seen after 15 days.	Exaggerated lip-smacking and tongue movements, mental confusion, auditory hallucinations, irrelevant talking, difficulty in walking without support, and a second episode of falling	MRI: normal.	Videotape.

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Shuyi *et al*	300 mg	Normal	10 years	12 days	PHT withdrawal	Complete recovery	-	Paroxysmal dysbasia and facial involuntary movements	-	Chinese
Thodeson *et al*	-	17.9 ug/ml	Single-dose	8 hours	PHT withdrawal	Complete recovery	Concurrent medications included oxcarbazepine, levetiracetam, and valproic acid.	Hemi-dyskinesias with nystagmus that stopped during sleep	EEG: normal.	Videotape.
Gill *et al*	-	-	-	Few days	PHT withdrawal	-	-	Choreiform movements, eliciting repetitive, jerky, involuntary movements in all extremities.	-	-
Finsterer *et al*	1000 mg	29.79 ug/ml	Single-dose	2 days	PHT withdrawal	Complete recovery	-	Overshooting movements of the head, upper limbs, and lower limbs became apparent.	EEG: normal.	-
Panachiyil *et al*	7.5 mg/kg	-	11 days	-	PHT withdrawal	-	-	She found it difficult to keep her tongue inside her mouth and the involuntary movements subsided following the withdrawal of the drug	EEG, MRI: normal.	-
Patel *et al*	300 mg	Normal	2 months	3 days	PHT withdrawal	Complete recovery	Chorea reappeared 30 days after the reintroduction of PHT.	-	-	Adverse drug reactions should be considered despite normal PHT levels.
Salim *et al*	20 mg/kg	14 ug/ml	6 days	5 days	PHT withdrawal	Complete recovery	Phenytoin was withdrawn then oral valproic acid and intravenous diphenhydramine was added.	Involuntary, continuous, uncontrolled jerky movement of the head, upper limbs, and lower limbs.	-	-
Chouksey *et al*	-	-	-	-	-	-	-	3 tardive DKN and 1 acute DKN	-	Study with 97 individuals with drug-induced movement disorders.
Keerty *et al*	-	70.6 ug/ml	3 years	10 days	PHT withdrawal	-	-	Worsening ataxia, difficulty with short-term memory, headaches, photophobia, involuntary movements, and vision changes.	EEG: normal.	Pharmacokinetics of 5FU and PHT

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Nagireddy *et al*	300 mg	11.75 ug/ml	4 days	1 day	PHT withdrawal	Complete recovery	Rechallenge of PHT, the choreiform movements reappeared and subsided when PHT was stopped again	Choreiform movements in upper and lower limbs.	MRI: normal.	Videotape
Marefi *et al*	-	29.79 ug/ml	Single-dose	2 days	PHT withdrawal	Complete recovery	GABRB3 pathogenic variants	Dyskinesia of face, arm, and leg.	-	Videotape
Myoclonus (MCL)										
Engel *et al*	300 mg	-	-	1 week	PHT withdrawal	-	-	Nystagmus, ataxia, dysarthria.	-	-
Murphy *et al*	300 mg	39 ug/ml	5 days	1 week	PHT withdrawal	Complete recovery	Asterixis, ataxia, and nystagmus.	Confusion, disorientation, and spontaneous involuntary muscle contractions mainly involved the upper extremities.	-	Ammonium tolerance curves.
	400 mg	38.7 ug/ml	1 week	1 week	PHT withdrawal	Complete recovery	-	Asterixis and nystagmus.	-	Ammonium tolerance curves.
Chadwick *et al*	300 mg	18.4 ug/ml	-	4 weeks	PHT withdrawal	-	-	Ataxia, asterixis	-	-
	300 mg	7.3 ug/ml	-	2 days	PHT withdrawal	-	-	Nystagmus, ataxia, asterixis	-	-
	300 mg	33.8 ug/ml	-	1 week	PHT withdrawal	-	-	Nystagmus, ataxia, orofacial DKN, and asterixis	-	-
	200 mg	32.3 ug/ml	-	1 week	PHT withdrawal	-	-	Nystagmus, ataxia, dysarthria, orofacial DKN, cervical dystonia, and asterixis	-	-
Gitlin *et al*	-	-	-	-	-	-	-	-	-	-
Trauner *et al*	11 mg/Kg	Normal	4 weeks	1 week	PHT withdrawal	Complete recovery	PHT was changed to phenobarbital.	She exhibited generalized myoclonus whenever touched or moved. She was diffusely hypertonic, slightly greater on the right than on the left, with hyperactive, symmetric reflexes and 10 to 12 beats of ankle clonus.	EEG: burst-suppression pattern. Cranial CT scan: normal.	-

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Sandford *et al*	300 mg	39.65 ug/ml	-	1.5 week	PHT withdrawal	Complete recovery	-	Both individuals had encephalopathy, characterized by confusion, disturbed conscious state, asterixis, and nystagmus, which was resistant to treatment with protein restriction, lactulose, and neomycin, but responsive to the withdrawal of phenytoin.	EEG: diffusely slow.	-
Murphy *et al*	-	-	-	-	-	-	-	-	-	-
Duarte *et al*	300 mg	34 ug/ml	4 weeks	6 months	PHT withdrawal	Complete recovery	PHT was changed to phenobarbital.	Abrupt, brief, rhythmical contractions in all limbs. They appeared with posture and action; disappeared with sleep and rest.	EEG and Cranial CT scan: normal	-
Vogt *et al*	-	Normal	-	-	-	-	The MCL occurred during the use of PHT, valproate, and lamotrigine. Possible drug interaction.	-	-	-
Chi *et al*	300 mg	37 ug/ml	17 days	-	PHT-dose reduced	Complete recovery	-	Bilateral asterixis of the upper limbs, truncal ataxia, and a broad-based gait.	-	-
Miralles *et al*	-	-	-	-	-	-	-	-	-	-
Yoo *et al*	300 mg	Normal	-	-	PHT withdrawal	Complete recovery	Though thalamic lesion can cause asterixis, her asterixis may have been induced by phenytoin, because it was bilateral and subsided after stopping phenytoin.	Bilateral asterixis.	-	A thalamic lesion can cause asterixis.
Kemper *et al*	300 mg	28 ug/ml	-	-	PHT withdrawal	1 death, other unknown	Both had low serum albumin concentrations.	Disorientation, myoclonia, hallucinations, and drowsiness in the first patient and a comatose state in the second	EEG, Cranial CT scan	Low serum albumin levels are associated with increased concentrations of the free fraction of phenytoin.

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Supplementary Table 2: Contd...

Author	PHT-dose (mg)	PHT levels	Time from PHT-start to symptoms	Time from management to recovery	Management	Follow-up	Important clinical history (CH) and clinical management (CM)	Neurological symptoms	Neuroimaging - Computed tomography or Magnetic resonance imaging	Notes
Nair *et al*	1000 mg	-	Single-dose	-	PHT-dose maintained	Complete recovery	Possible interaction among PHT, lorazepam, sodium valproate, midazolam, and thiopentone sodium.	Involuntary twitches involving her upper limbs and face	MRI. EEG: intermittent rhythmic activity arising from the right temporal leads.	-
Pal *et al*	-	18.4 ug/ml	-	-	-	-	Of the 27 phenytoin-associated asterixis cases, six occurred after phenytoin loading. The total phenytoin level, after the loading dose was given, ranged from 8.4 to 23 ug/mL; the average level was 18.4 ug/ml. Of the remaining 21 phenytoin-associated cases (the cases not related to phenytoin loading), levels were not checked in 3 cases.	-	-	27 o 103 asterixes were associated with PHT
Verma *et al*	500 mg	>40 µg/ml	1 month	2 weeks	PHT withdrawal	Complete recovery	PHT dose was increased and MCL appeared. Phenytoin was stopped and levetiracetam 500 mg bd and clonazepam 0.5 mg TDS were started. All his symptoms including opsoclonus-myoclonus were gradually disappeared over the next 15 days.	Opsoclonus-myoclonus syndrome. Chaotic multidirectional movement of eyes suggestive of opsoclonus with evidence of myoclonic jerks involving all four limbs	EEG, MRI: normal.	Videotape

Dystonia (DTN)

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Supplementary Table 2: Contd...

Author	PHT-dose (mg)	PHT levels	Time from PHT-start to symptoms	Time from management to recovery	Management	Follow-up	Important clinical history (CH) and clinical management (CM)	Neurological symptoms	Neuroimaging - Computed tomography or Magnetic resonance imaging	Notes
Chadwick	600 mg	43.4 ug/ml	-	1 week	-	-	-	Ataxia, dysarthria, confusion	-	-
	200 mg	31.3 ug/ml	-	-	-	-	-	-	-	-
	-	-	-	-	-	-	-	-	-	-
Chalhub *et al*	-	Normal	2 hours	-	-	-	-	-	EEG: without new abnormalities.	Movement disorder secondary to PHT can occur at therapeutic serum concentrations of this drug.
Crosley *et al*	-	Normal	-	-	-	-	The patient was in the use of PHT and carbamazepine.	-	-	-
Stark *et al*	400 mg	50.5 ug/ml	8 weeks	2 months	PHT withdrawal	Complete recovery	After PHT-induced DTN, PHT was reintroduced in a lower dose without occurring abnormal movements.	Horizontal and vertical nystagmus, and diplopia on extremes of horizontal gaze. The tone was slightly increased in the arms, and markedly so in the legs, with some clasp-knife effect and sustained clonus at both knees and ankles	-	-
Corey *et al*	600 mg	30 ug/ml	-	1 day	PHT withdrawal	Complete recovery	-	Horizontal nystagmus, slight bilateral intention tremor, and focal dystonia of the right leg, consisting of sustained plantar flexion and inversion of the foot.	Cranial CT scan: normal	-
Choonara *et al*	500 mg	23.8 ug/ml	-	-	PHT withdrawal	-	-	Acute dystonic movements of the right side of his face and body.	Cranial CT scan: normal	-
Moss *et al*	5 mg/Kg	19.4 ug/ml	4 days	1 day	PHT withdrawal	No	PHT was changed to phenobarbital. Diphenhydramine was used to control de abnormal movements. Orofacial DKN did not improve.	She was noted to have DTN posturing of the right arm and orofacial DKN consisting of chewing movements, eye-blinking, and tongue-thrusting. There was no nystagmus.	-	-

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Pillai *et al*	-	30 ug/ml	5 days	-	PHT withdrawal	No	Possible case of PHT-induced DTN, but the movement disorder description was poor.	Ataxia without nystagmus, scissoring gait.	-	-
Digby *et al*	1500 mg	-	Single-dose	-	-	-	Possible interaction haloperidol, benzodiazepines, phenytoin, propofol.	Stereotyped tonic movements involving arching of the back, an extension of the arms, and contraction of opposing muscle groups.	EEG: without new abnormalities. CT scan: insular infarct.	-
Gupta *et al*	900 mg	68 ug/ml	-	-	PHT withdrawal	-	The patient had been prescribed 3 times his home dosage of phenytoin.	Severe agitation, nystagmus, and dystonia.	EEG, Cranial CT scan: normal	System errors
Acar *et al*	10 mg/ Kg	-	12 hours	7 days	PHT withdrawal	Complete recovery	Biperiden hydrochloride was administered intramuscularly; primidone was added to the treatment regimen.	At the 12th hour of the patient follow-up, dystonic movements involving legs and arms were noticed.	EEG: bilateral generalized slow wave paroxysm with high amplitude.	-
Chouksey *et al*	-	-	-	-	-	-	-	3 tardive DTN and 1 acute DTN	-	Study with 97 individuals with drug-induced movement disorders.
Rajkumar *et al*	2000mg	60 ug/ml	Intoxication	7 days	-	-	20 tablets of phenytoin (100 mg)	Opisthotonic posturing in trunk and neck and associated dystonic posturing of all four limbs.	-	-

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Mteshana *et al*	-	-	Single-dose	8 days	PHT withdrawal	-	She was initially managed with intravenous immunoglobulins and methylprednisolone for presumed autoimmune encephalitis. However, she tested positive for SARS-CoV-2 and met the clinical and laboratory criteria for MIS-C.	Dystonia, choreoathetosis, and facial grimacing with hypotonia and normal reflexes.	-	COVID19
Tics										
Drake *et al*	300 mg	Normal	-	1 week	PHT withdrawal	Complete recovery	PHT was changed by carbamazepine with complete recovery of tics.	Grunting, throat-clearing, sniffing, tongue-clacking, habitual scratching of his nose, fidgeting and shoulder shrugging, and tendency to repeat what was said to him.	EEG and Cranial CT scan: normal.	-
Kurlan *et al*	-	-	Days	-	PHT withdrawal	No	He was in the use of carbamazepine and PHT. The symptoms improved after the withdrawal of both medications.	-	EEG: normal.	-
Parraga *et al*	100 mg	Normal	-	-	PHT-dose maintained	Complete recovery	Possible interaction between PHT and imipramine.	-	-	-
Zadikoff *et al*	-	-	-	-	-	-	He was diagnosed with seizures at the age of 49 years and was taking a combination of phenytoin and clobazam.	-	-	Valproate and carbamazepine were most commonly associated with tremors, followed by PHT.

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Guilhoto *et al*	-	-	-	-	PHT withdrawal	-	Possible interaction between PHT and lacosamide.	-	-	-
Stuttering										
McClean *et al*	200 mg	Normal	-	-	PHT withdrawal	Complete recovery	Phenytoin was changed by carbamazepine.	-	-	Extended speech analysis with dysfluency graphs and fine motor control assessment.
Ekici *et al*	5 mg/ Kg	-	10 days	10 days	PHT withdrawal	Complete recovery	Phenytoin was changed by valproate	-	Brain MRI: normal.	-
Sudo *et al*	300 mg	5.1 ug/ml	-	-	-	-	Possibly related to the PHT, but the authors believed that was associated with the brain abscess.	Stuttering-like disfluencies.	-	-
Restless Legs Syndrome (RLS)										
Drake *et al*	-	19 ug/ml	-	-	PHT withdrawal	No	Both patients have improvement of the symptoms, but they remained with occasional discomfort and restless sleep. One of the individuals had the symptoms with methsuximide, carbamazepine, and phenytoin. The other was in phenytoin monotherapy.	-	EEG, ENMG, Cranial CT scan without remarkable signs.	-

PHT: Phenytoin, CH: Clinical history, CM: Clinical management, PKN: Parkinsonism, DKN: Dyskinesias, MRI: Magnetic resonance imaging, MCL: Myoclonus, DTN: Dystonia, RLS: Restless Legs Syndrome, EEG: Electroencephalographic, EMG: Electromyography, PET: Positron emission tomography, CT: Computer tomographic, 5FU: 5-fluorouracil, SPECT: Single-photon emission computed tomography, p-HPPH: phenytoin metabolite-5-(parahydroxyphenyl)-5-phenylhydantoin, TDS: Three times a day, MIS-C: Multisystem inflammatory syndrome in children