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Valproate-associated Movement Disorder: A Literature Review

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Abstract: Valproate (VPA) was first synthesized in 1882, but it was only in the early 1960s that its anticonvulsant properties were discovered. The aim of this literature review is to evaluate the clinical epidemiological profile, pathological mechanisms, and management of VPA-associated movement disorder (MD). Relevant reports in six databases were identified and assessed by two reviewers without language restriction. A total of 138 reports containing 362 cases of subjects who developed a MD secondary to VPA were reported. The MD identified were parkinsonism (PKN) (252), myoclonus (MCL) (54), dystonia (DTN) (17), dyskinesia (DKN) (16), stutters (4), tics (3), akathisia (AKT) (1). In the not clearly defined group, 15 extrapyramidal symptoms, 3 AKT, 2 DTN, 1 rigidity, 1 unstable gait were assessed. The mean and median age was 55.8 (SD: 16.58) and 61 years (range: 4–87 years). The most common VPA-indication was epilepsy, and 51.36% were males. The mean and median time from the VPA start to the MD onset was 32.75 (SD: 30.05) and 21.15 months (range: 1 day – 20 years). The mean and median time from the VPA withdrawal until the MD recovery was 2.89 (SD: 2.79) and 3 months (1 day – 12 months). The most common management was drug withdrawal. A complete recovery was obtained in 80.61%. VPA-associated MD was extensively reported in the literature. PKN was the most well-described. Future studies need to clearly report the clinical history of the patient, considering the full investigation of other adverse events during their entire life.

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Introduction

Valproate (VPA), and its pharmacological forms such as valproic acid, sodium valproate, and valproate semisodium are anticonvulsants (Figure 1). In 1882, Beverly Burton synthesized VPA for the first time; this compound was used for almost eighty years as an inert solvent in laboratories (Lempérière, 2001). Pierre Eymard, in the early 1960s, during animal studies to develop a new antiepileptic drug, noted that the substances dissolved in VPA had apparently better anticonvulsant properties (Henry, 2003). After this observation, many clinical studies showed the efficacy and safety of VPA for the management of focal seizures (Brugger et al., 2016). In 1967, it was approved as an antiepileptic drug in France (Henry, 2003). Only in 1983, the Food and Drug Administration approved this medication for the treatment of epilepsy (Lempérière, 2001). The first study assessing the efficacy of VPA in bipolar disorder was done by Lambert et al. at the end of the 1960s in France, soon after the approval for epilepsy, which showed good results, but for many years these data were believed to be incidental, due to the small number of subjects studied (Henry, 2003). About ten years later, German clinical trials followed by North American studies supported the hypothesis of Lambert et al. In 1995, VPA was approved as monotherapy during manic episodes by the FDA (Lempérière, 2001).

The mechanism of action of VPA is not completely understood (Figure 2) (Lempérière, 2001; Löscher, 2002; Bowden, 2003; Henry, 2003; Brugger et al., 2016). Its main interactions are related to the voltage-gated sodium channels blockage and increased brain levels of gamma-aminobutyric acid (GABA) (Löscher, 2002). The increased concentration of this neurotransmitter is believed to occur due to indirect inhibition of the GABA's reuptake and degradative enzymes. Also, it is worth mentioning that this GABAergic mechanism probably explains the anticonvulsant and antimanic properties of this drug (Bowden, 2003). Other pathways that VPA is related include the Kv7.2, AKAP5, and histone deacetylase (Löscher, 2002). It is hypothesized that the inhibition of the histone deacetylase may have neuroprotective effects due to the increased uncoiling of DNA promoting more transcriptional activity of chromatin structures (Bowden, 2003).

The adverse effects of this medication that affect more than ten percent of users are nausea, vomiting, headache, coagulation disorders (Rissardo et al.,

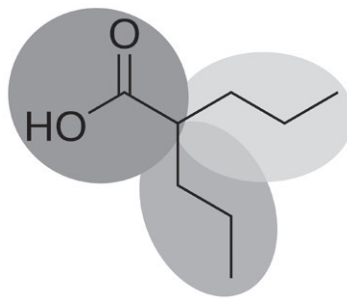

Figure 1 – Skeletal formula of the anticonvulsant drug valproic acid, also known as 2-propylvaleric acid.

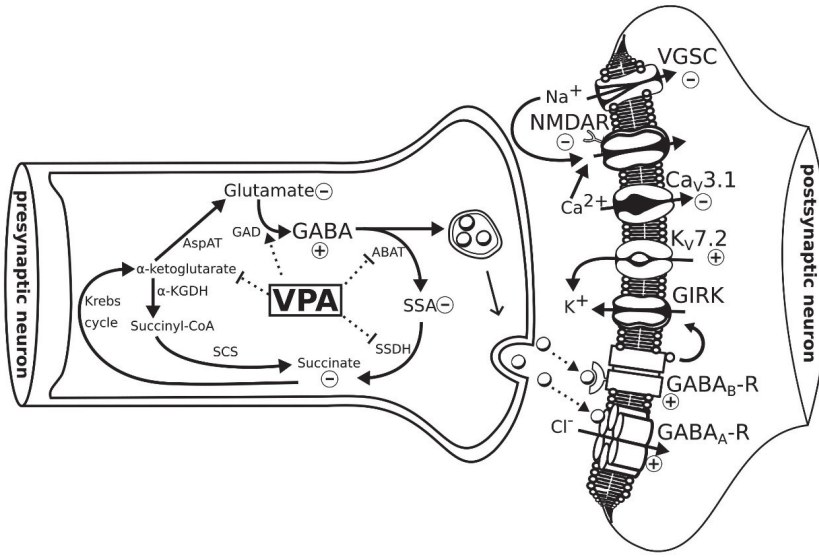

Figure 2 – Representation of proposed mechanisms of action for valproate (VPA). α-KGDH – alpha-ketoglutarate dehydrogenase; ABAT – 4-aminobutyrate aminotransferase; AspAT – aspartate aminotransferase; CaV3.1 – voltage-gated calcium channel; GABA – gamma-aminobutyric acid; GABAA/B-R – GABAA/B receptor; GAD – glutamate decarboxylase; GIRK – G protein-gated inwardly rectifying potassium channel; KV7.2 – voltage-gated potassium channel; NMDAR – N-methyl-D-aspartate receptor; SCS – succinyl CoA synthetase; SSA – succinic semialdehyde; SSDH – succinate-semialdehyde dehydrogenase; VGSC – voltage-gated sodium channel.

2019), alopecia, asthenia, somnolence, amblyopia, diarrhea, dizziness, dyspepsia, nystagmus, and tinnitus (Bowden, 2003). In the label of VPA, there is a black box warning about hepatotoxicity in susceptible individuals (those with mitochondrial diseases), teratogenicity, and pancreatitis (Löscher, 2002). Other common side effects secondary to VPA are movement disorders (MD) such as tremor and ataxia, which can significantly impact the quality of life of an important percentage of the VPA users. Moreover, these abnormal movements are challenging to diagnose and manage in the clinical practice, because the majority of affected individuals have a pre-existing psychiatric or neurologic comorbidity.

In the literature, there are few reviews about VPA and MD that were not focused solely on tremors. To be more specific, we found two reviews about VPA-induced parkinsonism (PKN). Mahmoud and Tampi published a study about this topic in 2011; they objectively selected elderly patients, and a total of thirteen case reports were analysed. In 2016, Brugger et al. searched on four databases for papers in English about VPA and PKN, a total of 116 patients were evaluated; their purpose was to discuss the possible hypotheses for these adverse effects. In this context, the aim of the present literature review is to evaluate the clinic-epidemiological profile, pathological mechanisms, and management of VPA-associated MD.

Methods

Search strategy

We searched six databases and also abstracts of the "International Congress of the Parkinson's Disease and Movement Disorders (1990–2019)" in an attempt to locate any and all existing reports on movement disorders (MD) secondary to VPA published between 1975 and 2019 in electronic form. Excerpta Medica (Embase), Google Scholar, Latin American and Caribbean Health Sciences Literature (Lilacs), Medline, Scientific Electronic Library Online (Scielo), and ScienceDirect were searched. Search terms were "parkinsonism, dyskinesia, dystonia, stuttering, myoclonus, restless legs syndrome, akathisia, tremor, chorea, tics, restlessness, ataxia, ballism, hyperkinetic, hypokinetic, bradykinesia, movement disorder". These terms were combined with "valproate, valproic acid" (Table 1).

Inclusion and exclusion criteria

Case reports, case series, original articles, letters to the editor, bulletins, and poster presentations published from 1975 to 2019 were included in this review with no language restriction. The authors independently screened the titles and abstracts

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

Category	Search terms	Results
Parkinsonism	((((((“valproate”[All Fields] OR “valproate’s”[All Fields]) OR “valproates”[All Fields]) OR “valproic acid”[MeSH Terms]) OR (“valproic”[All Fields] AND “acid”[All Fields])) OR “valproic acid”[All Fields]) OR “valproate”[All Fields]) AND ((((((((((“parkinson disease”[MeSH Terms] OR (“parkinson”[All Fields] AND “disease”[All Fields])) OR “parkinson disease”[All Fields]) OR “parkinson’s”[All Fields]) OR “parkinsons”[All Fields]) OR “parkinson”[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])	180
Tics	((((((“valproate”[All Fields] OR “valproate’s”[All Fields]) OR “valproates”[All Fields]) OR “valproic acid”[MeSH Terms]) OR (“valproic”[All Fields] AND “acid”[All Fields])) OR “valproic acid”[All Fields]) OR “valproate”[All Fields]) AND (“TIC”[Journal] OR “TIC”[All Fields])	15
Dyskinesia	((((((“valproate”[All Fields] OR “valproate’s”[All Fields]) OR “valproates”[All Fields]) OR “valproic acid”[MeSH Terms]) OR (“valproic”[All Fields] AND “acid”[All Fields])) OR “valproic acid”[All Fields]) OR “valproate”[All Fields]) AND ((((“dyskinesiae”[All Fields] OR “dyskinesias”[MeSH Terms]) OR “dyskinesias”[All Fields]) OR “dyskinesia”[All Fields]) OR “dyskinesis”[All Fields])	576

Category	Search terms	Results
Dystonia	((((((“valproate”[All Fields] OR “valproate’s”[All Fields]) OR “valproates”[All Fields]) OR “valproic acid”[MeSH Terms]) OR (“valproic”[All Fields] AND “acid”[All Fields])) OR “valproic acid”[All Fields]) OR “valproate”[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])	54
Stuttering	((((((“valproate”[All Fields] OR “valproate’s”[All Fields]) OR “valproates”[All Fields]) OR “valproic acid”[MeSH Terms]) OR (“valproic”[All Fields] AND “acid”[All Fields])) OR “valproic acid”[All Fields]) OR “valproate”[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])	10
Myoclonus	((((((“valproate”[All Fields] OR “valproate’s”[All Fields]) OR “valproates”[All Fields]) OR “valproic acid”[MeSH Terms]) OR (“valproic”[All Fields] AND “acid”[All Fields])) OR “valproic acid”[All Fields]) OR “valproate”[All Fields]) AND (((“myoclonias”[All Fields] OR “myoclonus”[MeSH Terms]) OR “myoclonus”[All Fields]) OR “myoclonia”[All Fields])	345
Restless legs syndrome	((((((“valproate”[All Fields] OR “valproate’s”[All Fields]) OR “valproates”[All Fields]) OR “valproic acid”[MeSH Terms]) OR (“valproic”[All Fields] AND “acid”[All Fields])) OR “valproic acid”[All Fields]) OR “valproate”[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])	17
Akathisia	((((((“valproate”[All Fields] OR “valproate’s”[All Fields]) OR “valproates”[All Fields]) OR “valproic acid”[MeSH Terms]) OR (“valproic”[All Fields] AND “acid”[All Fields])) OR “valproic acid”[All Fields]) OR “valproate”[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])	122
Tremor	((((((“valproate”[All Fields] OR “valproate’s”[All Fields]) OR “valproates”[All Fields]) OR “valproic acid”[MeSH Terms]) OR (“valproic”[All Fields] AND “acid”[All Fields])) OR “valproic acid”[All Fields]) OR “valproate”[All Fields]) AND (((((“trembling”[All Fields] OR “tremor”[MeSH Terms]) OR “tremor”[All Fields]) OR “tremors”[All Fields]) OR “tremoring”[All Fields]) OR “tremorous”[All Fields])	222
Chorea	((((((“valproate”[All Fields] OR “valproate’s”[All Fields]) OR “valproates”[All Fields]) OR “valproic acid”[MeSH Terms]) OR (“valproic”[All Fields] AND “acid”[All Fields])) OR “valproic acid”[All Fields]) OR “valproate”[All Fields]) AND ((“chorea”[MeSH Terms] OR “chorea”[All Fields]) OR “choreas”[All Fields])	124

Category	Search terms	Results
Restlessness	((((((“valproate”[All Fields] OR “valproate’s”[All Fields]) OR “valproates”[All Fields]) OR “valproic acid”[MeSH Terms]) OR (“valproic”[All Fields] AND “acid”[All Fields])) OR “valproic acid”[All Fields]) OR “valproate”[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])	124
Ataxia	((((((“valproate”[All Fields] OR “valproate’s”[All Fields]) OR “valproates”[All Fields]) OR “valproic acid”[MeSH Terms]) OR (“valproic”[All Fields] AND “acid”[All Fields])) OR “valproic acid”[All Fields]) OR “valproate”[All Fields]) AND ((“ataxia”[MeSH Terms] OR “ataxia”[All Fields]) OR “ataxias”[All Fields])	205
Ballism	((((((“valproate”[All Fields] OR “valproate’s”[All Fields]) OR “valproates”[All Fields]) OR “valproic acid”[MeSH Terms]) OR (“valproic”[All Fields] AND “acid”[All Fields])) OR “valproic acid”[All Fields]) OR “valproate”[All Fields]) AND ((“dyskinesias”[MeSH Terms] OR “dyskinesias”[All Fields]) OR “ballism”[All Fields])	542
Hyperkinetic	((((((“valproate”[All Fields] OR “valproate’s”[All Fields]) OR “valproates”[All Fields]) OR “valproic acid”[MeSH Terms]) OR (“valproic”[All Fields] AND “acid”[All Fields])) OR “valproic acid”[All Fields]) OR “valproate”[All Fields]) AND (“hyperkinetic”[All Fields] OR “hyperkinetics”[All Fields])	20
Hypokinetic	((((((“valproate”[All Fields] OR “valproate’s”[All Fields]) OR “valproates”[All Fields]) OR “valproic acid”[MeSH Terms]) OR (“valproic”[All Fields] AND “acid”[All Fields])) OR “valproic acid”[All Fields]) OR “valproate”[All Fields]) AND ((“hypokinesia”[MeSH Terms] OR “hypokinesia”[All Fields]) OR “hypokinetic”[All Fields])	9
Bradykinesia	((((((“valproate”[All Fields] OR “valproate’s”[All Fields]) OR “valproates”[All Fields]) OR “valproic acid”[MeSH Terms]) OR (“valproic”[All Fields] AND “acid”[All Fields])) OR “valproic acid”[All Fields]) OR “valproate”[All Fields]) AND (((“hypokinesia”[MeSH Terms] OR “hypokinesia”[All Fields]) OR “bradykinesia”[All Fields]) OR “bradykinesias”[All Fields])	12
Movement disorder	((((((“valproate”[All Fields] OR “valproate’s”[All Fields]) OR “valproates”[All Fields]) OR “valproic acid”[MeSH Terms]) OR (“valproic”[All Fields] AND “acid”[All Fields])) OR “valproic acid”[All Fields]) OR “valproate”[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])	466
Total		**3043**

of all papers found in the initial search. Disagreements between the authors were resolved through discussion.

Cases where the cause of MD was already known and either motor symptoms did not worsen or were not related to VPA were excluded. Also, cases that were not accessible by electronic methods, even after a formal request to the authors (by e-mail) were excluded. Reports that had more than one factor contributing to the MD were evaluated by the probability of occurrence of the event based on the Naranjo algorithm.

Data extraction

For VPA a total of 6,443 papers were found; 5,279 were irrelevant and 1,026 were unrelated to the complication, duplicate, inaccessible electronically, or provided insufficient data (Figure 3). Data abstraction was performed. When provided, we extracted author, department, year of publication, country of origin, number of patients affected, VPA indication including off-label uses, time from first VPA-dose until MD onset, time from VPA withdrawal or management to symptoms improvement, patient's status at the last follow-up, and important findings of clinical history and management. The majority of the reports did not provide specific

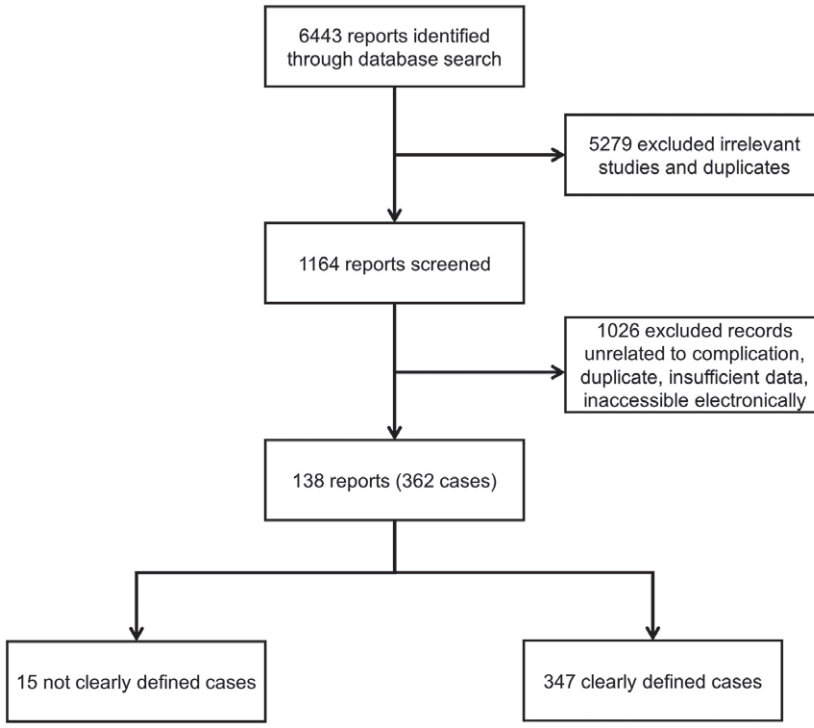

Figure 3 – Flow chart of the screening process for valproate (VPA).

information about the times of MD onset and recovery. Data were extracted by two independent authors, double-checked to ensure matching, and organized by whether or not the MD was a side effect of VPA use.

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

Definitions
The clinical characteristics and definitions of the MDs such as parkinsonism, tics, dyskinesia, dystonia, myoclonus, restless legs syndrome, akathisia, tremor, chorea, ataxia, and ballism were obtained from the reference Jankovic and Tolosa (2007). The clinical diagnosis for the psychiatric conditions was obtained from the Diagnostic and Statistical Manual of Mental Disorders (DSM-5®) (American Psychiatric Association, 2013). The Naranjo algorithm was used for determining the likelihood of whether an adverse drug reaction was actually due to the drug rather than the result of other factors (Naranjo et al., 1981). In the cases where the non-English literature was beyond the authors' proficiency (English, Portuguese, Spanish, Italian, French, and German) and the English abstract did not provide enough data, such as Japanese, Korean, Chinese, Russian, and Dutch, Google Translate service was used (De Vries et al., 2018).

Results

For the years 1975 to 2019, a total of 138 reports containing 362 cases, from thirty-three countries, of individuals who developed a movement disorder (MD) secondary to valproate (VPA) were reported (Table 2). Figure 4 shows the number of reports

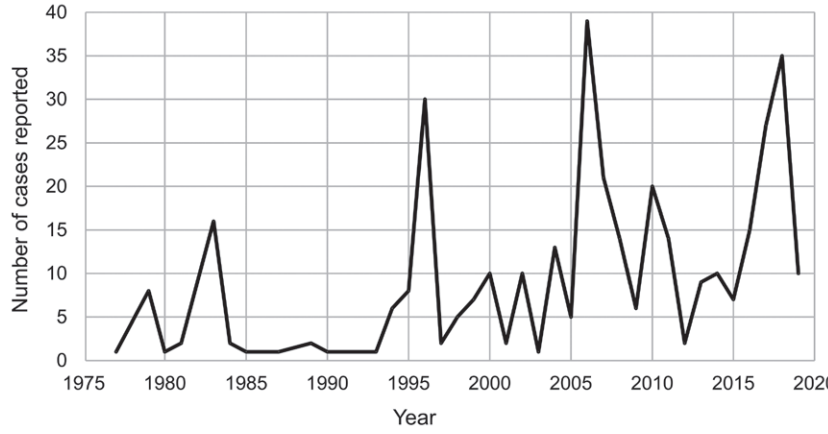

Figure 4 – Graphic showing the number of clinical reports of valproate (VPA)-associated movement disorders (MD) from 1975 to 2019.

Table 2 – Clinical reports of VPA-associated MD

Reference	Country/ year	No. of cases	Age (mean)/ sex	VPA				Follow-up	Important clinical history (CH) and clinical management (CM)
				indication	dose (mg)	MD onset	MD recovery		
MYOCLONUS									
Lance and Anthony	Australia 1977	1	adult/F	EPI	1200	months	NA	NA	
Nutt et al.	USA 1979	1	57/M	PD	1000–2000	33 days	NA	NA	CH: asterixis CM: drug withdrawal
Bodensteiner et al.	USA 1981	2	NA	EPI	NA	NA	NA	NA	
Campostrini et al.	Italy 1983	2	adult/ 1 M + 1 F	EPI	NA	NA	NA	NA	CH: hyperammonemia
Zaccara et al.	Italy 1984	2	19.5/ 1 M + 1 F	EPI	800 (mean)	2 weeks (mean)	4 days	CR	CH: asterixis, one cortical, other subcortical; apparently threshold-effect. CM: in one patient the MCL appeared after a dose increase. The dose was reduced but the symptoms persisted. VPA withdrawal with symptoms recovered
Gastaut and Mege	France 1985	1	adult/ NA	EPI	NA	NA	NA	NA	CH: hyperammonemia without hepatic insufficiency
Aguglia et al.	Italy 1995	6	39.83/ 3 F + 3 M	EPI	1200	1 week	2–6 days	CR	CH: cortical asterixis. CM: VPA withdrawal
Vogt and Mothersill	Switzerland 2000	3	43/3 F	EPI	NA	NA	NA	CR	CH: subcortical, EEG-based. Possible interaction with oxcarbazepine and lamotrigine. CM: drug withdrawal

Shirasaka and Mitsuyoshi	Japan 1999	1	10/F	EPI	NA	1 month	weeks	CR	CH: cortical asterixis; dose-dependent effect: dose increase caused an increase of MCL frequency: VPA withdrawal
Rottach et al.	Germany 2000	1	28/NA	BD	600	2 weeks	4 days	CR	CH: cortical asterixis, EEG-based. CM: VPA withdrawal
Kao et al.	Taiwan 2001	1	51/F	EPI	1500	2 weeks	< 1 week	CR	CH: subcortical asterixis; hyperammonemia; possible interaction with CBZ. CM: VPA withdrawal
Reif et al.	Germany 2004	1	42/M	DPS	2000	7 day	2 days	CR	CH: cortical MCL, EEG-based. CM: VPA withdrawal
Brefel-Courbon et al.	France 2006	20	NA	NA	NA	NA	NA	NA	
Dealberto and Sarazin	Canada 2008	1	41/F	mood	1000	1 year	2 days	CR	CH: cortical asterixis, EEG-based; hyperammonemia. CM: VPA withdrawal
Fan et al.	Taiwan 2008	1	72/F	mood	900	3 months	1 week	CR	CH: cortical asterixis, EEG-based; possible interaction with lamotrigine; hyperammonemia. CM: VPA withdrawal
Yoon et al.	Korea 2008	1	56.7/M	EPI	NA	NA	NA	NA	
Gardner et al.	USA 2009	1	66/F	mood	750	NA	NA	CR	CH: multifocal MCL. CM: VPA withdrawal
Mangewala et al.	USA 2013	1	17/M	EPI	1500	5 months	NA	no (only improve-ment	CH: asterixis; hyperammonemia. CM: VPA-dose decrease with partial improvement of the symptoms
Nayak et al.	India 2012	1	35/F	EPI	1000	2 weeks	< 6 weeks	CR	CH: subcortical asterixis; possible interaction with antipsychotics. CM: VPA withdrawal

Reference	Country/ year	No. of cases	Age (mean)/ sex	VPA				Follow-up	Important clinical history (CH) and clinical management (CM)
				indication	dose (mg)	MD onset	MD recovery		
Surendran et al.	India 2016	1	57/M	BD	1500–2000	7 years	3 weeks	CR	CH: cortical asterixis, EEG-based; hyperammonemia; possible interaction with risperidone. CM: VPA withdrawal
DYSTONIA									
Dick and Saunders	USA 1980	1	adult/M	DTN	600–1800	days–weeks	NA	NA	CH: worsening of cervical + axial DTN. CM: VPA withdrawal
Kiuru and Iivanainen	Finland 1987	1	23/F	EPI	1200–1500	months	1 week	CR	CH: axial DTN that occurred after a dose increase. Previous history of hepatopathy due to CBZ + VPA + lynestrenol interaction. CM: VPA-dose decreased with the resolution of the symptoms
Dunayevich and Strakowski	USA 1999	1	40/F	schizo-phrenia	1250	7 months	NA	no	CH: choreoathetotic DKN + (blepharospasm + oromandibular + cervical) DTN; possible interaction with olanzapine; previous history of blepharospasm with loxapine. CM: olanzapine-dose decrease and clozapine started with partial recovery
Oh et al.	Korea 2004	1	40/M	EPI	1200	days	1 week	CR	CH: spasmodic dysphonia. CM: VPA-dose reduction with the recovery of the symptoms
Teive et al.	Brazil 2004a	1	8/M	EPI	NA	NA	NA	NA	CH: VPA was present when the status DTN occurred

Werner et al.	Switzerland 2006	1	elderly/ NA	NA	NA	NA	NA	NA	CH: possible differential with DTN; dropped head syndrome was more severe in patients using VPA
Yohanan et al.	USA 2006	1	65/M	schizo-phrenia	1500	several months	weeks	CR	CH: axial DTN; possible interaction with CBZ + risperidone. CM: VPA withdrawal
Habermeyer et al.	Switzerland 2007	1	60/F	mood	900	4 days	NA	CR	CH: axial DTN (anterocollis). CM: VPA and quetiapine-dose decrease and biperiden started with symptoms recovery
Lee et al.	Korea 2007	1	64/F	EPI	600	days	NA	NA	CH: patient with probable Creutzfeldt-Jakob disease that worsened DTN and MCL when VPA was started
Zadikoff et al.	Canada 2007	2	47.5/ 1 F + 1 M	EPI	NA	NA	NA	NA	CH: one task specific DTN, other hemi-DTN
Czarnecki et al.	USA 2008	1	59/M	BD	NA	days	NA	no	CH: axial DTN (anterocollis) + PKN + AKT; possible interaction with risperidone + quetiapine. CM: all drugs withdrawal without improvement; he received the diagnosis of frontotemporal dementia
Duggal	USA 2008	1	20/M	schizo-phrenia	1000	3 days	1 day	CR	CH: axial DTN (laterocollis); possible interaction with ziprasidone. CM: benztropine was started with an improvement of the symptoms
Bayram et al.	Turkey 2013	1	4/F	EPI	NR	6 months	NA	CR	CH: cervical DTN; possible interaction with butamirate citrate

Reference	Country/ year	No. of cases	Age (mean)/ sex	VPA				Follow-up	Important clinical history (CH) and clinical management (CM)
				indication	dose (mg)	MD onset	MD recovery		
Faridhosseini et al.	Iran 2015	1	33/F	schizo-phrenia	1000	months	1 month	CR	CH: axial DTN; possible interaction with clozapine. CM: clozapine-dose reduced and biperiden started
Bermudez et al.	Brazil 2017	1	62/F	BD	1000	3 days	NA	CR	CH: trismus, possible oromandibular DTN. CM: biperiden and clonazepam were prescribed without response. VPA withdrawal with symptoms resolution
DYSKINESIA									
Friis et al.	Denmark 1983	3	32.33/1 F + 2 M	several	1400 (mean)	NA	NA	NA	CH: all the subjects had DKN associated with some degree of AKT
Lancman et al.	USA 1994	3	21/2 F + 1 M	EPI	1466 (mean)	4 years	NA	CR	CH: 2 individuals were in use of phenytoin, possible interaction. CM: cessation of VPA or the substitution to VPA sprinkles improved the symptoms
Gara and Roberts	Canada 2000	2	5.37/1 F + 1 M	EPI	1125	years	NA	CR	CH: orofacial DKN, but oromandibular DTN cannot be excluded; possible interaction with methylphenidate. CM: Pt1 VPA withdrawal; Pt2 methylphenidate replaced by clonidine
Gunal et al.	Turkey 2002	1	38/M	EPI	1500	2 months	2 months	CR	CH: choreiform DKN. CM: VPA withdrawal

Hall and Ringel	USA 2004	1	42/F	nonketotic hyper-glycinemia	NA	NA	NA	NA	CH: chorea in the presence of VPA after protein loading; the combination of chronic VPA administration and a meal high in protein could have contributed to the DKN
Morrison et al.	USA 2006	1	11/F	nonketotic hyper-glycinemia		NA	5 days	NA	CH: choreiform DKN. CM: VPA withdrawal
Srinivasan and Lok	Singapore 2010	1	53/M	EPI	1900	months	2 days	CR	CH: hemichoreiform DKN; the MD occurred after one week of VPA-dose in a dose higher than the prescribed. CM: VPA withdrawal; after VPA rechallenge without the occurrence of new symptoms
van de Velde et al.	Belgium 2011	1	80/F	migraine	1200	4 years	days-weeks, < 6 months	CR	CH: choreiform DKN, weeks after the VPA-dose increase. CM: VPA withdrawal and haloperidol started
Yilmaz et al.	Turkey 2013	1	7/M	EPI	500	NA	NA	CR	CH: orofacial DKN after 2 days in the use of methylphenidate + VPA
Giordano et al.	Italy 2014	1	53/F	EPI	900	days	1 week	CR	CH: choreiform DKN + axial DTN. CM: VPA withdrawal
Bruno et al.	UK 2016	1	36/M	EPI	1000	single IV	1 week	CR	CH: choreiform DKN + multifocal MCL. CM: VPA withdrawal
					STUTTER				
Bowdle et al.	USA 1979	2	22/NA	none	1000–1500	days–weeks	NA	NA	CH: the adverse effects started appearing at 1,000 mg. The speaking was characterized as stammering

Reference	Country/ year	No. of cases	Age (mean)/ sex	VPA				Follow-up	Important clinical history (CH) and clinical management (CM)
				indication	dose (mg)	MD onset	MD recovery		
Mukherjee et al.	India 2015	1	56/M	BD	1500	1 week	< 1 week	CR	CH: his articulation, intensity, timings of utterance, rhythm were affected. CM: VPA withdrawal; VPA rechallenge caused symptoms reappearance
AKATHISIA									
Clos	Scotland 2001	1	38/F	BD	1200	1 month	NA	no	CH: possible interaction with lithium. CM: VPA withdrawal with partial improvement of the symptoms
TIC									
Alonso-Navarro et al.	Spain 2007	1	14/M	EPI	1500	1 day	NA	CR	CH: motor + phonic tics. CM: ziprasidone started with the improvement of the symptoms
Zadikoff et al.	Canada 2007	1	47/M	EPI	NA	NA	NA	NA	CH: excessive eye blinking
Thome-Souza et al.	Brazil 2012	1	18/F	EPI	1000	1.2 years	NA	CR	CH: motor tics; possible interaction with lamotrigine. CM: lamotrigine and VPA-dose decrease with symptoms improvement
PARKINSONISM									
Lautin et al.	USA 1979	1	52/M	schizo-phrenia	1000	4 days	2 days	CR	CH: he had a history of metoclopramide and haloperidol developing PKN. CM: benztropine and trihexyphenidyl started with symptoms permanence. VPA was withdrawal

Nutt et al.	USA 1979	4	56.6/2 F + 2 M	PD	2000	28 days	NA	NA	CH: the four patients developed worsening of PKN features. Two developed MCL. CM: drug withdrawal; after the study, the doses of these subjects affected needed to be significantly increased
Friis et al.	Denmark 1983	11	37/1 F + 10 M	several	1700	NA	NA	NA	CH: all the subjects had some level of AKT associated to the PKN. 5 subjects had PKN + DKN
van der Zwan	Australia 1989	2	adult/NA	EPI	NA	NA	NA	CR	
Power et al.	Canada 1990	1	adult/NA	EPI	NA	NA	NA	NA	
Alvarez-Gomez et al.	Spain 1993	1	12/F	EPI	600	7 days	1 month	CR	CM: VPA replaced by CBZ with symptoms resolution
Froomes and Stewart	Australia 1994	1	67/F	EPI	1400	months	3 days	CR	CH: possible interaction with CBZ. CM: CBZ withdrawal with symptoms resolution
Sasso et al.	Italy 1994	2	23/2 M	EPI	1250	16 months	5 weeks	CR	CM: VPA maintenance and symptoms improved over time
del Real Francia et al.	Spain 1995	2	70.5/2 F	NA	1500	years	weeks	CR	CM: VPA withdrawal
Armon et al.	USA 1996	27	51.5/NA	EPI	1400	44.8 months	< 3 months	CR (96%)	CM: VPA withdrawal
Gwinn and Caviness	USA 1997	1	69/M	BD	500	11 months	NA	no	CH: PKN + orofacial DKN; possible interaction with risperidone. CM: drug withdrawal with the permanence of DKN

Reference	Country/ year	No. of cases	Age (mean)/ sex	VPA				Follow-up	Important clinical history (CH) and clinical management (CM)
				indication	dose (mg)	MD onset	MD recovery		
Onofrj et al.	Italy 1998	2	65.5/1 F + 1 M	EPI	1150	6.5 years	< 3 months	CR	CH: in one of the patients a dose increase was reported 6 months before the MD onset; patients assessed by Unified Parkinson's Disease Rating Scale; possible interaction with CBZ
Park-Matsumoto and Tazawa	Japan 1998	3	73/2 F + 1 M	EPI	800	21 months	4.3 months	CR	
Conforti et al.	Italy 1999	1	69/F	BD	1200	< 3 months	days–weeks	CR	CH: possible interaction with nortriptyline + venlafaxine. The PKN started with the added of nortriptyline. CM: nortriptyline-dose reduce improved the symptoms
Lapierre et al.	Canada 1999	1	62/F	BD	1400	days–weeks	4 days	CR	CH: possible PKN marked stiffness and motor slowness. CM: VPA-dose reduced with a full recovery
Nouzeilles et al.	Argentina 1999	3	60.33/NA	EPI	1259	NA	NA	NA	
Kim et al.	Korea 2000	1	69/F	EPI	1200	2 months	< 1 month	CR	
Masmoudi et al.	France 2000	5	64/2 F + 3 M	EPI	1400	6 months–10 years	weeks–months	CR	CH: dementia characterized by an insidious onset was associated in three cases and bradypsychia in one case. CM: VPA withdrawal
Shill and Fife	USA 2000	1	67/F	EPI	NA	2 years	3 months	CR	CH: multiple system atrophy-like syndrome. CM: VPA withdrawal

Barroso	France 2002	1	72/NA	NA	NA	NA	NA	NA	
Foley et al.	USA 2002	6	70/6 M	3 EPI + 3 BD	1166.7	21.3 months	NA	CR	CH: gait abnormality was the most common presenting symptom
Iijima	Japan 2002	1	77/M	behavior control	300	1 week	NA	CR	CM: VPA withdrawal
Raja and Azzoni	Italy 2002	1	38/NA	NA	NA	NA	NA	CR	CH: possible PKN and interaction with quetiapine
Reif et al.	Germany 2003	1	62/F	mood	1200	10 days	7 days	CR	CH: possible interaction with lithium; hyperammonemia. CM: VPA and lithium withdrawal; amantadine started
Easterford et al.	UK 2004	5	60.2/4 M + 1 F	EPI	1220	> 1 year	NA	CR (2/5)	CH: normal β-CIT-SPECT. CM: VPA withdrawal
Ferrari et al.	Italy 2004	3	52.66/3 M	EPI	1250	4.6 year	NA	CR	CH: one of the patients had PKN after IV VPA; dose-unrelated side effect
Lee	Korea 2004	1	61/M	BD	1500	days–weeks	< 7 days	CR	CM: PKN partially relieved by the coadministration of anticholinergic agents and disappeared after discontinuation of VPA
Dergalust et al.	USA 2005	1	adult/NA	NA	NA	NA	NA	NA	
Macphee	Scotland 2005	1	73/M	mood	1500	3 months	3 months	CR	CH: FP-CIT SPECT scan was normal. CM: VPA withdrawal
Ricard et al.	France 2005	1	58/M	BD	1000	7 months	1 month	CR	CH: PKN + cognitive impairment + hyperammonemia. CM: VPA withdrawal
Thygesen and Wolf	Denmark 2005	2	64/1 F + 1 M	EPI	1400	10 months	weeks	CR	CH: PKN + cognitive impairment. CM: VPA withdrawal
Gaubert et al.	France 2006	1	82/M	EPI	2000	17 months	3 weeks	CR	CM: VPA withdrawal

Reference	Country/ year	No. of cases	Age (mean)/ sex	VPA				Follow-up	Important clinical history (CH) and clinical management (CM)
				indication	dose (mg)	MD onset	MD recovery		
Ristić et al.	Serbia 2006	5	59.9/4 F + 1 M	EPI	1100	12.9 months	NA	no (only improvement)	CH: early identification of PKN and discontinuation of the drug led to complete recovery in affected patients
Borroni et al.	Italy 2007	1	61/F	EPI	1200	10 years	NA	no (only improvement)	CH: multiple system atrophy-like syndrome. CM: VPA withdrawal
Hommet et al.	France 2007	1	81/M	EPI	500	2 months	3 months	CR	CH: possible PKN. CM: VPA-dose decrease without improvement; VPA withdrawal with full recovery
Jamora et al.	USA 2007	6	42.16/4 F + 2 M	EPI	750	76.16 months	NA	no (only improvement)	
Macphee and Stewart	Scotland 2007	1	67/F	EPI	600	10 years	NA	no (only improvement)	CH: FP-CIT SPECT scan was normal. CM: VPA withdrawal
Zadikoff et al.	Canada 2007	6	44.5/4 F + 2 M	EPI	1425	7.33 years	NA	NA	
Aguilar and Ondo	USA 2008	4	63.2/NA	NA	NA	71.4 months	NA	NA	
Maximov and Maximov	Bulgaria 2008	1	75/M	EPI	2000	NA	NA	No	CM: levodopa was started with improvement of the symptoms
Salazar et al.	Argentina 2008	1	67/M	mood	1000	days	2 months	CR	CH: PKN + axial DTN (laterocollis); a history of Huntington's disease. CM: VPA withdrawal

Sechi et al.	Italy 2008	1	39/F	palatal MCL	1000	3 months	1 month	CR	CH: a history of Alexander's disease. CM: VPA withdrawal
Toribio-Díaz et al.	Spain 2008	1	78/F	EPI	1500	2 months	2 months	CR	CH: PKN + cognitive impairment. CM: VPA withdrawal
Abreu et al.	Brazil 2009	1	47/F	BD	2500	7 months	NA	no (only improve-ment)	CH: PKN + cognitive impairment. CM: VPA withdrawal
Lidbom et al.	Sweden 2009	1	72/F	mood	1400	11 years	NA	NA	CH: PKN + cognitive impairment. CM: VPA withdrawal
Louter and Tromp	Netherlands 2009	1	57/F	NA	NA	NA	NA	NA	
Schreur et al.	Netherlands 2009	2	70/2 M	EPI	850	2.5 years	NA	CR	CH: PKN + cognitive impairment. CM: VPA withdrawal
Andrade et al.	Cuba 2010	1	52/F	EPI	1140	2 months	2 months	CR	CH: PKN + cognitive impairment. CM: VPA withdrawal
Khwaja et al.	India 2010	1	26/F	EPI	1000	2 years	3 months	CR	CH: progressive supranuclear palsy-like syndrome. CM: VPA withdrawal
Lyell et al.	UK 2010	2	76/NA	NA	NA	NA	NA	NA	
Munhoz et al.	Brazil 2010	13	67.6/NA	NA	NA	NA	NA	NA	
Penot and Pradeau	France 2010	1	75/F	EPI	1000	1 week	2 months	CR	CH: possible PKN + axial DTN and interaction with aspirin. CM: VPA-diose decrease with the improvement of the symptoms
Sleegers et al.	Netherlands 2010	1	70/F	EPI	1000	months	5 weeks	CR	CH: PKN + cognitive impairment; a history of systemic lupus erythematous. CM: VPA withdrawal
Bondon-Guitton et al.	France 2011	10	NA	NA	NA	NA	NA	NA	

Reference	Country/ year	No. of cases	Age (mean)/ sex	VPA				Follow-up	Important clinical history (CH) and clinical management (CM)
				indication	dose (mg)	MD onset	MD recovery		
Evans et al.	USA 2011	1	65/F	EPI	1000	13 years	NA	no (only improvement)	CH: PKN + cognitive impairment; normal pressure hydrocephalus-like presentation. CM: VPA withdrawal
Sarna and Pringsheim	Canada 2011	1	63/F	BD	NA	1–2 years	NA	no (only improvement)	CH: progressive supranuclear palsy-like syndrome. CM: VPA withdrawal
Gosala Raja Kukkuta et al.	India 2013	1	56/M	EPI	800	6 months	4 days	CR	CH: progressive supranuclear palsy-like syndrome; hyperammonemia. CM: VPA withdrawal
Silver and Factor	USA 2013	5	63/3 F + 2 M	2 DPS + 1 MCL + 1 BD + 1 EPI	1000	1.81 months	9 months	CR (3/5)	CH: PKN + cognitive impairment (3/5). CM: VPA withdrawal
Athauda et al.	UK 2015	1	65/M	EPI	3000	8 years	NA	no (only improvement)	CH: due to continuous PKN signs after management a DaTSCAN was performed which showed abnormal uptake and he received the diagnosis of idiopathic PD. CM: VPA withdrawal
Jopowicz and Kurkowska-Jastrzebska	Poland 2014	1	76/M	EPI	1000	3 months	NA	no (only improvement)	CM: VPA-dose reduce with the improvement of the symptoms
Prakash et al.	Denmark 2015	1	76/F	EPI	1200	years	NA	no (only improvement)	CH: PKN + cognitive impairment. CM: VPA withdrawal
Desai and Desai	India 2015	3	NA	NA	NA	NA	NA	NA	

Hassamal et al.	USA 2016	1	71/F	BD	1250	8 years	12 months	CR	CH: PKN + cognitive impairment. CM: VPA withdrawal
Irons et al.	UK 2015	1	87/M	NA	NA	NA	NA	no (only improvement)	CH: multiple system atrophy-like syndrome; DaTSCAN positive. CM: VPA withdrawal
Bhattacharjee et al.	UK 2016	1	54/M	BD	NA	NA	NA	no (only improvement)	CH: PKN that persisted after management; DaTSCAN positive. CM: VPA withdrawal
Botturi et al.	Italy 2016	1	59/M	EPI	900	3 months	3 months	CR	CH: axial DTN + PKN; hyperammonemia. CM: VPA withdrawal
Simões et al.	Portugal 2016	8	72/6 M + 2 F	6 EPI + 2 psychitric condition	1379	4 months	8 months	CR	CM: VPA withdrawal
Tada et al.	Japan 2017	1	75/F	BD	1000	6 months	NA	no (only improvement)	CH: PKN + cognitive impairment. CM: VPA withdrawal
Bhattacharjee et al.	UK 2017	24	68/NA	NA	NA	NA	NA	NA	assessment of the DAT-SPECT scans conducted for the diagnosis of drug-induced versus idiopathic PKN
Caruana Galizia et al.	UK 2017	1	60/F	EPI	1700	20 years	2 weeks	CR	CH: PKN + cognitive impairment; symptoms occurred after the withdrawal of phenytoin, so possible interaction cannot be ruled out. CM: VPA withdrawal

Reference	Country/ year	No. of cases	Age (mean)/ sex	VPA				Follow-up	Important clinical history (CH) and clinical management (CM)
				indication	dose (mg)	MD onset	MD recovery		
Aykut et al.	Turkey 2018	1	72/M	BD	2500	10 years	6 days	CR	CH: PKN + axial DTN. CM: VPA withdrawal
Kim et al.	Korea 2018	1	69/F	EPI	1200	3 years	1 week	CR	CH: 18F-FP-CITPET was normal. CM: VPA withdrawal
Patel et al.	India 2018	1	58/M	EPI	500	7 years	NR	CR	CM: VPA withdrawal
Yomtoob et al.	USA 2018	17	64.54/10 F + 7 M	NA	NA	4.3 years	NA	NA	
Baizabal-Carvallo and Alonso-Juarez	Mexico 2021	2	35.9/NA	EPI	1365	NA	NA	NA	
Bennet and Rosen	USA 2019	2	71/2 F	1 BD + 1 DPS	NA	6 months	NA	CR	CH: PKN + cognitive impairment. CM: VPA withdrawal
Dal and Whyte	Australia 2019	2	77.5/2 M	EPI	1200	2.5 years	NA	no (only improvement)	CH: PKN, after withdrawal the patients did not have recover; levodopa was started and the PKN alleviated. CM: VPA withdrawal
Davoudi-Monfared et al.	Iran 2019	1	54/M	mood	1500	NA	weeks	CR	CH: possible PKN + cognitive impairment. CM: VPA withdrawal
Randhawa and Mehanna	USA 2019	1	NA	BD	NA	3 months	NA	no (only improvement)	CH: possible interaction with risperidone; normal DAT-SPECT scan even after the permanence of PKN symptoms
Kohlhase et al.	Germany 2019	2	61/2 M	EPI	1525	years	NA	CR	CH: PKN; 1 hyperammonemia; normal DAT-SPECT scan. CM: VPA withdrawal

CASES NOT CLEARLY DEFINED				
Leclair-Visonneau et al.	France 2016	NA	PKN	Assessment of the efficacy of VPA in progressive supranuclear palsy. The progressive supranuclear palsy rating scale at 12 months was significantly higher in the VPA than in the placebo group but was similar between the two groups at 24 months. According to the authors' this strongly suggests poor tolerability due to side effects than permanent neurological damage.
Wang et al.	Germany 2016	NA	EPS, DTN, AKT, rigidity	Assessment of the efficacy of VPA in schizophrenia. The studies compared VPA + antipsychotic to antipsychotic; none of the adverse effects were significant. They encountered AKT (3/186, RR 1.06 [0.36, 3.06]); ataxia (2/115, RR 2.42 [0.37, 15.92]); DTN (2/130, RR 1.00 [0.30, 3.37]); rigidity (1/33, RR 2.83 [0.12, 64.89]); unstable gait (1/19, RR 0.27 [0.02, 3.39]). Interesting, the VPA was associated with a significant decrease of DKN of –3.31 (–4.91, –1.71).
Makhlouf et al.	Tunisia 2018	15	EPS	Assessment of the incidence of VPA side effects in a Tunisian population. 15 subjects complained of slowness of execution of movements, and EPS was observed in every one of these subjects.

AKT – akathisia; BD – bipolar disorder; CBZ – carbamazepine; CH – clinical history; CM – clinical management; CR – complete recovery; DKN – dyskinesia; DPS – depression; DTN – dystonia; EEG – electroencephalogram; EPI – epilepsy; EPS – extrapyramidal symptoms; F – female; M – male; MCL – myoclonus; MD – movement disorder; NA – not applicable/not available; PKN – parkinsonism; PD – Parkinson's disease; RR – risk ratio; SPECT – single-photon emission computed tomography; VPA – valproic acid/valproate

Table 3 – Resume of VPA-associated MD

MD		PKN	MCL	DTN	DKN	Stutter	Tic	AKT	Others	General data
Cases (%)		252 (69.61)	54 (14.91)	17 (4.69)	16 (4.41)	4 (1.10)	3 (0.82)	1 (0.27)	15 (4.14)	362
Continent (%)	Africa	0	0	0	0	0	0	0	15 (100)	15
	Australia	0	1 (1.85)	0	0	0	0	0	0	1
	Asia	17 (6.74)	6 (11.11)	4 (23.52)	3 (18.75)	1 (25.00)	0	0	0	31
	Europe	122 (48.41)	36 (66.66)	3 (17.64)	6 (37.50)	1 (25.00)	1 (33.33)	1 (100)	0	170
	N. America	90 (35.71)	11 (20.37)	8 (47.05)	7 (43.75)	2 (50.00)	1 (33.33)	0	0	119
	S. America	23 (9.12)	0	2 (11.76)	0	0	1 (33.33)	0	0	26
Sex (%)	Female	74 (29.36)	15 (27.77)	8 (47.05)	8 (50.00)	0	1 (33.33)	1 (100)		107
	Male	83 (32.93)	10 (18.51)	8 (47.05)	8 (50.00)	2 (50.00)	2 (66.66)	0		113
	Unknown	95 (37.69)	29 (53.70)	1 (5.88)	0	2 (50.00)	0	0		142
Age (y)	Range	12–87	10–72	4–65	5.37–80	22–56	14–47	38		4–87
Mean	60.87	40.85	40.26	30.67	36.25	26.33	38		55.88 (SD: 16.58) Mn: 32.75 mo (SD: 30.05) Mn: 2.89 mo (SD: 2.79)	(Md: 61)
VPA-dose (Mn mg)		1315	1223	1113	1274	1150	1250	1200		1296 (SD 365; Rg 300–3000; Md 1379)
*VPA-indication		EPI (123/172)	EPI (27/34)	EPI (5/14)	EPI (10/18)	BD (1/4)	EPI (3/3)	BD (1/1)		EPI (170/246)
MD onset	Range	4 d – 20 y	7 d – 7 y	3 d – 7 mo	1 d – 4 y	4 d – wks	1 d – 1.2 y	1 mo		1 d – 20 y
Mean (y)	3.38	0.49	0.23	2.21	0.02	0.60	1 mo			(Md: 21.15 mo)
MD recovery	Range	2 d – 12 mo	2 d – 6 wk	1 d – 1 mo	2 d – 2 mo	3 d – 1 wk	NA	NA		1 d – 12 mo
Mean (mo)	3.41	0.33	0.40	0.95	0.16	NA	NA			(Md: 3 mo)
Follow-up – % CR (number of reports)		77.02% (114/148)	95.23% (20/21)	81.81% (9/11)	100% (11/11)	100% (2/2)	100% (2/2)	0% (0/1)		80.61% (158/196)

AKT – akathisia; BD – bipolar disorder; CR – complete recovery; d – day; DKN – dyskinesia; DTN – dystonia; EPI – epilepsy; MCL – myoclonus; MD – movement disorder; Md – median; Mn – mean; mo – month; NA – not available/not applicable; PKN – parkinsonism; SD – standard deviation; Rg – range (minimum–maximum); VPA – valproic acid/valproate; y – year; wk – week; in the "Others" subgroup are cases not specified about the movement disorder such as extrapyramidal symptoms; *main VPA-indication (no/total)

of VPA-associated MD over time. There were 170 reports from Europe, 119 North American, 31 Asian, 26 South American, 15 African, and 1 Australian. The MDs identified were parkinsonism, with 252 cases, 54 cases of myoclonus, 17 of dystonia (DTN), 16 of dyskinesia, 4 of stutters, 3 of tics, and 1 of akathisia (AKT). In the "not clearly defined group", 15 cases of extrapyramidal symptoms, 3 of AKT, 2 of DTN, 1 of rigidity, and 1 of unstable gait were assessed.

The summary data about VPA-associated MD is provided in Table 3. Herein, we will describe the general data of all clearly defined cases.

The abnormal movements occurred in males in 51.36% of the cases. The mean and median age was 55.8 (SD: 16.58) and 61 years (age range: 4–87 years). The indication of VPA in descending order of frequency was epilepsy 69.10% (170/246), bipolar disorder (25), "mood related" (12), DKN (dyskinesia) in Parkinson's disease (5), schizophrenia (5), depression (4), myoclonus (MCL) (2), DTN (1), migraine (1), twitch eyelids (1), and others non-specified psychiatric conditions (20).

The mean and median time from starting VPA use to the MD onset was 32.75 (SD: 30.05) and 21.15 months (MD onset time range: 1 day – 20 years), respectively. About 75% of the individual had abnormal movement within 50 months of the VPA treatment. The mean and median time from the VPA withdrawal until the MD recovery was 2.89 (SD: 2.79) and 3 months (MD recovery time range: 1 day – 12 months), respectively. In the subgroup of subjects that had improvement of the symptoms, the complete recovery was achieved within 9 months of the drug withdrawal in almost all cases (99%). Figure 5 shows a comparison between the percentage of patients who developed a MD since the beginning of the treatment and the percentage of patients recovering after drug withdrawal when outliers were removed.

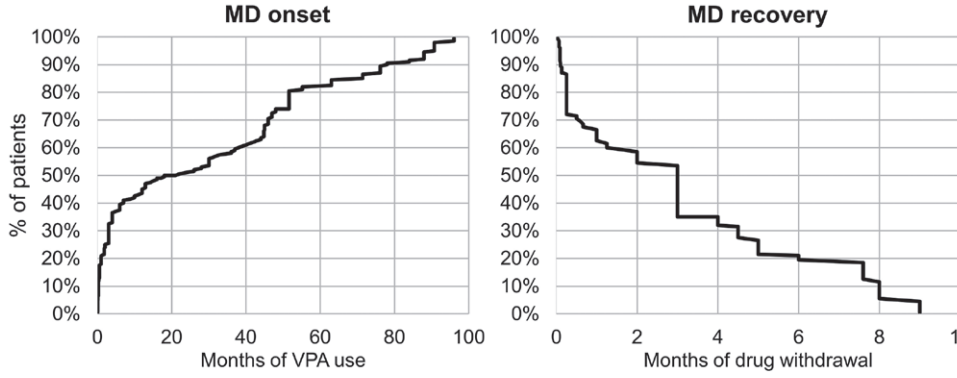

Figure 5 – Comparison between the percentage of patients developing movement disorders (MD) since the beginning of the drug treatment and the percentage of patients recovering after drug withdrawal.

The most common management was drug withdrawal. Other options were the VPA-dose reduction, replacement of the drug probably interacting with VPA, and the prescription of other drugs after the VPA discontinuation, such as levodopa, benztropine, benzodiazepines, biperiden, haloperidol, and diphenhydramine. In addition, the replacement of VPA in tablet form for the same dosage in sprinkles presentation was sufficient to improve the symptoms in one case. A complete recovery was observed in 80.61% of the patients (158/196).

Discussion

General

VPA-associated MD was widely reported in the literature. We believe that the availability, costs, and some historical factors of VPA probably had contributed to this. VPA is among the safest and most effective medicines needed in a health system, as attested by the World Health Organization's List of Essential Medicines, and it is marketed in the majority of countries. Also, VPA was the 126th most prescribed medication in the USA with almost six million prescriptions in 2017 (ClinCalc, 2020). Furthermore, the well-known description of flunarizine and cinnarizine developing PKN in 1984, promoted the awareness of the drug-induced MD resulting in an increasing number of reports about all abnormal movements secondary to medications including those associated with VPA (Teive et al., 2004b).

Based on the data available in Table 2, we can hypothetically illustrate a case. A middle-aged European male with poorly controlled epilepsy resorts to his neurologist. VPA 250 mg with a gradual increase until five-six tablets a day was prescribed. Within three years, the patient started complaining of stiffness, rigidity, and resting tremor; neurological examination revealed bradykinesia, and a diagnosis of PKN secondary to VPA was done. VPA was established and lamotrigine or carbamazepine was started. In the follow-up after three months, the patient had a full recovery and was able to walk without assistance and the tremor disappeared.

The majority of the incidences of abnormal movements associated with VPA are not well described in the literature. Table 3 is a summary of the percentages of some abnormal movements secondary to VPA (Anthony, 1977; Bowdle et al., 1979; Friis et al., 1983; Zaccara et al., 1984; van der Zwan, 1989; Armon et al., 1996; Nouzeilles et al., 1999; Easterford et al., 2004; Ristić et al., 2006; Jamora et al., 2007; Zadikoff et al., 2007; Lance and; Leclair-Visonneau et al., 2016; Makhlouf et al., 2018; Baizabal-Carvallo and Alonso-Juarez, 2021); the data was extracted from the clinical trials and population-based studies that provide sufficient data for Table 2. The incidences of VPA-associated abnormal movements extensively vary throughout the literature. For example, VPA-induced PKN was observed from 1.37 to 75% of the individuals.

Herein, we would like to discuss some of the MDs in subtopics to allow a better comprehension of the data.

Parkinsonism (PKN)

History

In 1979, Lautin et al. reported the first case of VPA-induced PKN. They described a middle-aged male who was prescribed VPA 1,000 mg for schizophrenia; four days later, the patient complained of PKN symptoms. Benztropine and trihexyphenidyl were started, but the symptoms did not alleviate. Only when VPA was withdrawn the patient had a full recovery. Also, the individual had a previous history of PKN secondary to metoclopramide and haloperidol. Therefore, we believe that this has contributed significantly to the literature because a similar presentation of VPA and antidopaminergic drugs in the same individual suggested a common neuronal pathway associated with extrapyramidal symptoms of these two drug classes.
It is worth mentioning that in the same year Nutt et al. (1979) published the cases of four individuals with Parkinson's disease with worsening gait and resting tremors that were using VPA.

Epidemiology

The incidence of PKN following VPA use found in the literature was 1.37, 1.60, 2.27, 5.04, 6.00, 10.16, 10.71, 73.33, and 75.00% (Table 4). The majority of the individuals reported were males, the mean age was 60.87 years, the mean VPA-dose was 1,315 mg. The time since starting VPA until MD onset, and the time until resolution after VPA discontinuation were 3.38 years and 3.41 months, respectively. When we compare the present study with the Brugger et al. (2016); the main differences encountered are that the present work has assessed a greater number of patients (252 vs. 116), of which the majority was male (52.86% vs. 41.4%); interestingly, the findings of Brugger et al. (2016) for mean age (63.5 years), VPA main indication (epilepsy) and median VPA dose (1,250 mg) were almost identical to those already described in this revision.

Presentation and clinical diagnosis

The presentation in the majority of the cases was a symmetric akinetic-rigid syndrome, with predominant postural/action over the resting tremor. Sometimes signs and symptoms of cognitive impairment were observed. The severity of the clinical presentation ranged from mild to severe with loss of physical independence. Some patients had pre-existing diseases other than the indication for VPA prescription such as Parkinson's disease, multiple system atrophy, progressive supranuclear palsy, Huntington's disease, systemic lupus erythematosus, and some brain damage. Interestingly, multiple system atrophy-like and progressive supranuclear palsy-like syndromes were reported as the presenting symptoms.
A clear distinction between VPA-induced MD and idiopathic Parkinson's disease based only on clinical criteria is challenging in clinical practice. Therefore, we proposed some clinical tools to help with the diagnosis of this syndrome (Table 5).

Table 4 – Incidence of some abnormal movements associated with VPA in the literature

MD	Reference	Year	NR	N	Incidence (%)	Studied disease
MCL	Lance and Anthony	1977	1	60	1.66	EPI
Ataxia	Lance and Anthony	1977	1	60	1.66	EPI
Tremor	Lance and Anthony	1977	2	60	3.33	EPI
Stutter	Bowdle et al.	1979	2	6	33.33	healthy
AKT	Friis et al.	1983	15	15	100.00	several
PKN	Friis et al.	1983	11	15	73.33	several
DKN	Friis et al.	1983	8	15	53.33	several
MCL	Zaccara et al.	1984	2	38	5.26	EPI
PKN	van der Zwan	1989	2	88	2.27	EPI
PKN	Armon et al.	1996	27	36	75.00	EPI
Tremor	Armon et al.	1996	16	36	44.44	EPI
Bradykinesia	Armon et al.	1996	22	35	62.85	EPI
PKN	Nouzeilles et al.	1999	3	28	10.71	EPI
Intentional tremor	Nouzeilles et al.	1999	15	28	53.57	EPI
Postural tremor	Nouzeilles et al.	1999	16	28	57.14	EPI
PKN	Easterford et al.	2004	3	50	6.00	EPI
Tremor	Easterford et al.	2004	11	50	22.00	EPI
PKN	Ristić et al.	2006	5	364	1.37	EPI
Tremor	Ristić et al.	2006	28	364	7.69	EPI
Ataxia	Ristić et al.	2006	7	364	1.92	EPI
PKN	Jamora et al.	2007	6	119	5.04	EPI
PKN	Zadikoff et al.	2007	6	59	10.16	EPI
Postural/ action tremor	Zadikoff et al.	2007	6	59	10.16	EPI
DTN	Zadikoff et al.	2007	2	59	3.38	EPI
Tic	Zadikoff et al.	2007	1	59	1.69	EPI
Worsening of the gait	Leclair-Visonneau et al.	2016	3	28	10.71	PSP
Movements slowness	Makhlouf et al.	2018	15	74	20.27	EPI
PKN	Baizabal-Carvallo and Alonso-Juarez	2021	2	125	1.60	EPI/migraine

AKT – akathisia; DKN – dyskinesia; DTN – dystonia; EPI – epilepsy; MCL – myoclonus; MD – movement disorder; N – number of individuals in the study using VPA; NR – number of reports with the movement disorder; PKN – parkinsonism; PSP – progressive supranuclear palsy; VPA – valproic acid/valproate

Table 5 – Clinical tools for the diagnosis of VPA-induced PKN

1) History of VPA use
2) PKN after therapy with VPA use (at least two of the following symptoms: bradykinesia, rigidity, and postural instability)
3) Usually, symmetrical PKN with prominent action/postural over resting tremor
4) More commonly affects elderly individuals
5) Recovery with VPA withdrawal
6) Other possible causes of PKN excluded

PKN – parkinsonism; VPA – valproic acid/valproate

Pathophysiological mechanism

In the literature, we found five possible pathophysiological mechanisms to explains the VPA-induced PKN (Figure 6) (Brugger et al., 2016). First, the VPA can increase the concentration of GABA (Löscher, 2002), which inhibits the globus pallidus connections with the thalamus, decreasing activity of the direct pathway. Second, another effect of VPA is the inhibition of the histone deacetylase that may increase the expression of some genes and decrease others such as those involved in the synaptic transmission (Löscher, 2002), which was already suggested in cell studies. Third, most affected individuals were elderly, so they may already have an imbalance of dopaminergic and cholinergic activity, and when VPA is used, a decrease in dopamine occurs, favoring the indirect pathway (Sawle et al., 1990). Fourth, VPA can, in a normal concentration of neurotransmitters (balanced state), affect mitochondrial enzymes causing cellular energy deficiency, what increases the

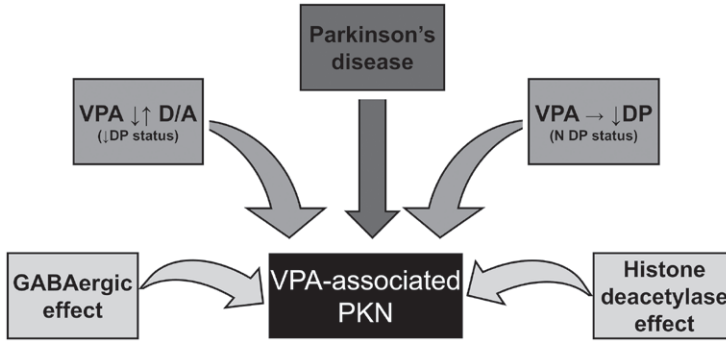

Figure 6 – Schematic diagram of the possible pathophysiological mechanisms to explains the valproate (VPA)-induced parkinsonism (PKN). The first pier represented by the GABAergic and histone deacetylase effects, which are directly related to the mechanism of action of valproate (VPA). The second pier is dependent on the dopamine (DP) status of the patient that could be decreased (↓) or normal (N), in which the presence of VPA can causes a disbalance (↓↑) of dopaminergic and cholinergic activity (D/A). The third pier is those individuals with coexisting Parkinson's disease.

likelihood of an oxidative stress and consequently a neurodegenerative process, especially in the dopaminergic system (Löscher, 2002); a supporting fact for this theory is that individuals with particular mitochondrial lesions are more susceptible to the development of side effects related to VPA (Henry, 2003). Fifth, the diagnosis of Parkinson's disease in a significant percentage of the patients cannot be ruled out; as a result, perhaps the use of VPA was only by chance present in these individuals, who may develop uncorrelated Parkinson's disease.

Management

The most commonly reported management was the VPA discontinuation, adopted in more than seventy-five percent of the individuals. In some cases, dopamine precursors were attempted to manage and a partial improvement of the PKN symptoms was achieved; in the follow-up, levodopa showed to be effective and reduced the recovery time, but apparently these cases were after diagnosed with Parkinson's disease. One individual received bromocriptine, but no details were provided regarding treatment response. The VPA-induced PKN had the second-worst prognosis, full recovery was obtained in 77.02% of the subjects; about 10% of subjects only had partial improvement of the symptoms, with permanence of at least one symptom even after the last follow-up.

Myoclonus (MCL)

MCL was the first VPA-associated MD identified and was the second most commonly reported in the literature. The incidence of MCL related to VPA use found in the literature was 1.66–5.26% (Table 4). MCL-individuals were approximately twenty years younger than those affected by PKN, also, the VPA dose was lower, and MD onset and recovery happened sooner than in general data. The majority of the subjects involved were female (3:2). The presentation was asterixis and multifocal MCL. The MCL source was cortical and subcortical. It is worth mentioning that an important percentage of the cases only describe the neurological examination, giving the diagnosis without providing the findings of the electrodiagnostic studies. The management was drug withdrawal or the reduction of VPA-dose.

A feature reported in an important percentage of the patients, and possibly related to the mechanism of VPA-induced MCL, is the high serum concentrations of ammonia, with no sign of liver failure described in the eight individuals assessed. Therefore, some authors believe that the explanation for MCL in the group of hyperammonemic individuals is the decrease of inhibitory neurotransmitters caused by ammonia, turning the individuals more susceptible to the development of MCL (Campostrini et al., 1983; Gastaut and Mege, 1985). On the other hand, the possibility that the ammonia levels found in these cases may be incidental cannot be excluded, as clinical trials with VPA already reported higher levels of this compound in individuals without any complaint (Löscher, 2002; Bowden, 2003). Also, this

hypothesis can support the idea that perhaps VPA action on the central nervous system may lead to the development of MCL. Moreover, we hypothesized that the mechanism behind VPA-induced MCL is probably related to VPA interaction with serotonin. In rat models, VPA caused both increase and decrease in serotonin concentration, depending on the site of action (Baf et al., 1994).

Dystonia (DTN)

In the DTN group, the data obtained for doses and times until onset and recovery from MD are comparable to general data on drug-induced DTN found in literature. Dick and Saunders (1980) probably described the first case of VPA-associated DTN. They reported the case of an individual with cervical and axial DTN that they attempted to treat with VPA, and the DTN-symptoms worsened.

The presentation in descending order of frequency was axial, cervical, oromandibular, blepharospasm, status dystonicus, and spasmodic dysphonia. We included the spasmodic dysphonia in the DTN group, but some authors believe that this disorder is a different entity, which goes beyond the aim of this review (Oh et al., 2004). In the same way, dropped head syndrome commonly reported with anticonvulsants may or may not be related to DTN (Werner et al., 2006). Possible interactions with clozapine, risperidone, quetiapine, and butamirate citrate were described.

One of the possible assumptions to explain the VPA-induced DTN is based on the GABAergic neurotransmission (Löscher, 2002). We believe that due to increased GABA levels by VPA the direct and indirect pathways that go to the thalamus might be interrupted. But the indirect pathway subactivity could probably predominate, and this disruption can increase the thalamocortical drive and eventually lead to DTN (Rissardo and Caprara, 2019). Another hypothesis related to dopaminergic activity in a mechanism similar to that proposed for the VPA-induced PKN can also be assumed (Brugger et al., 2016).

Dyskinesia (DKN)

Friis et al. (1983) reported in 53.33% of the individuals receiving VPA the development of DKN (Table 4). The presentation was orofacial, choreiform, hemichoreiform, and choreoathetotic. The association with another MD was observed with axial DTN and multifocal MCL. The DKN, stutter, and tics had the best prognosis with 100% recovery after the management.

The effects of VPA in the dopaminergic system probably explain the VPA-induced DKN. One fact that can support this hypothesis is the long time from starting VPA treatment until the MD onset, which was after 2.21 years. It is believed that due to the dopamine blockage, antipsychotics trigger inflammatory processes and the release of reactive oxygen species causing abnormal adaptations of the striatal organization, and ultimately leading to overactivation of the direct pathway (Lepping et al., 2011).

The most frequent management was VPA withdrawal. Another option was the VPA-dose reduction in those individuals that a possible interaction related to protein intake or other medications was assumed. Moreover, Lancman et al. (1994) reported in one subject the substitution from VPA tablet to sprinkles improving the symptoms. A possible relation with the higher VPA plasma concentration and the DKN occurrence can be proposed in this case, since the sprinkles have their peak within four hours and other VPA formulation in one hour, especially the syrup (Cloyd et al., 1992).

Stutter, tic, and akathisia (AKT)

In our analysis, we included stutter because of the possible differential diagnosis of DTN, MCL, and even DKN due to poor description of the neurological examination. It was observed only in young adult males with bipolar disorder. The MD's times of onset and recovery were the shortest, and the VPA-dose was the lowest reported in relation to the general data. These features can support the assumption of possible DTN diagnosis. Also, the prognosis was excellent, with 100% recovery. The most effective treatment was the drug withdrawal. Mukherjee et al. (2015) attempted the VPA reintroduction, which caused the reappearance of the symptoms. Thus, in the VPA-induced stuttering, we believe that the rechallenge of VPA should not be done.

Tics were observed in three individuals and corresponded to less than one percent of VPA-induced MD reports. In the data extraction of the Zadikoff et al. (2007) study, the percentage of individuals developing tics with VPA use was 1.69%. The patients presented with motor, motor and phonic, or only excessive eye blinking tics. Two cases reported had possible drug interactions, so a clear association can only be suspected. The drugs interacting with VPA were ziprasidone and lamotrigine; VPA can increase the levels of ziprasidone/lamotrigine by decreasing their metabolism (Alonso-Navarro et al., 2007; Thome-Souza et al., 2012). The VPA-dose decrease was enough for the achievement of a full recovery in the reports.

The less frequent MD published in the literature in association with VPA was AKT. But, it is noteworthy that this does not represent clinical practice. Friis et al. (1983) assessed 15 individuals using VPA, all of them developed some degree of AKT. Clos (2001) reported the case of a young adult female with bipolar disorder who was prescribed VPA 1,200 mg, and within one month she developed AKT-symptoms, but the diagnosis may be doubtful because the individual was in concomitant use of lithium.

Conclusion

In sum, VPA-associated MD was extensively reported in the literature probably due to availability, costs, and some historical factors of VPA. The most frequent and well described MD was PKN. In descending order of frequency, the following MD related

to VPA were encountered: PKN > MCL > DTN > DKN > Stutter > Tic > AKT. Further studies are warranted to elucidate the occurrence of these MD associated with VPA and its underlying pathophysiology. Future reports need to clearly describe the clinical history of the patient considering a full investigation of other adverse events during their entire life as well as a long-term follow-up. We believe that the knowledge of VPA-associated MD raises the awareness about MD, and especially those drug-induced, which sometimes are challenging in the clinical practice to diagnose and manage.

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