Expert Review of Neurotherapeutics

ISSN: 1473-7175 (Print) 1744-8360 (Online) Journal homepage: http://www.tandfonline.com/loi/iern20

Treatment options for chorea

H. Bashir & J. Jankovic

To cite this article: H. Bashir & J. Jankovic (2018) Treatment options for chorea, Expert Review of Neurotherapeutics, 18:1, 51-63, DOI: 10.1080/14737175.2018.1403899

To link to this article: https://doi.org/10.1080/14737175.2018.1403899

Accepted author version posted online: 09 Nov 2017.
Published online: 15 Nov 2017.

EXPERT REVIEW OF NEUROTHERAPEUTICS, 2018
VOL. 18, NO. 1, 51–63
https://doi.org/10.1080/14737175.2018.1403899

Taylor & Francis
Taylor & Francis Group

REVIEW

Treatment options for chorea

H. Bashir and J. Jankovic

Parkinson's Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, Houston, TX, USA

ABSTRACT

Introduction: Chorea is defined as jerk-like movements that move randomly from one body part to another. It is due to a variety of disorders and although current symptomatic therapy is quite effective there are few etiology- or pathogenesis-targeted therapies. The aim of this review is to summarize our own experience and published evidence in the treatment of chorea.

Areas covered: After evaluating current guidelines and clinical practices for chorea of all etiologies, PubMed was searched for the most recent clinical trials and reviews using the term 'chorea' cross referenced with specific drug names.

Expert commentary: Inhibitors of presynaptic vesicular monoamine transporter type 2 (VMAT2) that cause striatal dopamine depletion, such as tetrabenazine, deutetrabenazine, and valbenazine, are considered the treatment of choice in patients with chorea. Some clinicians also use dopamine receptor blockers (e.g. antipsychotics) and other drugs, including anti-epileptics and anti-glutamatargics. 'Dopamine stabilizers' such as pridopidine and other experimental drugs are currently being investigated in the treatment of chorea. Deep brain stimulation is usually reserved for patients with disabling chorea despite optimal medical therapy.

ARTICLE HISTORY
Received 25 September 2017
Accepted 8 November 2017

KEYWORDS
Chorea; Huntington's disease; dyskinesia; tetrabenazine; deutetrabenazine; antipsychotics; neuroleptics; DBS

1. Introduction

Chorea is a hyperkinetic movement disorder consisting of abrupt, irregular, random, jerk-like movements that can affect any part of the body [1]. The term athetosis is used to describe a slow form of chorea manifested by writhing movements predominantly involving distal parts of extremities. Sometimes it is considered a form of dystonia as some patients with acute hemichorea evolve into hemiathetosis and then to hemidystonia [2]. Ballism typically consists of high amplitude, flinging movements of proximal limbs and may affect only one side of the body (hemiballism). Indeed, all three movements may be found in a single patient, for example after a stroke involving the subthalamic nucleus, starting with ballism and evolving into chorea or athetosis.

There are many causes of chorea, including Huntington's disease (HD), neuroacanthocytosis (a group of neurologic conditions including 'chorea-acanthocytosis') [3], various autoimmune and metabolic disorders, certain drugs, and structural lesions involving the basal ganglia (Figure 1) [4]. Chorea is also seen as part of tardive dyskinesia (TD) and paroxysmal movement disorders. Chorea is thought to develop as a result of dysfunction in the complex networks connecting the basal ganglia, thalamus and motor cortex [5]. Specifically, the dysfunction arises in the two GABAergic striatopallidal pathways modulating the globus pallidus internal segment (GPi). The 'direct' pathway, named such because it is a single neuron pathway, facilitates movement by inhibiting the GPi thus promoting thalamocortical stimulation. The 'indirect' pathway, named such because it connects through the globus pallidus external segment (GPe) and subthalamic nucleus (STN), excites the GPi thus reducing thalamocortical stimulation and inhibiting movement. Overall control of movement is achieved by a modulation of these two pathways [4]. Degeneration of the indirect pathway in HD, overstimulation of the direct pathway in levodopa-induced dyskinesia (LID) of Parkinson's disease (PD) or destruction of the STN by stroke, ultimately leads to excessive thalamocortical stimulation and the hyperkinetic state of chorea. This model, however, may be too simplistic. For example, recent studies have provided evidence that changes in cortical excitability may play an important role in generation of chorea but it remains unknown if these precede or follow striatal changes [4,6,7]. Additionally, clinical improvement in LID seen after pallidotomy, which would expect to create a hyperkinetic state by destroying the GPi, is inconsistent with the current model.

Neurodegeneration and chorea in HD may be related to various alterations in the balance of glutamate and dopamine neurotransmission of the striatum and cortex [8]. A hyperdopaminergic state underlying chorea is supported by the observation that reducing dopamine neurotransmission, either by dopamine depletion or by blocking dopamine receptors, ameliorates chorea [9]. Striatal degeneration in HD may be the result of excitotoxicity mediated by complex interactions between glutamate, dopamine, and abnormal receptor regulation. Studies of HD mouse models have shown increased glutamate neurotransmission in the direct and indirect pathways, which may reflect the underlying pathophysiology of altered firing rates of the GPi and GPe seen in HD patients [8,10].

CONTACT J. Jankovic josephj@bcm.edu Parkinson's Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, 7200 Cambridge, Suite 9A, Houston, TX 77030-4202, USA

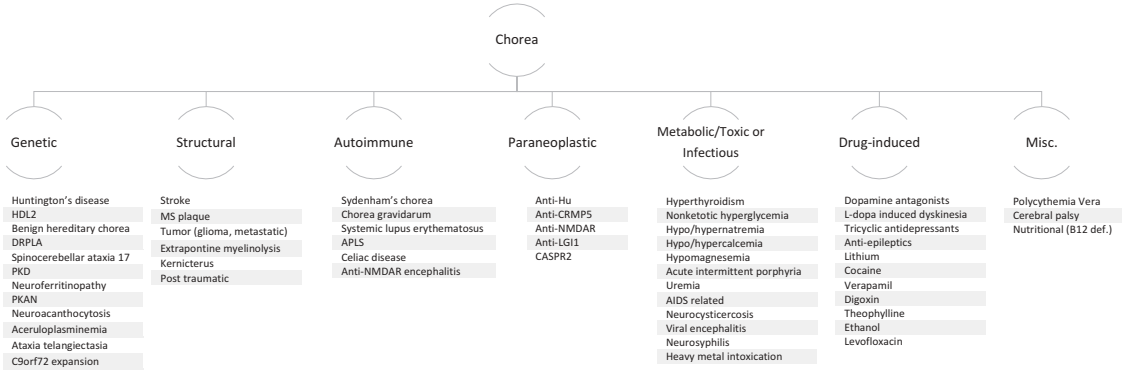
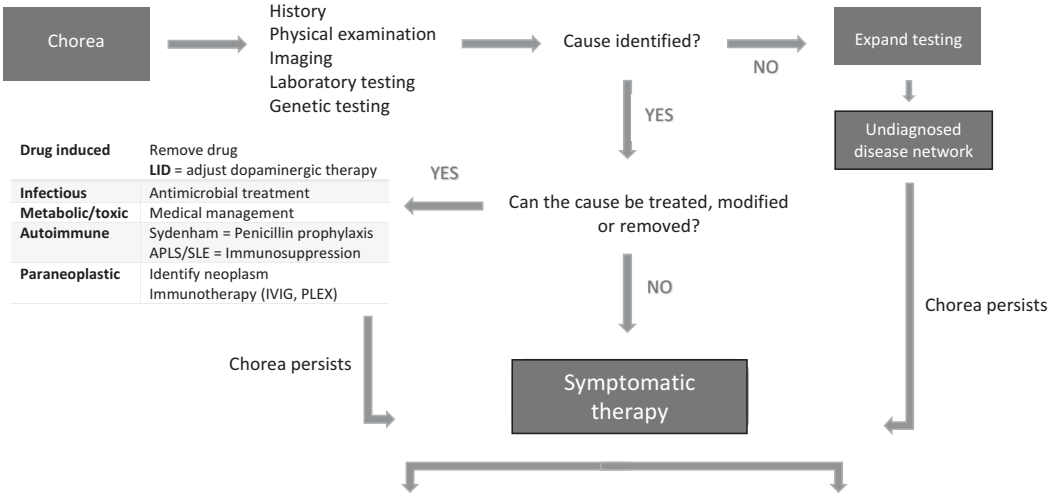


Figure 1. Etiological classification of chorea. AIDS = acquired immune deficiency syndrome, APLS = antiphospholipid antibody syndrome, CASPR = contactin associated protein, CRMP = collapsin response mediator protein, DRPLA = dentatorubropallidoluysian atrophy, HDL = Huntington's disease-like, L-dopa = levodopa, LGI = leucine-rich glioma-inactivated, MS = multiple sclerosis, NMDAR = N-methyl-D-aspartate receptor, PKAN = pantothenate-kinase associated degeneration, PKD = paroxysmal kinesigenic dyskinesia.

The approach to the treatment of chorea always begins with a detailed clinical assessment to identify the cause as some may be treatable (Figure 2) [11]. If a reversible or treatable cause cannot be found, then symptomatic therapy can be considered based on severity. Some patients may not even be aware of their chorea and many may find it only socially embarrassing. For others, chorea may be quite severe and disabling. Therefore, therapy ranges from simple reassurance and education to pharmacologic and surgical interventions. Chorea usually requires treatment when it impairs the patient's quality of life, function, or safety [9,12]. Most studies into the treatment of chorea have been conducted on patients with HD, which will



Cause	First line	Second line	Adjunctive	Surgical
Huntington's disease	Deutetrabenazine TBZ Antipsychotic - Tiapride (EU), olanzapine (UK)	Antipsychotic (olanzapine, quetiapine, other)	Amantadine Clonazepam Levetiracetam Other (cannabinoid etc.)	GPi Other targets under study
BHC	Levodopa, dopamine depleter	Dopamine depleter, anti-psychotic	-	-
Tardive Dyskinesia	Valbenazine, deutetrabenazine	Dopamine depleter, anti-epileptic	BoNT, clonazepam	GPi or STN
LID	Amantadine	Reduce levodopa	Clonazepam	GPi or STN
PKD	CBZ, PHT	Other anti-epileptics	TBZ, levodopa	-
Sydenham's	Antipsychotic VPA, CBZ (mild-moderate) Steroids (severe)	Dopamine depleter Immunotherapy (IVIG, PLEX)	Clonazepam	-
Unspecified	Dopamine depleter	Antipsychotic	Several	Consider DBS, rTMS

Figure 2. Approach to chorea and treatment. APLS = antiphospholipid antibody syndrome, BHC = benign hereditary chorea (secondary to *NKX2-1* mutation), BoNT = botulinum toxin, CBZ = carbamazepine, DBS = deep brain stimulation, EU = European Union, GPi = globus pallidus internus, IVIG = intravenous immunoglobulin, LID = levodopa-induced dyskinesia; PHT = phenytoin, PKD = paroxysmal kinesigenic dyskinesia, PLEX = plasma exchange/plasmapheresis, rTMS = repetitive transcranial magnetic stimulation, SLE = systemic lupus erythematosus, STN = subthalamic nucleus, TBZ = tetrabenazine, UK = United Kingdom, VPA = valproic acid.

be the focus of this review [1,13]. Studies of the progression of motor symptoms in HD show that chorea decreases over time, whereas hypokinetic-rigid symptoms slightly increase [14]. Therefore, as a rule, all patients with chorea should be frequently reassessed for adjustments in treatment.

2. Medical therapy

2.1. Dopamine depleters

The currently available dopamine depleters tetrabenazine, deutetrabenazine, and valbenazine act by inhibiting presynaptic vesicular monoamine transporter type 2 (VMAT2) [9]. Reserpine was one of the first monoamine depleters used (for the treatment of hypertension) but due to a variety of adverse effects it has been discontinued from the US market. Another depleter, α-methylparatyrosine (AMPT) which acts by inhibiting tyrosine hydroxylase, is also no longer available partly due to the emergence of safer and more effective monoamine depleters [15]. One notable benefit of the dopamine depleters in contrast to dopamine receptor blockers (also referred to as neuroleptics or antipsychotics) is that they do not cause TD [16–18]. Table 1 provides a comparison between the three VMAT2 inhibitors available in the USA.

2.1.1. Tetrabenazine

Tetrabenazine (TBZ) was originally developed in the 1950s to treat psychosis and in 1971 it was introduced in the UK for the treatment of hyperkinetic movement disorders [19]. Although one of the authors (JJ) has used TBZ in over a thousand patients under a compassionate protocol since 1979, the drug was not readily available in the USA until 2008 when it became the first FDA-approved treatment for chorea associated with HD. In 2017, deutetrabenazine (discussed below) was also approved for the treatment of HD-related chorea [20]. TBZ reversibly and selectively inhibits brain VMAT-2 that normally facilitates uptake of dopamine (and to a lesser extent serotonin and norepinephrine) from the cytoplasm into presynaptic vesicles [16]. Inhibition of VMAT2 results in degradation of presynaptic dopamine by monoamine oxidases leading to dopamine depletion. TBZ is quickly metabolized into alpha and beta-dihydrotetrabenazine (half-life 5–7 h) via hepatic isoenzyme CYP2D6. Because of its short half-life, TBZ is typically dosed three times a day [21].

The TETRA-HD study, the pivotal trial that led to TBZs approval by the FDA, was a multicenter, double-blind, placebo-controlled, randomized trial that clearly demonstrated the efficacy of TBZ in HD chorea [22]. It involved 84 ambulatory patients with HD, 54 of whom were randomized to TBZ and 30 received placebo. TBZ was associated with decreased chorea severity by a mean of 5.0 units on the total maximal chorea score of the Unified Huntington Disease Rating Scale (UHDRS) compared with a decrease of mean 1.5 units with placebo treatment at 12 weeks. Adverse events attributed to TBZ included one suicide, increased suicidal ideation and depression, prompting a black-box warning and warning that the drug is contraindicated in patients who are actively suicidal or have inadequately treated depression [19,23]. An open-label extension study was conducted for up to 80 weeks to assess its long-term safety and efficacy [24]. It showed a sustained significant reduction of 4.6 units (SD 5.5, $p < 0.001$) in the mean UHDRS total maximal chorea score although somnolence, depression, akathisia, and parkinsonism were reported as TBZ-related adverse effects.

Essentially all TBZ-related adverse effects have been shown to be dose related and decrease with dose reduction [23]. They can be also managed with stimulants, antidepressants, and other pharmacologic strategies if patients otherwise benefit from TBZ. Discontinuation of TBZ has been shown to be relatively safe but might worsen chorea [22,25]. It is important that physicians be educated about the pharmacology and use of TBZ, including the need to start at low doses (12.5–25 mg per day) and carefully titrate with close monitoring for adverse effects and periodic reassessment of continued need for treatment. It is recommended by the FDA that patients receiving more than 50 mg of TBZ per day be genotyped for CYP2D6 although this recommendation may need reconsideration based on a retrospective review and genotypic data [21,23]. In 2012, the American Academy of Neurology (AAN) evidence-based guidelines assigned a level B recommendation for TBZ in the treatment of HD-related chorea (along with amantadine and riluzole) [26]. Based on a Cochrane Database systematic review of controlled trials, only TBZ showed a clear efficacy for the control of chorea and no drug studied provided disease-modifying effect in HD [27,28].

In addition to HD, TBZ has also been shown to be effective (off-label) in treating other choreas, including choreoathetosis or hemiballism following stroke [29–31], neuroferritinopathy [32], benign hereditary chorea (caused by NKX2-1 and ADCY5

Table 1. Comparison of VMAT2 inhibitors.

Drug	Tetrabenazine	Deutetrabenazine	Valbenazine
Mechanism of action	Reversibly binds VMAT2	Reversibly binds VMAT2	Reversibly binds VMAT2
Active metabolites	Yes	Yes	Yes
Half-life (hours)	5 (Alpha-HTBZ)–7 (Beta-HTBZ)	9–10	15–22
Dose range (recommended)	12.5–100 mg/day If >50 mg/day, then must genotype for CYP2D6	6–48 mg/day	40–80 mg/day
HD trials	TETRA-HD	FIRST-HD, ARC-HD	None
Side effects	1. Depression 2. Parkinsonism 3. Akathisia 4. Peripheral (rare)	Similar to placebo Peripheral (rare)	1. Fatigue 2. Headache 3. Somnolence 4. Peripheral (rare)
FDA approval	HD chorea	HD chorea, TD	TD

HD: Huntington's disease; TD: tardive dyskinesia; HTBZ: dihydrotetrabenazine; VMAT2: vesicular amine transporter protein 2.
Peripheral side effects include orthostatic hypotension and gastrointestinal side effects such as nausea, vomiting and diarrhea.

mutations) [33–35], autoimmune diseases [36,37], myoclonus [38], tics associated with Tourette syndrome [16,39], TD [17], and paroxysmal kinesigenic dyskinesia [40].

2.1.2. Deutetrabenazine

Driven largely by the adverse effect profile of TBZ and its relatively short half-life other VMAT2 inhibitors have been developed and brought to the market in the recent past [41]. Deutetrabenazine is a novel VMAT2 inhibitor that incorporates six atoms of the naturally occurring and nontoxic isotope deuterium or 'heavy hydrogen' in its molecule. Deuterium-carbon bonds are stronger than hydrogen-carbon bonds and therefore more resistant to metabolizing cytochrome P450 enzymes like CYP2D6 [42]. This increases half-life without altering target pharmacology so that fewer and lower doses are needed for the same benefit. Deutetrabenazine received FDA approval for treatment of chorea in HD in April 2017 [20] based largely on the data from the FIRST-HD study, a multicenter, randomized, double-blind, placebo-controlled trial [43]. In this trial, 90 participants received either deutetrabenazine ($n = 45$) or placebo ($n = 45$) for 12 weeks which was divided into an 8-week titration phase and 4-week maintenance phase followed by one week of washout. Deutetrabenazine, taken twice a day, was shown to improve chorea with a reduction in the mean UHDRS total maximal chorea score of 2.5 points compared to placebo ($p < 0.001$) as well as improve overall motor function by a reduction of mean 4.0 points in the UHDRS total motor score ($p = 0.002$). There was no increase in sedation, depression, or suicidal ideation compared to the placebo arm of the study. When data from the TETRA-HD study were compared to those in the FIRST-HD study, deutetrabenazine was found to be associated with a significantly lower risk of adverse effects including agitation, akathisia, depression, somnolence, and parkinsonism compared to TBZ [44]. Additionally, there was less frequent dose reduction or adjustment with deutetrabenazine. In a study of 37 patients switching overnight from three times daily TBZ to twice-daily deutetrabenazine was shown to be safe and efficacious [45]. The ARC-HD study, which began in December 2013, is an ongoing open-label, longitudinal, safety study examining long-term safety and efficacy of deutetrabenazine. The apparently better safety profile of deutetrabenazine compared to TBZ is attributed to its pharmacokinetic properties resulting in lower peak concentrations, larger area under the curve, and reduced plasma fluctuations [15,46]. There is currently no head-to-head study comparing tetrabenazine and deutetrabenazine.

Given its recent arrival on the market and frequent denials by third party payers, there is limited experience with deutetrabenazine in its off-label use for treatment of other types of hyperkinetic movement disorders. The AIM-TD study is a randomized, placebo-controlled, phase III trial that studied deutetrabenazine in TD and demonstrated significant efficacy as well as safety and tolerability [47]. As a result, deutetrabenazine recently obtained FDA approval for the treatment of TD.

2.1.3. Valbenazine

Valbenazine, a prodrug of an isomer of TBZ, is a highly selective and potent reversible VMAT2 inhibitor. It is slowly converted to a highly selective and potent metabolite (the R,R,R-isomer of HTBZ – dihydrotetrabenazine) resulting in a half-life of approximately 20 h thereby allowing convenient once-a-day dosing [15]. R,R,R-HTBZ has the highest VMAT2-binding affinity (implied by the lowest K_i, the inhibitor constant) when compared to its parent drug valbenazine, TBZ and other metabolites of both drugs [48]. TBZ also shares this R,R,R-HTBZ metabolite but due to the collective effect of several other metabolites, both TBZ and valbenazine have different overall pharmacologic profiles. This difference was shown in a recent pharmacological characterization study using *in vitro* and *in vivo* outcomes to measure the potency, selectivity, and specificity of valbenazine and TBZ [48]. Results suggest that since R,R,R-HTBZ is the dominant metabolite of valbenazine, it has higher potency, selectivity, and specificity of VMAT2 binding than TBZ. The study also demonstrated that valbenazine has less off-target serotonin or dopamine (D1 and D2) receptor interactions. Valbenazine has not been studied in HD so far. The drug received FDA approval for the treatment of TD in April 2017 [49]. The approval was based largely on the findings from the KINECT-3 study of valbenazine in psychiatric patients with TD [50].

Valbenazine has been also studied in children and adults with Tourette syndrome but, based on information from company (Neurocrine) press releases, neither study met the prespecified primary end point which was the change-from-baseline between the placebo and active groups in the Yale Global Tic Severity Scale (YGTSS) at Week 6 and Week 8, respectively. Although secondary outcome measures favored valbenazine, 'underdosing' was offered as an explanation for the failure to meet the primary end point. As a result, the company is now repeating the studies using higher dosages.

2.2. Dopamine antagonists

The dopamine antagonists (also referred to as antipsychotics or neuroleptics) are commonly used in the treatment of chorea, especially if there is associated psychosis, like in HD and TD. Antipsychotics have varying affinity for and dissociation from the D2 receptor which determines their propensity to cause TD. Although the second and third generation of neuroleptics (atypical antipsychotics) may have a better safety profile than the classic neuroleptics they are still associated with a large variety of side effects including parkinsonism, TD, cognitive impairment, hypotension, sedation, school phobia, weight gain, metabolic syndrome, and many other potential adverse effects [51–53]. An international survey of HD chorea management practices among experts found the majority of clinicians in Europe favor an antipsychotic as first line with a near equal split with TBZ among experts in North America and Australia [54]. Interestingly, the AAN evidence-based guidelines concluded there was insufficient evidence for efficacy of antipsychotics to make specific recommendations of their use in the treatment of HD-related chorea [26]. These guidelines have been criticized as they were based on arbitrarily chosen chorea score cutoffs and therefore may not reflect treatment recommendations by experts or standards established in common clinical practice [54,55].

While atypical antipsychotics are preferred in the USA (e.g. olanzapine, risperidone, quetiapine, clozapine, aripiprazole, ziprasidone, paliperidone, lurasidone), tiapride, a typical antipsychotic that is not available in the USA, is preferred in Europe [13,54]. However, many antipsychotics, such as risperidone, categorized as

'atypical' have a pharmacological profile of 'typical' antipsychotics. There are no placebo-controlled trials of typical antipsychotic agents (e.g. haloperidol, pimozide, and fluphenazine) in chorea and their use is based on case reports or small, nonrandomized studies mainly published before 1990 with variable results [9,13,51]. The exception is tiapride, where one randomized, placebo-controlled crossover trial in 1984 showed significant reduction of chorea in HD but this trial had some limitations making the results difficult to interpret [13,56].

Atypical antipsychotics are usually preferred due to their lower risk of TD compared to typical antipsychotics. In one study, the prevalence rates of TD were significantly lower with atypical antipsychotics (20.7%) vs. first-generation antipsychotics (30.0%) ($p = 0.002$) [57]. Olanzapine, generally safe and well tolerated with positive effects on chorea and neuropsychiatric manifestations in small open-label studies, is the most commonly prescribed antipsychotic in the UK for motor and behavioral symptoms of HD [9,51,58]. Quetiapine has the lowest D2 antagonism in comparative reviews of antipsychotics and therefore carries a low risk of TD and drug-induced Parkinsonism [59]. This has earned it the title of the 'most atypical' of the atypical antipsychotics [51]. Several case series have demonstrated its anti-choreic effect and it is used by 12% of experts as a first-line drug in HD chorea [13,54]. Clozapine, which has the lowest risk of TD of all antipsychotics, has been found to significantly reduce chorea in one randomized control study of 33 HD patients, but the trial was terminated early due to its adverse effects, such as increased risk of seizures, sedation, and cardiometabolic risks [51]. Furthermore, its efficacy is counterbalanced, if not superseded, by the increased risk of agranulocytosis (0.5–2% patients) which requires absolute neutrophil count monitoring weekly from initiation to 6 months, every 2 weeks from 6 to 12 months and then monthly after 12 months of therapy. This is difficult to achieve in cognitively impaired HD patients. As noted above, risperidone, while classified as 'atypical,' behaves more like a typical antipsychotic and has a relatively higher risk of TD [60]. Both risperidone and ziprasidone have been shown to have positive effects on chorea with tolerable adverse effects, but these drugs have only been studied in either retrospective studies, case reports, or case series [13,51]. Aripiprazole deserves special mention as it is one of the most widely prescribed drugs for psychiatric disorders. It has been shown to reduce chorea to a degree comparable to TBZ in case reports and one-blinded cross over study [61,62]. However, similar to other atypical antipsychotics, it has also been shown to be associated with TD [63].

Haloperidol, risperidone, and olanzapine are used as second-line agents in the symptomatic treatment of Sydenham's chorea if valproic acid and carbamazepine are ineffective, although VMAT2 inhibitors may be equally or even more effective [64]. Low-dose haloperidol can be safely used in chorea during pregnancy (chorea gravidarum) in the second and third trimesters, although the involuntary movement often resolves spontaneously [65]. Antipsychotics have also been used with variable success in autoimmune chorea [37], paraneoplastic chorea with anti-CRMP5 (collapsin response-mediator protein 5) and anti-Hu autoantibodies [36], vascular chorea [30], neuroacanthocytosis [66], paroxysmal non-kinesigenic dyskinesia [40], and neuroferritinopathy [67]. It is generally recommended to start at a low dose and slowly increase, titrating to clinical effect and either reducing dose or switching agent if intolerable adverse effects develop. Once patients are receiving antipsychotic drugs, it is imperative that they are fully compliant with the prescribed treatment and do not suddenly stop the drug as an abrupt withdrawal can increase the risk of TD. We recommend using antipsychotics as second-line agents to treat chorea given the availability of newer and better studied drugs such as the VMAT2 inhibitors that do not have risk of TD.

2.3. Anti-glutamatergic

It has been suggested that excitotoxicity mediated through glutamate plays a role in HD as it does in animal models of neurodegenerative conditions [8]. These drugs, therefore, may not only exert disease modifying effects, but may also improve chorea [26].

2.3.1. Amantadine

Amantadine is a noncompetitive N-methyl-D-aspartic acid (NMDA) receptor antagonist, but its effects on the dopaminergic system have not been well elucidated. It is considered the most effective agent to treat LID in PD [68]. Several small randomized trials have studied amantadine as an anti-chorea agent, but doses of 400 mg/day or higher may be needed to meaningfully suppress chorea, which may increase the risk of intolerable adverse effects such as aggression, anxiety, insomnia, and hallucinations [69–71]. Amantadine has also been successfully used as initial or adjunctive treatment for motor symptoms including chorea in TD, neuroacanthocytosis, ataxia-telangiectasia, and spinocerebellar ataxia (SCA) 17 [17,66,72,73]. It is not known whether extended-release amantadine, Govovri (previously ADS-5102), recently approved by the FDA for the treatment of LID, will be evaluated in the treatment of chorea [74].

2.3.2. Riluzole

Riluzole is a glutamate release inhibitor currently approved by the FDA for the treatment of amyotrophic lateral sclerosis. The Huntington Study Group (HSG) conducted a multicenter, randomized, double-blind study to evaluate the dosage-related effect of riluzole on chorea in 63 patients and found a reduction in chorea at 8 weeks ($p < 0.01$) with doses of 200 mg/day but not 100 mg/day compared to placebo [75]. The drug, however, caused a significant elevation of liver transaminases. A more recent and larger 3-year randomized controlled study found no benefit in chorea or in functional independence with riluzole at any time point [76]. Riluzole has not been studied in other forms of chorea. Given its limited success in HD and despite its level B recommendation by the AAN [26], we do not generally recommend the drug in the treatment of HD-related chorea.

2.4. Antiepileptics

The antiepileptics are frequently used in the treatment of hyperkinetic movement disorders including tremor, dystonia, tics, and chorea [1]. Carbamazepine is the most effective treatment of paroxysmal kinesigenic dyskinesia, which may be manifested by chorea [24]. If ineffective, other antiepileptic drugs, such as phenytoin, topiramate, levetiracetam, valproic acid, oxcarbazepine,

and lacosamide can be tried [40]. These drugs are also sometimes used as symptomatic therapy in Sydenham's chorea, although VMAT2 inhibitors are probably more effective [36,64]. Myoclonus, which can sometimes resemble and occur in addition to chorea in HD patients, may respond to valproic acid [77]. Valproic acid has also been reported as efficacious in treating chorea due to other causes such as kernicterus, post-traumatic, post-anoxic, and stroke [4,30]. Valproic acid and levetiracetam may help in motor symptoms of neuroacanthocytosis, whereas involuntary movements such as motor tics may worsen with some antiepileptics such as lamotrigine [78–80]. Studies of the use of antiepileptics in HD chorea are very limited. Two small open-label studies have looked at efficacy of levetiracetam. One reported significant improvement in UHDRS scores and functional capacity after 6 months of treatment without adverse effects [81]. The second reported no significant changes in UHDRS total motor scores [82]. Parkinsonism has been reported as a possible side effect, which reversed with discontinuation of levetiracetam [83].

As the understanding of the genetics of both chorea and epilepsy is growing, an increasing overlap is being found in gene mutations originally reported in epileptic encephalopathies but later also being associated with isolated movement disorders such as chorea [84]. For example, chorea is the most frequent movement disorder in carriers of mutations in FOXG1, a gene encoding a repressor protein that plays an essential role in the fetal telencephalon. Mutations in FOXG1 are associated with congenital Rett-like syndrome and epilepsy [85]. A single missense mutation in SCN8A, which encodes a voltage-gated Na-channel widely expressed in the central nervous system, has been linked to paroxysmal kinesigenic dyskinesia and infantile seizures [86]. The GNAO1 gene encodes a Gα protein-regulating GABA-B, α2-receptors and neurotransmitter release and mutations can lead to epileptic encephalopathy with severe, fluctuating hyperkinetic movements including chorea that respond to neuroleptics, TBZ, and topiramate [87,88]. Further identification of such ion channels and gene protein products may lead to specific treatments.

2.5. Benzodiazepines

No clinical trials have been performed to assess the effect of benzodiazepines on chorea; however, many experts use these drugs as adjunctive therapy, particularly if anxiety is a comorbid factor [54]. Two case reports have suggested improvement in HD chorea with clonazepam at doses up to 5.5 mg/day, however, at this dosage, sedation becomes a potential adverse effect [13,89]. Benzodiazepines can decrease the frequency and severity of attacks in paroxysmal non-kinesigenic dyskinesia [40]. Clonazepam reduces involuntary movements in TD but this effect wanes over months of continuous use and therefore only short-term use is recommended (less than 3 months) [17]. Successful use of clonazepam has been reported in various cases of vascular chorea such as limb monochorea and hemiballism, but well-designed controlled trials are needed [30,90].

2.6. Pridopidine

Pridopidine (previously known as ACR-16) is a novel drug that belongs to a recently developed class of 'dopamine stabilizers' known as the dopidines [91]. Its pharmacodynamics are complex and thought to be state dependent such that it increases striatal dopaminergic transmission when the dopaminergic tone is low and behaves as a dopaminergic antagonist when dopaminergic activity is high [91]. Studies of HD mouse models suggest that pridopidine mediates its effects through sigma-1 receptors (S1R) to prevent striatal Ca^{2+} dysregulation and synaptic loss characteristic of HD [92]. S1R is an endoplasmic reticulum transmembrane protein and could be a potential target for HD therapy.

Two randomized placebo-controlled trials, the HD ACR16 Randomized Trial (HART) and the Multinational European Multicenter ACR16 study in HD (MermaiHD), investigated efficacy of pridopidine in HD and used the UHDRS modified motor score (mMS) as a primary outcome [93,94]. The mMS showed improvement that did not reach statistical significance; however, its calculation excludes measurement of chorea. The UHDRS total motor score (TMS), which includes chorea in its calculation, was a secondary outcome and did show significant improvement but this was mostly driven by dystonia and eye movement scores, not chorea. Pridopidine was well tolerated with an adverse effect profile similar to placebo. The ongoing PRIDE-HD study (currently in open-label phase, Open PRIDE-HD) was designed to build on the findings of HART and MermaiHD using UHDRS-TMS as a primary outcome measure. Preliminary findings, presented at the 9th European Huntington Disease Network Plenary Meeting in September 2016, showed mixed results with further evaluation in process to determine potential benefits in reducing chorea [13]. These results suggest that further studies are needed including potential or expanding to other forms of chorea.

2.7. Levodopa

Levodopa is the mainstay of therapy in PD and long-term therapy can lead to levodopa-induced dyskinesias [68]. Only one distinct form of chorea has been reported to respond to levodopa: NKX2-1-related disorders, an autosomal dominant disorder also known as brain-lung-thyroid syndrome. Mutations in NKX2-1 cause a spectrum of disorders of which one is 'benign hereditary chorea' which may be associated with athetosis (choreoathetosis), dystonia, ataxia and other movement disorders, intellectual impairment, microcephaly, congenital hypothyroidism neonatal respiratory distress and other conditions [95]. The term 'benign hereditary chorea' may be misleading and inappropriate as many patients have more than chorea and the multifactorial disorder can be progressive and disabling. Although levodopa has been reported to improve chorea and gait impairment in this disorder [33,79,95], we have not found it helpful in our patients with chorea associated with *NKX2-1* mutation. Benign hereditary chorea has also been shown to be caused by mutations in ADCY5 which may not be as responsive to TBZ or levodopa [34,35]. Levodopa may also be considered second-line treatment, after antiepileptics, in patients with paroxysmal kinesigenic dyskinesia [40].

2.8. Cannabinoids

There has been considerable interest in the use of cannabinoids (CB) in treating neurological disease with particular focus on movement disorders. CB receptors are highly

expressed in the basal ganglia where they modulate the release of GABA and glutamate [96]. The endocannabinoid system has been shown to be involved in the pathogenesis of HD and PD animal models which naturally led to studies in its application in neurodegenerative diseases. The 2012 AAN pharmacotherapy guidelines for HD concluded that nabilone, a CB1 receptor agonist and class 2 controlled substance with high abuse potential, provided modest improvement in chorea based on a randomized controlled trial [26,97]. Drowsiness and forgetfulness were the most frequent adverse effects. In contrast, Savitex, a mouth spray with approximately equal amounts of tetrahydrocannabinol (THC) and cannabidiol (CBD), provided no symptomatic benefit in HD over a 12-week period [98]. A deficiency in endocannabinoid transmission is thought to contribute to LID; however, to date there has not been reliable evidence that treatment with cannabinoids is helpful [68].

3. Disease-specific therapy

3.1. Autoimmune chorea

Although rare, autoimmune chorea is likely second only to HD as a cause of chorea in adults [99]. Sydenham's chorea (SC) is a delayed neurological manifestation of rheumatic fever, a complication of beta-hemolytic strep infection [23]. Although typically a transient childhood disorder manifested chiefly by asymmetric chorea, various motor and behavioral sequelae, such as obsessive compulsive disorder may persist for many years or decades. In rare instances, the chorea may be so severe that it is disabling – a variant known as chorea paralytica [64]. Therefore, Sydenham disease may be considered a more appropriate term. SC is usually described as a self-limited condition that spontaneously remits after approximately 8–9 months; however, up to 50% of patients may continue to manifest chorea even up to 2 years thereby necessitating symptomatic therapy [36]. Few patients have an active infection when chorea appears; however, a 10-day course of oral or a single intramuscular injection of penicillin is recommended at the time of SC diagnosis. The World Health Organization recommends secondary prophylaxis with intramuscular penicillin every 21 days and the duration depends on the severity of cardiac involvement. If no carditis, prophylaxis can stop after 5 years or until age 18 (whichever is longer); if mild carditis then continue for 10 years or until age 21; and if moderate-to-severe carditis then prophylaxis is lifelong [64].

A double-blind, placebo-controlled study of prednisone showed beneficial effects on the course of SC [100]. The use of VMAT2 inhibitors, neuroleptics, and antiepileptics (valproic acid, carbamazepine) in the treatment of chorea associated with SC has been discussed above. If these fail or if treating more severe SC, particularly chorea paralytica, immunomodulatory treatment with prednisone, intravenous immunoglobulin (IVIG), and plasmapheresis has been supported by several case reports and case series [64]. Steroids, both oral prednisone and IV methylprednisolone, have the strongest evidence and IVIG or plasmapheresis are typically considered only after a steroid trial fails. Persistent chorea associated with other autoimmune conditions such as systemic lupus erythematosus and primary phospholipid antibody syndrome is treated similarly [36,37,101,102]. Neither of these treatments, however, has been examined in controlled studies.

Paraneoplastic chorea is an increasingly recognized entity and should be considered in all forms of adult-onset chorea if genetic testing for HD is negative. The onset of chorea typically antecedes the diagnosis of cancer (typically an adenocarcinoma or small cell lung cancer), sometimes by years, and may be accompanied by other neurologic findings such as seizures, peripheral neuropathy, or cognitive impairment [36]. Autoantibodies associated with chorea include anti-CRMP5, anti-Hu (also known as ANNA-1), anti-NMDAR, LGI1, and CASPR2 among others [36,37,101,102]. These are not always associated with a neoplasm. Patients with anti-IgLON5 antibodies develop characteristic sleep disorders as part of a syndrome that may include chorea, ataxia, or even parkinsonism [101,103]. Detection and appropriate treatment of any underlying neoplasm with concurrent immunomodulatory therapy (steroids, IVIG, plasmapheresis, rituximab, or cyclophosphamide) is the standard of care. If chorea persists, TBZ or other VMAT2 inhibitors and neuroleptics may be needed for effective symptomatic control [36,99].

3.2. Polycythemia Vera

Polycythemia Vera (PV) is a myeloproliferative disorder in which neurological complications are common. Chorea may be seen in 0.5–5% of cases likely due to hyperviscosity causing basal ganglia hypoperfusion or altered platelet dopamine metabolism [104]. Recognizing PV-related chorea is important because with prompt treatment it is usually reversible. Treatment includes repeat phlebotomies with chemotherapy to achieve remission, coupled with VMAT2 inhibitors [104,105].

4. Diet

Celiac disease has been associated with various neurologic manifestations including chorea, which may respond to gluten-free diet [37,106]. Strict diet can postpone onset of chorea among other symptoms in several childhood metabolic disorders including GLUT1 deficiency (ketogenic diet), phenylketonuria (phenylalanine-reduced), and glutaric acidemia type 1 (lysine-reduced diet) [107].

5. Surgical therapy

Surgical procedures have been successfully used to treat dyskinesias for many years with ablative procedures gradually being replaced by thalamic and pallidal deep brain stimulation (DBS) over the past two decades. The effectiveness of DBS is well recognized in movement disorders such as PD, essential tremor, dystonia, and other hyperkinetic movement disorders including chorea [108]. Surgery is rarely needed to treat chorea, but it is a viable option for persistent or medically refractory patients with either inherited or acquired forms.

5.1. Deep brain stimulation

5.1.1. HD chorea

HD poses a challenge to DBS given the coexistence of hyperkinetic and hypokinetic signs in addition to progressive neurodegeneration causing cognitive impairment and motor decline such that every HD patient is a 'moving target.' Experience with PD patients has shown that ventral GPi stimulation has an anti-kinetic effect and dorsal stimulation has a pro-kinetic effect [108]. Given this and the success of GPi stimulation in LID, the GPi has been the most frequent target in studies of DBS in HD. To date, there have been multiple case reports, case series and one prospective randomized, double-blind study demonstrating reduction of chorea with DBS in HD that target bilateral GPi at frequencies ranging from 40 to 180 Hz [109,110]. A prospective open-label study of 7 HD patients who underwent MRI-guided bilateral GPi DBS with median duration of follow up of 3 years, showed a significant reduction of chorea with regular off-stimulation testing confirming a persistent therapeutic effect of DBS on chorea [111].

Most, but not all studies, have found a positive correlation between frequency and chorea suppression; however, several demonstrated DBS-induced bradykinesia and dystonia at higher frequencies that offset the improvement in chorea [110]. This has prompted consideration of other targets to enhance global benefit. In one case, quadruple GPi and STN DBS showed a reduced side effect of bradykinesia but STN DBS alone did not improve chorea, nor provide additional chorea control during quadruple stimulation than GPi alone [112]. A randomized, double-blind controlled study evaluated 6 patients, including 2 with juvenile (Westphal) variants for equivalence of GPi and GPe stimulation with an open-label 6-month follow up to assess chronic treatment effects [113]. Beneficial treatment effects did not differ between the two nuclei and DBS was safe and effective overall. Of note, no improvement was seen in the 2 juvenile variant cases which is why such cases are excluded from an ongoing European, multicenter, randomized, quadruple-blind, prospective trial looking at pallidal DBS in HD that will measure the difference between groups in the UHDRS-TMS at 12 weeks postoperatively compared to baseline as its primary outcome (NCT02535884).

Smith et al. analyzed several case reports and case series with bilateral GPi DBS and found a mean improvement in UHDRS total score of 24.4% and chorea subscore of 58.2% with a follow-up period ranging from 8 months to 4 years [109]. While improvement in chorea was sustained over time, other motor features of HD such as dystonia and parkinsonism did not respond as well. This is very relevant when considering DBS in HD as chorea is the predominant phenotype early in the disease while rigidity and other Parkinsonian signs may develop later. Despite marked variability, overall good clinical results have been reported up to 5 years postoperatively [114,115].

5.1.2. Non-HD chorea

Several case reports and series have evaluated DBS in neuroacanthocytosis [108]. The largest series is by Miquel et al. who carried out a worldwide, multicenter, retrospective review of 15 cases of bilateral GPi DBS in neuroacanthocytosis and found that it effectively reduced the severity of drug-resistant hyperkinetic movements, whereas Parkinsonism did not improve [116]. Chorea returned when DBS was turned off. A study of two cases described better outcomes with combination GPi and thalamic (VOP) stimulation in neuroacanthocytosis; where GPi DBS apparently improved abnormalities of posture and VOP DBS had more robust effects on chorea [117]. There was progressive improvement in chorea over 1 year of follow up.

Several case series of GPi DBS (and rare STN DBS) have reported immediate or delayed improvement in symptoms (by at least 50%) in patients with TD [17]. The American Academy of Neurology has deemed the level of evidence on the use of DBS in the treatment of TD as insufficient (level U) [118]. Improvement with DBS has been reported in cases of medically refractory paroxysmal nonkinesigenic dyskinesia that targeted GPi and Vim [109,119], 'senile chorea' targeting GPi and VOP [115], generalized chorea in cerebral palsy targeting GPi and Vim [109] and chorea or hemiballism seen with diabetes, thalamic or basal ganglia stroke and developmental anomalies targeting different combinations of nuclei [30,109]. Both GPi and STN DBS have been found to improve various forms of LID [68]. A recent cases series of 3 patients with GNAO1 mutations causing severe, life-threatening, hyperkinetic exacerbations (including chorea, dystonia and orofaciolingual dyskinesias) demonstrated significant improvement with bilateral GPi DBS [88]. Controlled studies are needed to help identify the ideal candidates for surgery. The possibility of publication bias in DBS studies is well recognized as negative outcomes are far less likely to be published [115,120].

6. Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) has been studied in small cohorts of LID and HD with variable success [68,121]. Improvement of mood in HD after low-frequency repetitive TMS has been reported [110]. Given its brief duration of benefit (in the range of minutes) and absence of well-designed, controlled, long-term studies, it is currently not a recommended treatment option.

7. Conclusion

This review provides a description of the clinical practices and current evidence for the treatment options of chorea. An approach to treatment and the available options are summarized in Figure 2. Information on current, ongoing phase II and III clinical trials investigating treatments for chorea obtained from clinicaltrials.gov as of August 2017 are listed in Table 2.

8. Expert commentary

Chorea is one of several hyperkinetic movement disorders, characterized by jerk-like, random movements. In most cases, there is no pathogenesis-targeted therapy and only symptomatic treatment can be offered. Few randomized controlled studies have examined the effects of medical or surgical treatments of chorea, mostly in patients with HD. Clinical trials are difficult to design in HD given the variations in phenotype and its tendency to change over time. Additionally, pharmaceutical interest in clinical trials for older agents is limited. Clinical practice is variable across experts and influenced by availability, cost, adverse effect profile, and patient comorbidity. Antipsychotics are the most commonly

Table 2. Results of search term 'chorea' at clinicaltrials.gov as of August 2017.

Study	Status	Phase	Design	Conditions	Intervention	Outcome measures	Study duration
ARC-HD (NCT01897896)	Active, not recruiting	III	Multicenter, open-label, long term safety extension of FIRST-HD	Huntington's disease	SD-809 (deutetrabenazine) 6, 9, or 12 mg/day	1. Incidence of AEs 2. Change in baseline UHDRS, laboratory parameters, vital signs, ECG parameters	November 2013–October 2017
HD-DBS (NCT02535884)	Recruiting	II	Multicenter, prospective, randomized, controlled, quadruple-blind study	Huntington's disease	ACTIVA® PC neurostimulator (Model 37601)	1. UHDRS-TMS difference 2. Difference in UHDRS-chorea among others	July 2014–September 2019
SIGNAL (NCT02481674)	Enrolling by invitation	II	Multi-center, randomized, double-blind, placebo-controlled study	Huntington's disease	VX15/2503	1. Safety and tolerability, laboratory test 2. Changes in UHDRS-motor among others	July 2015–June 2019
TRIHEP3 (NCT02453061)	Recruiting	II	Randomized, quadruple-blind, placebo-controlled study	Huntington's disease	Triheptanoin oil 1 g/kg/day	1. 31-P MRS change, caudate atrophy 2. Change in UHDRS among others	June 2015–June 2017
REVHD (NCT02336633)	Recruiting	III	Randomized, quadruple-blind, placebo-controlled study	Huntington's disease	Resveratrol 80 mg/day	1. Rate of caudate atrophy 2. UHDRS among others	July 2015–January 2019
LEGATO-HD (NCT02215616)	Recruiting	II	Multicenter, randomized, triple-blind, placebo-controlled efficacy and safety study	Huntington's disease	Laquinimod 0.5, 1, 1.5 mg/day	1. Change in baseline UHDRS total motor score 2. UHDRS total functional capacity score among others	November 2014–August 2018
OPEN-HART (NCT01306929)	Active, not recruiting	II	North-American, open-label, extension of PRIDE-HD	Huntington's disease	Pridopidine 45 mg twice daily	1. Incidence of AEs 2. UHDRS total motor score over time	March 2011–April 2021

Only Phase II and III trails with 'recruiting', 'active, not recruiting', 'enrolling by invitation' status, drug or device intervention, and a motor outcome measure are shown. AE's: adverse effects; HD: Huntington's disease; MRS: magnetic resonance spectroscopy; UHDRS: Unified Huntington's Disease Rating Scale.

used drugs based on the available retrospective analyses and international surveys but these are now dated and may not reflect current practice [54,58]. In our experience, the most robust evidence supports the use of dopamine depleters such TBZ and deutetrabenazine, considered the first-line therapy for HD-related chorea. Both have received FDA approval but TBZ appears to have more adverse effects, particularly depression and sedation, whereas deutetrabenazine has been shown to have adverse effects profile not much different than placebo [43]. Valbenazine and deutetrabenazine are FDA approved for TD and should be considered first line if chorea is part of a tardive syndrome. The dopamine depleters provide an advantage over antipsychotics in that they do not cause TD [15,17]. Amantadine is first line for LID and frequently used as adjunctive therapy in all forms of chorea [68]. Antipsychotics continue to present a double-edged sword. Recent reviews acknowledge that although decades of case reports and case series support their use in chorea, especially if psychiatric comorbidities exist, the benefit is counterbalanced by motor adverse effects such as TD, dystonia, and parkinsonism [51]. We consider them second-line treatment in chorea and when used, atypical agents such as quetiapine or olanzapine are preferred. Low-dose haloperidol can be used safely in chorea during pregnancy in the second and third trimesters [65]. There is no recent evidence to support benzodiazepines but they are frequently used as adjunctive therapy in chorea. There is little evidence to support the use of antiepileptics in HD chorea but they are frequently used in non-HD chorea. Valproic acid is used frequently to treat chorea associated with SC and carbamazepine is the most effective treatment for paroxysmal kinesigenic dyskinesia [36,40]. Paraneoplastic chorea is typically approached initially by surgical resection of the underlying neoplasm followed by immunomodulatory therapy. If chorea persists, it can be managed with dopamine depleters or antipsychotics. The endocannabinoid system plays a role in neurodegenerative disease but more studies are needed to determine the effectiveness of cannabinoid drugs. For medically refractory chorea, DBS is a feasible option although no controlled studies exist. DBS has been shown to be effective in the treatment of chorea associated with HD, NA, TD, and various acquired forms of chorea [108,109]. The most frequent target is GPi and other targets have been rarely studied.

9. Five-year view

Despite discovering the mutation in HD over two decades ago, there is still no therapy that treats the underlying pathogenesis; only symptomatic therapy is available. A similar situation applies to many other forms of chorea. Several investigational symptomatic and disease-modifying drugs for HD are currently in phase I and II of development. TBZ and the new dopamine depleters, deutetrabenazine and valbenazine, are gaining widespread use in the treatment of chorea and other hyperkinetic movement disorders. Their use, however, is limited by high cost and frequent denials by third party payers, particularly for off-label indications. The evidence to support the use of antipsychotics remains scattered and limited to case reports and small studies. They remain valuable in patients with

psychiatric comorbidities; however, this advantage may be offset by the increasing use of dopamine depleters that have been shown to have utility in psychiatric disorders too. Novel molecules such as the 'dopamine stabilizer' dopidines may eventually replace antipsychotics given that their proposed mechanism of action helps to normalize dopamine transmission rather than simply block it. The best studied is pridopidine (previously known as ACR 16) which has shown promising results in three studies of HD-related chorea. As the understanding of the neurophysiology and genetics of chorea grows, an increasing overlap with other neurological disorders such as ataxias and genetic encephalopathies is being recognized. This potentially opens the way to new treatment options. Registries such as ENROLL-HD may provide valuable observational data that can guide future areas of study. Surgical management continues to pose a complex challenge given the heterogeneous presentation of patients with chorea. However, evolving neuromodulation technology offers hope and ongoing clinical experience and research continues to add new data. Controlled studies will help identify the ideal candidates for surgery as well as the most effective surgical targets. Table 2 lists the ongoing clinical trials for the treatment of chorea. More randomized controlled trials for the symptomatic treatment of chorea are needed to assess the efficacy of potential drugs. Head-to-head studies are needed to compare relative efficacy and adverse effect profiles.

Key issues

- Chorea is a common hyperkinetic movement disorder with a broad differential diagnosis, but Huntington's disease is the most common cause.
- Tetrabenazine and deutetrabenazine are the only drugs with formal approval for treatment of chorea in Huntington's disease; deutetrabenazine and valbenazine have been also approved for the treatment of tardive dyskinesia.
- Atypical antipsychotics may not be as effective in the treatment of chorea as the classic antipsychotics but tend to be better tolerated and carry a smaller, but still meaningful, risk of tardive dyskinesia.
- Novel drugs such as the 'dopamine stabilizer' dopidines, such as pridopidine, show some promise in the treatment of chorea but further studies are needed to prove their long-term efficacy.
- DBS is an option for medically refractory cases of chorea but has been studied only in a small cases series. The most frequent target is bilateral GPi. High frequencies are associated with bradykinesia and dystonia.
- There are several specific therapies for unique chorea syndromes.
- A growing understanding of the neurophysiology and genetics of chorea will help open the way to potential treatment options.

Funding

This paper was not funded.

Declaration of interest

J Jankovic has received research or training grants from: Adamas Pharmaceuticals Inc, Allergan, Biotie Therapies, CHDI Foundation, Civitas/Acorda Therapeutics, Dystonia Coalition, Dystonia Medical Research Foundation, Hoffman-LaRoche, Huntington Study Group, Kyowa Haako Kirin Pharma, Medtronic Neuromodulation, Merz Pharmaceuticals, Michael J Fox Foundation for Parkinson's Research, National Institutes of Health, Neurocrine, Biosciences, NeuroDerm Ltd, Parkinson's Foundation, Parkinson Study Group, Pfizer, Prothena Biosciences, Psyadon Pharmaceuticals, Revance Therapeutics, Sangamo Biosciences, St Jude Medical, and Teva Pharmaceuticals. He has served as a consultant or on the advisory board for: Adamas Pharmaceuticals, Allergan, Pfizer, Prothena Biosciences, Revance Therapeutics, Teva Pharmaceuticals. He has received royalties or other payments from: Cambridge, Elsevier, Future Science Group, Hodder Arnold, Medlink, Neurology, Lippincott Williams and Wilkins, and Wiley-Blackwell. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

A peer reviewer on this manuscript has declared receipt of honoraria from Temmler, AOP Orphan, Destin, and Teva but have no other relevant financial relationships to disclose.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Jankovic J. Treatment of hyperkinetic movement disorders. Lancet Neurol. 2009;8:844–856.
2. Pettigrew LC, Jankovic J. Hemidystonia: a report of 22 patients and a review of the literature. J Neurol Neurosurg Psychiatry. 1985;48:650–657.
3. Jankovic J, Killian JM, Spitz MC. Neuroacanthocytosis syndrome and choreoacanthocytosis (Levine-Critchley syndrome). (Letter) Neurol. 1679;1985:35.
4. Cardoso F, Seppi K, Mair KJ, et al. Seminar on choreas. Lancet Neurol. 2006;5:589–602.
5. DeLong MR, Wichmann T. Circuits and circuit disorders of the basal ganglia. Arch Neurol. 2007;64:20–24.
6. Khedr EM, Ahmed MA, Ali AM, et al. Changes in motor cortical excitability in patients with Sydenham's chorea. Mov Disord. 2015;30:259–262.
7. Li JY, Chen R. Increased intracortical inhibition in hyperglycemic hemichorea-hemiballism. Mov Disord. 2015;30:198–205.
8. André VM, Cepeda C, Levine MS. Dopamine and glutamate in Huntington's disease: a balancing act. CNS Neurosci Ther. 2010;16:163–178.
9. Wyant KJ, Ridder AJ, Dayalu P. Huntington's Disease-Update on Treatments. Curr Neurol Neurosci Rep. 2017;17:33.
10. Starr PA, Kang GA, Heath S, et al. Pallidal neuronal discharge in Huntington's disease: support for selective loss of striatal cells originating the indirect pathway. Exp Neurol. 2008;211:227–233.
11. Jinnah HA, Albanese A, Bhatia KP, et al. Treatable inherited rare movement disorders. Mov Disord. 2017. [Epub ahead of print]. DOI: 10.1002/mds.27140.
12. Jankovic J, Roos RAC. Chorea associated with Huntington's disease: to treat or not to treat? Mov. Disord. 2014;29:1414–1418.
13. Coppen EM, Roos RAC. Current pharmacological approaches to reduce chorea in Huntington's disease. Drugs. 2017;77:29–46.
•• **Detailed and comprehensive review of pharmacological treatments for HD-related chorea.**
14. Jacobs M, Hart EP, Van Zwet EW, et al. Progression of motor subtypes in Huntington's disease: a 6-year follow-up study. J Neurol. 2016;263:2080–2085.
15. Jankovic J. Dopamine depleters in the treatment of hyperkinetic movement disorders. Expert Opin Pharmacother. 2016;17:2461–2470.
•• **Detailed review of VMAT2 inhibitors in the treatment of hyperkinetic movement disorders.**

16. Jankovic J, Clarence-Smith K. Tetrabenazine for the treatment of chorea and other hyperkinetic movement disorders. Expert Rev Neurother. 2011;11:1509–1523.
17. Vijayakumar D, Jankovic J. Drug-induced dyskinesia, part 2: treatment of tardive dyskinesia. Drugs. 2016;76:779–787.
•• **Comprehensive review of therapeutic strategies in the treatment of tardive dyskinesia.**
18. Waln O, Jankovic J. An update on tardive dyskinesia: from phenomenology to treatment. Tremor Other Hyperkinet Mov (N. Y). 2013;3:1–11.
19. Chen JJ, Ondo WG, Dashtipour K, et al. Tetrabenazine for the treatment of hyperkinetic movement disorders: a review of the literature. Clin Ther. 2012;34:1487–1504.
20. Schmidt C. First deuterated drug approved. Nat Biotechnol. 2017;35:493–494.
21. Mehanna R, Hunter C, Davidson A, et al. Analysis of CYP2D6 genotype and response to tetrabenazine. Mov Disord. 2013;28:210–215.
22. Huntington Study Group. Tetrabenazine as antichorea therapy in Huntington disease: a randomized controlled trial. Neurology. 2006;66:366–372.
•• **Report of the pivotal trial of TBZ that led to the approval of the drug by the FDA for the treatment of HD-related chorea.**
23. Kenney C, Hunter C, Jankovic J. Long-term tolerability of tetrabenazine in the treatment of hyperkinetic movement disorders. Mov Disord. 2007;22:193–197.
24. Frank S. Tetrabenazine as anti-chorea therapy in Huntington disease: an open-label continuation study. Huntington Study Group/TETRA-HD Investigators. BMC Neurol. 2009;9:62.
25. Frank S, Ondo W, Fahn S, et al. A study of chorea after tetrabenazine withdrawal in patients with Huntington disease. Clin Neuropharmacol. 2008;31:127–133.
26. Armstrong MJ, Miyasaki JM. American Academy of Neurology. Evidence-based guideline: pharmacologic treatment of chorea in Huntington disease: report of the guideline development subcommittee of the American Academy of Neurology. Neurology. 2012;79:597–603.
27. Mestre T, Ferreira J, Coelho MM, et al. Therapeutic interventions for disease progression in Huntington's disease. Cochrane Database Syst Rev. 2009 Jul 8;(3):CD006455.
28. Mestre TA, Ferreira JJ. An evidence-based approach in the treatment of Huntington's disease. Parkinsonism Relat Disord. 2012;18:316–320.
29. Miguel R, Mendonça MD, Barbosa R, et al. Tetrabenazine in treatment of hyperkinetic movement disorders: an observational study. Ther Adv Neurol Disord. 2017;10:81–90.
30. Mehanna R, Jankovic J. Movement disorders in cerebrovascular disease. Lancet Neurol. 2013;12:597–608.
31. Calabrò RS, Polimeni G, Gervasi G, et al. Postthalamic stroke dystonic choreoathetosis responsive to tetrabenazine. Ann Pharmacother. 2011;45:e65.
32. Ondo WG, Adam OR, Jankovic J, et al. Dramatic response of facial stereotype/tic to tetrabenazine in the first reported cases of neuroferritinopathy in the United States. Mov Disord. 2010;25:2470–2472.
33. Gras D, Jonard L, Roze E, et al. Benign hereditary chorea: phenotype, prognosis, therapeutic outcome and long term follow-up in a large series with new mutations in the TITF1/NKX2-1 gene. J Neurol Neurosurg Psychiatry. 2012;83:956–962.
34. Chang FCF, Westenberger A, Dale RC, et al. Phenotypic insights into ADCY5-associated disease. Mov Disord. 2016;31:1033–1040.
35. Carecchio M, Mencacci NE, Iodice A, et al. ADCY5-related movement disorders: frequency, disease course and phenotypic variability in a cohort of paediatric patients. Parkinsonism Relat Disord. 2017;41:37–43.
36. Cardoso F. Autoimmune choreas. J Neurol Neurosurg Psychiatry. 2017;88:412–417.
• **A succinct and comprehensive review of autoimmune choreas.**
37. Baizabal-Carvallo JF, Jankovic J. Movement disorders in autoimmune diseases. Mov Disord. 2012;27:935–946.
38. Caviness JN. Treatment of myoclonus. Neurotherapeutics. 2014;11:188–200.
39. Roth J. The colorful spectrum of Tourette syndrome and its medical, surgical and behavioral therapies. Parkinsonism Relat Disord 2017. [Epub ahead of print]. DOI: 10.1016/j.parkreldis.2017.08.004
40. Waln O, Jankovic J. Paroxysmal movement disorders. Neurol Clin. 2015;33:137–152.
• **Comprehensive review of paroxysmal movement disorders including treatment.**
41. Reilmann R. Deutetrabenazine-not a revolution but welcome evolution for treating chorea in Huntington disease. JAMA Neurol. 2016;73:1404–1406.
42. Mullard A. Deuterated drugs draw heavier backing. Nat Rev Drug Discov. 2016;15:219–221.
43. Huntington Study Group, Frank S, Testa CM, et al., Effect of deutetrabenazine on chorea among patients with Huntington disease: a randomized clinical trial. JAMA. 2016;316:40–50.
•• **Report of the pivotal trial of deutetrabenazine in the treatment of HD-related chorea.**
44. Claassen DO, Carroll B, De Boer LM, et al. Indirect tolerability comparison of deutetrabenazine and tetrabenazine for Huntington disease. J Clin Mov Disord. 2017;4:3.
45. Frank S, Stamler D, Kayson E, et al. Safety of converting from tetrabenazine to deutetrabenazine for the treatment of chorea. JAMA Neurol. 2017;74:977–982.
46. Stamler D, Bradbury M, Brown F. The pharmacokinetics and safety of deuterated-tetrabenazine (P07.210). Neurology. 2013;80:P07.210-P07.210.
47. Anderson KE, Stamler D, Davis MD, et al. Deutetrabenazine for treatment of involuntary movements in patients with tardive dyskinesia (AIM-TD): a double-blind, randomised, placebo-controlled, phase 3 trial. The Lancet Psychiatry. 2017;4:595–604.
48. Grigoriadis DE, Smith E, Hoare SRJ, et al. Pharmacologic characterization of valbenazine (NBI-98854) and its metabolites. J Pharmacol Exp Ther. 2017;361:454–461.
49. Davis MC, Miller BJ, Kalsi JK, et al. Efficient trial design - FDA approval of valbenazine for tardive dyskinesia. N Engl J Med. 2017;376:2503–2506.
50. Hauser RA, Factor SA, Marder SR, et al. KINECT 3: a phase 3 randomized, double-blind, placebo-controlled trial of valbenazine for tardive dyskinesia. Am J Psychiatry. 2017;174:476–484.
51. Unti E, Mazzucchi S, Palermo G, et al. Antipsychotic drugs in Huntington's disease. Expert Rev Neurother. 2017;17:227–237.
52. Linet LS. Tourette syndrome, pimozide, and school phobia: the neuroleptic separation anxiety syndrome. Am J Psychiatry. 1985;142:613–615.
53. Burn D. Oxford textbook of movement disorders. Oxford: Oxford University Press; 2013. p. 251–253.
54. Burgunder J-M, Guttman M, Perlman S, et al. An international survey-based algorithm for the pharmacologic treatment of chorea in Huntington's disease. PLoS Curr. 2011;3:RRN1260.
55. Reilmann R. Pharmacological treatment of chorea in Huntington's disease-good clinical practice versus evidence-based guideline. Mov Disord. 2013;28:1030–1033.
56. Deroover J, Baro F, Bourguignon RP, et al. Tiapride versus placebo: a double-blind comparative study in the management of Huntington's chorea. Curr Med Res Opin. 1984;9:329–338.
57. Carbon M, Hsieh C-H, Kane JM, et al. Tardive dyskinesia prevalence in the period of second-generation antipsychotic use: a meta-analysis. J Clin Psychiatry. 2017;78:e264–e278.
58. Priller J, Ecker D, Landwehrmeyer B, et al. A Europe-wide assessment of current medication choices in Huntington's disease. Mov Disord. 2008;23:1788.
59. Solmi M, Murru A, Pacchiarotti I, et al. Safety, tolerability, and risks associated with first- and second-generation antipsychotics: a state-of-the-art clinical review. Ther Clin Risk Manag. 2017;13:757–777.
60. Komossa K, Rummel-Kluge C, Schwarz S, et al. Risperidone versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev. 2011 Jan 19;(1):CD006626.
61. Brusa L, Orlacchio A, Moschella V, et al. Treatment of the symptoms of Huntington's disease: preliminary results comparing aripiprazole and tetrabenazine. Mov Disord. 2009;24:126–129.
62. Ciammola A, Sassone J, Colciago C, et al. Aripiprazole in the treatment of Huntington's disease: a case series. Neuropsychiatr Dis Treat. 2009;5:1–4.

63. Peña MS, Yaltho TC, Jankovic J. Tardive dyskinesia and other movement disorders secondary to aripiprazole. Mov Disord. 2011;26:147–152.
64. Dean SL, Singer HS. Treatment of Sydenham's chorea: a review of the current evidence. Tremor Other Hyperkinet Mov (N. Y). 2017;7:456.
65. Miyasaki JM, Aldakheel A. Movement disorders in pregnancy. Continuum (Minneap. Minn). 2014;20:148–161.
66. Walker RH. Management of neuroacanthocytosis syndromes. Tremor Other Hyperkinet Mov (N. Y). 2015;5:346.
67. Kumar N, Rizek P, Jog M. Neuroferritinopathy: pathophysiology, presentation, differential diagnoses and management. Tremor Other Hyperkinet Mov (N. Y). 2016;6:355.
68. Vijayakumar D, Jankovic J. Drug-induced dyskinesia, part 1: treatment of levodopa-induced dyskinesia. Drugs. 2016;76:759–777.
69. Verhagen Metman L, Morris MJ, Farmer C, et al. Huntington's disease: a randomized, controlled trial using the NMDA-antagonist amantadine. Neurology. 2002;59:694–699.
70. Lucetti C, Del Dotto P, Gambaccini G, et al. IV amantadine improves chorea in Huntington's disease: an acute randomized, controlled study. Neurology. 2003;60:1995–1997.
71. O'Suilleabhain P, Dewey RB. A randomized trial of amantadine in Huntington disease. Arch Neurol. 2003;60:996–998.
72. Nissenkorn A, Hassin-Baer S, Lerman SF, et al. Movement disorder in ataxia-telangiectasia: treatment with amantadine sulfate. J Child Neurol. 2013;28:155–160.
73. Park H, Jeon BS, Shin JH, et al. A patient with 41 CAG repeats in SCA17 presenting with parkinsonism and chorea. Parkinsonism Relat Disord. 2016;22:106–107.
74. Oertel W, Eggert K, Pahwa R, et al. Randomized, placebo-controlled trial of ADS-5102 (amantadine) extended-release capsules for levodopa-induced dyskinesia in Parkinson's disease (EASE LID 3). Mov Disord. 2017. [Epub ahead of print]. DOI: 10.1002/mds.27131.
75. Huntington Study Group. Dosage effects of riluzole in Huntington's disease: a multicenter placebo-controlled study. Neurology. 2003;61:1551–1556.
76. Landwehrmeyer GB, Dubois B, de Yébenes JG, et al. Riluzole in Huntington's disease: a 3-year, randomized controlled study. Ann Neurol. 2007;62:262–272.
77. Saft C, Lauter T, Kraus PH, et al. Dose-dependent improvement of myoclonic hyperkinesia due to Valproic acid in eight Huntington's Disease patients: a case series. BMC Neurol. 2006;6:11.
78. Wu CK, Santini VE, Dittus C, et al. Neuroacanthocytosis: a case with unusual clinical features & novel response to treatment. J Neurol Sci. 2017;373:346.
79. Walker RH. Update on the non-Huntington's disease choreas with comments on the current nomenclature. Tremor Other Hyperkinet Mov (N. Y). 2012;2:1–7.
80. Al-Asmi A, Jansen AC, Badhwar A, et al. Familial temporal lobe epilepsy as a presenting feature of choreoacanthocytosis. Epilepsia. 2005;46:1256–1263.
81. de Tommaso M, Di Fruscolo O, Sciruicchio V, et al. Efficacy of levetiracetam in Huntington disease. Clin Neuropharmacol. 2005;28:280–284.
82. Zesiewicz TA, Sullivan KL, Hauser RA, et al. Open-label pilot study of levetiracetam (Keppra) for the treatment of chorea in Huntington's disease. Mov Disord. 2006;21:1998–2001.
83. Zesiewicz TA, Sanchez-Ramos J, Sullivan KL, et al. Levetiracetam-induced parkinsonism in a Huntington disease patient. Clin Neuropharmacol. 2005;28:188–190.
84. Mencacci NE, Carecchio M. Recent advances in genetics of chorea. Curr Opin Neurol. 2016;29:486–495.
85. Papandreou A, Schneider RB, Augustine EF, et al. Delineation of the movement disorders associated with FOXG1 mutations. Neurology. 2016;86:1794–1800.
86. Gardella E, Becker F, Møller RS, et al. Benign infantile seizures and paroxysmal dyskinesia caused by an SCN8A mutation. Ann Neurol. 2016;79:428–436.
87. Sakamoto S, Monden Y, Fukai R, et al. A case of severe movement disorder with GNAO1 mutation responsive to topiramate. Brain Dev. 2017;39:439–443.
88. Waak M, Mohammad SS, Coman D, et al. GNAO1-related movement disorder with life-threatening exacerbations: movement phenomenology and response to DBS. J Neurol Neurosurg Psychiatry. 2017. [Epub ahead of print].
89. Frank S, Jankovic J. Advances in the pharmacological management of Huntington's disease. Drugs. 2010;70:561–571.
90. Pandey S, Gupta S. Lower limb monochorea from a globus pallidus infarct. J Clin Neurosci. 2014;21:1455–1457.
91. Shannon KM. Pridopidine for the treatment of Huntington's disease. Expert Opin Investig Drugs. 2016;25:485–492.
92. Ryskamp D, Wu J, Geva M, et al. The sigma-1 receptor mediates the beneficial effects of pridopidine in a mouse model of Huntington disease. Neurobiol Dis. 2017;97:46–59.
93. Huntington Study Group HART Investigators. A randomized, double-blind, placebo-controlled trial of pridopidine in Huntington's disease. Mov Disord. 2013;28:1407–1415.
94. de Yebenes JG, Landwehrmeyer B, Squitieri F, et al. Pridopidine for the treatment of motor function in patients with Huntington's disease (MermaiHD): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2011;10:1049–1057.
95. Patel NJ, Jankovic J. NKX2-1-related disorders. 2014 Feb 20 [Updated 2016 Jul 29]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017.
96. Kluger B, Triolo P, Jones W, et al. The therapeutic potential of cannabinoids for movement disorders. Mov Disord. 2015;30:313–327.
97. Curtis A, Mitchell I, Patel S, et al. A pilot study using nabilone for symptomatic treatment in Huntington's disease. Mov Disord. 2009;24:2254–2259.
98. López-Sendón Moreno JL, García Caldentey J, Trigo Cubillo P, et al. A double-blind, randomized, cross-over, placebo-controlled, pilot trial with Sativex in Huntington's disease. J Neurol. 2016;263:1390–1400.
99. O'Toole O, Lennon VA, Ahlskog JE, et al. Autoimmune chorea in adults. Neurology. 2013;80:1133–1144.
100. Paz JA, Silva CAA, Marques-Dias MJ. Randomized double-blind study with prednisone in Sydenham's chorea. Pediatr Neurol. 2006;34:264–269.
101. Mckeon A, Vincent A. Autoimmune movement disorders. Handb Clin Neurol. 1st. 2016;133: 301–315.
102. Baizabal-Carvallo JF, Bonnet C, Jankovic J. Movement disorders in systemic lupus erythematosus and the antiphospholipid syndrome. J Neural Transm. 2013;120:1579–1589.
103. Gaig C, Graus F, Compta Y, et al. Clinical manifestations of the anti-IgLON5 disease. Neurology. 2017;88:1736–1743.
104. Marvi MM, Lew MF. Polycythemia and chorea. Handb Clin Neurol. 2011;100:271–276.
105. Degnan AJ, Capek E, Bowman A. Chorea in the older adult: a full blooded answer. J R Coll Physicians Edinb. 2016;46:244–246.
106. Andrade C, Rocha H, Albuquerque A, et al. Gluten chorea. Clin Neurol Neurosurg. 2015;138:8–9.
107. Hermann A, Walker RH. Diagnosis and treatment of chorea syndromes. Curr Neurol Neurosci Rep. 2015;15:514.
108. di Biase L, Munhoz RP. Deep brain stimulation for the treatment of hyperkinetic movement disorders. Expert Rev Neurother. 2016;16:1067–1078.
    - **A comprehensive review of DBS in hyperkinetic movement disorders that includes commentary on current and potential targets.**
109. Smith KM, Spindler MA. Uncommon applications of deep brain stimulation in hyperkinetic movement disorders. Tremor Other Hyperkinet Mov (N. Y). 2015;5:278.
110. Hartmann CJ, Groiss SJ, Vesper J, et al. Brain stimulation in Huntington's disease. Neurodegener Dis Manag. 2016;6:223–236.
111. Gonzalez V, Cif L, Biolsi B, et al. Deep brain stimulation for Huntington's disease: long-term results of a prospective open-label study. J Neurosurg. 2014;121:114–122.
112. Gruber D, Kuhn AA, Schoenecker T, et al. Quadruple deep brain stimulation in Huntington's disease, targeting pallidum and subthalamic nucleus: case report and review of the literature. J Neural Transm. 2014;121:1303–1312.

113. Wojtecki L, Groiss SJ, Ferrea S, et al. A prospective pilot trial for pallidal deep brain stimulation in Huntington's Disease. Front Neurol. 2015;6:177.
114. Sharma M, Deogaonkar M. Deep brain stimulation in Huntington's disease: assessment of potential targets. J Clin Neurosci. 2015;22:812–817.
115. Edwards TC, Zrinzo L, Limousin P, et al. Deep brain stimulation in the treatment of chorea. Mov Disord. 2012;27:357–363.
116. Miquel M, Spampinato U, Latxague C, et al. Short and long term outcome of bilateral pallidal stimulation in chorea-acanthocytosis. Gonzalez-Alegre P, editor. PLoS One. 2013;8:e79241.
• **A worldwide, 12-center, cross-sectional, retrospective study that assessed the effectiveness of bilateral GPi DBS in a group of 15 patients affected by neuroacanthocytosis.**
117. Nakano N, Miyauchi M, Nakanishi K, et al. Successful combination of pallidal and thalamic stimulation for intractable involuntary movements in patients with neuroacanthocytosis. World Neurosurg. 2015;84:1177.e1–7.
118. Bhidayasiri R, Fahn S, Weiner WJ, et al. Evidence-based guideline: treatment of tardive syndromes: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2013;81:463–469.
119. van Coller R, Slabbert P, Vaidyanathan J, et al. Successful treatment of disabling paroxysmal nonkinesigenic dyskinesia with deep brain stimulation of the globus pallidus internus. Stereotact Funct Neurosurg. 2014;92:388–392.
120. Burgunder J-M. Recent advances in the management of choreas. Ther Adv Neurol Disord. 2013;6:117–127.
121. Shukla A, Jayarajan RN, Muralidharan K, et al. Repetitive transcranial magnetic stimulation not beneficial in severe choreiform movements of Huntington disease. J Ect. 2013;29:e16–7.