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Treatment of startle and related disorders

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"Startle" is defined as an intense involuntary movement of the body caused by a sudden tactile, visual and acoustic stimulus [1]. Startle has a quick jerk-like movement satisfying the motor component definition of myoclonus. Startle disorders may be familial or sporadic. Excessive startle disorders are often typified by intense motor responses to unexpected auditory, visual or somesthetic stimuli.

A thorough evaluation and classification for startle disorders is critical for the development of appropriate management plan which has been simplified in a flowchart shown in Fig. 3. Bakker MJ et al has classified startle syndromes into three heterogenous groups of startle syndromes on the basis of the abnormal responses, namely hyperekplexia, stimulus-induced disorders and neuropsychiatric syndromes [2]. The first group forms the hyperekplexia which are mainly hereditary, though there are major and minor forms. The second group are the stimulus-induced disorders where startling stimuli evokes an abnormal response pattern eg. startle epilepsy. The third group of disorders are the neuropsychiatric culture specific disorders where excessive startling occurs in combination with behavioural features. These culture-specific syndromes are restricted to a limited number of cultures primarily as a result of their psychosocial features.

Treatment of startle disorders remains challenging and thus require a comprehensive and multidisciplinary care (Fig. 1). The shared responsibility involves a neurologist/movement disorder specialist, physiotherapist, occupational therapist, neuropsychiatrist/psychologist and/or rehabilitation physician.

1. Search strategy and selection criteria

We searched PubMed for papers published in English between 1979 and 2023 with the terms "startle", "startle syndrome", "hyperekplexia", "reflex myoclonus", "cortical myoclonus", "reticular myoclonus", "propriospinal myoclonus", "stiff person syndrome", "Progressive encephalomyelitis with rigidity and myoclonus", "tetanus" and "startle induced tics" and selected clinical trials, *meta*-analysis, randomized controlled trials, review and systemic review. Main treatment approaches for startle and related disorders are illustrated in Fig. 2, and the supporting literature for these approaches are summarized in Table 1.

2. Hyperekplexia

Hyperekplexia is characterized by an exaggerated response to trivial stimuli that are mostly acoustic and tactile. The pathogenesis is associated with deficiency of glycine, an inhibitory central neurotransmitter [3]. Clonazepam is considered the medication of choice in hyperekplexia [4]. It potentiates the inhibitory neurotransmitter GABA by binding to benzodiazepine binding sites related to GABA receptors and has been clinically proven as an effective symptomatic treatment for severe hereditary or symptomatic hyperekplexia at a dose of (1 mg/day). In gene positive cases of GLRA1 and GlyT2, clonazepam (with an initial dose of 0.5 mg daily and titrated up to 6 mg daily) has been shown to be effective [4]. Its effect can also be appreciated when used in combination with other benzodiazepines. Combination of clobazam-clonazepam provided a dramatic and rapid reduction in stimulus-induced falling with improved ambulation in hyperekplexia in one paediatric case report [5,6]. However, the use of benzodiazepines are limited by their side effects, especially sedation. Though the clinical effect of clonazepam has been consistent in most studies, few isolated case reports with contradictory results have been published [7]. A case report has shown that sodium valproate, 5-hydroxytryptophan and piracetam improved startle in three patients whereas clonazepam and phenobarbital proved ineffective [8]. Aside from benzodiazepines, fluoxetine at a dose of 20 mg a day and 40 mg a day has also been shown to be beneficial in the reduction of startle activity in an isolated case report [9]. This suggests that serotonergic mechanism may be involved in modulation of movement and hyperekplexia. Similarly, the therapeutic effect of clonazepam and 5- hydroxytryptophan may also be due

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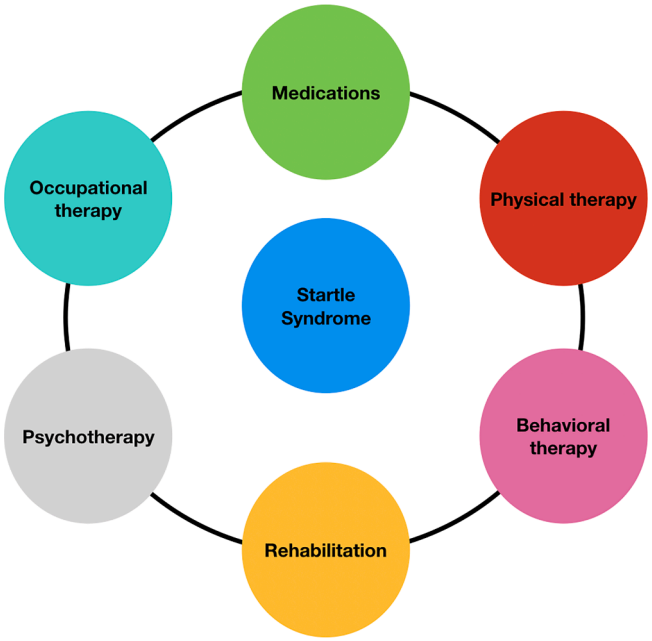

Fig. 1. Multidisciplinary approach in the treatment of startle and related disorders.

to their ability to activate the serotonin pathway in the brain, thus supporting the point that serotonergic mechanisms play a role in hyperekplexia. Vigabatrin, a GABA transaminase inhibitor was considered a good consideration in view of the pathogenesis of abnormal startle despite failure in a double-blind placebo-controlled cross-over study in 4 patients as opposed to clonazepam [6]. Anaesthetics that has the combined ability to potentiate both GABA-ergic and glycinergic transmission may be considered in patients with hyperekplexia [10]. Intravenous propofol has been shown to restore the function of hyperexplexic mutant glycine receptors in a mouse model [11]. There are conflicting results with depolarising and non-depolarising neuromuscular blocking agents and therefore should be used with caution and close monitoring [10].

Physical and cognitive therapy remains an important treatment to reduce fear of falling and improve walking. "Vigevano" maneuver, which consist of forced flexion of the head and legs toward the trunk may relieve attacks, especially in the newborn period [12]. Aside from symptomatic treatment, genetic work-up and counselling are also important as certain mutations have been found to be causative in hereditary hyperekplexia, ie, GLRA1, SLC6A5, GLRB, GPHN and ARHGEF9 [13].

Newer therapies target the GABAA-receptors. The function of GABAA receptors is affected by the interaction between GABAA and the mutated a1-subunit of GlyR whereby the mutant GlyR hijacks the GABAA receptor. The pre- and extra-synaptic GABAARs are deficient in hyperekplexia [14]. Dehydroxylcannabidiol (DH-CBD), a synthetic nonpsychoactive cannabinoid can restore GABAR GlyR functional deficiency in hereditary startle-hyperekplexia syndrome in mouse models [15].

3. Stimulus-induced disorders

The startle-induced disorders include startle epilepsy, reflex myoclonus, startle- induced stiffness and other rare diseases [16]. In this group of disorders, a startling stimulus can trigger an excessive response or startle reflex. The treatment of stimulus-induced disorders largely depends on the etiology of the condition. Startle-induced stiffness are broadly categorized into immune-mediated, toxin-related and infective cause [2]. Immune-medicated forms of startle-induced stiffness are stiff-person syndrome and progressive encephalomyelitis with rigidity (PERM) whereas an example of toxin-related startle disorder is strychnine poisoning. Tetanus, a lethal bacterial infection caused by the

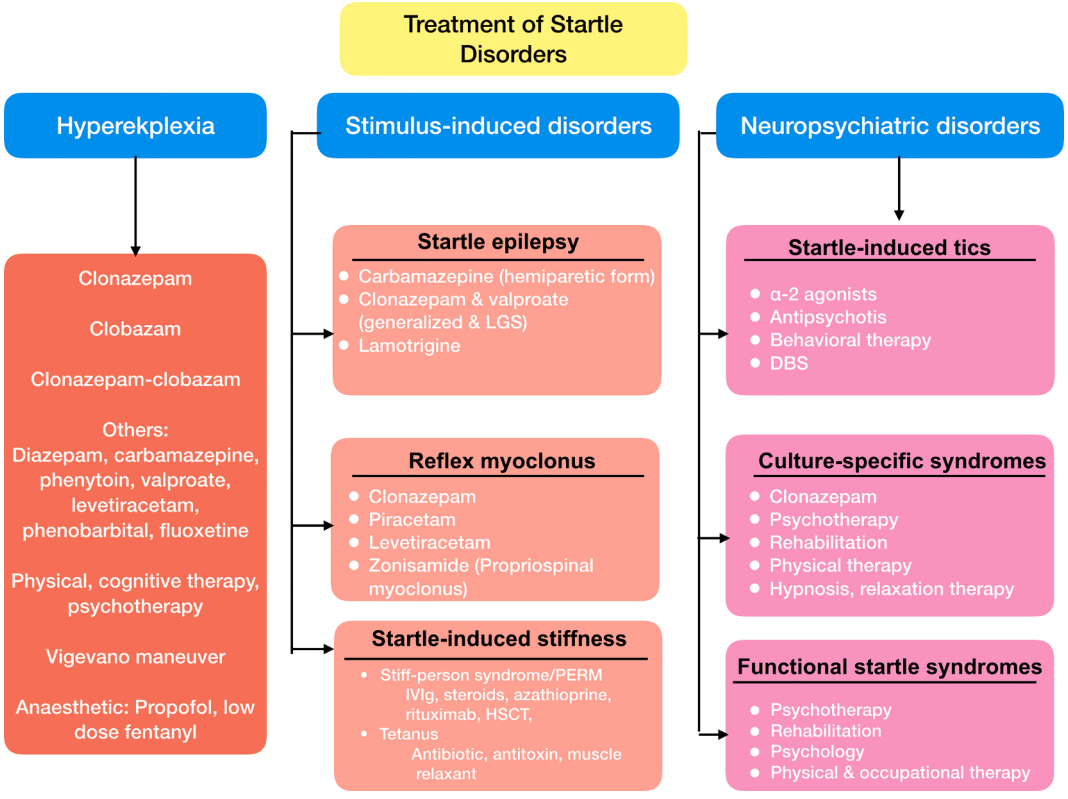

Fig. 2. Treatment algorithm of treatment of startle disorders.

neurotoxin presents typically with increase muscle stiffness and spasms in the back muscles (opisthotonos), jaw (trismus), face (risus sardonicus) and muscles of respiration and these stiffness occasionally occur with startle response. Other rare forms of startle-induced stiffness are paroxysmal kinesigenic dyskinesia, cataplexy, Creutzfeldt-Jakob disease, subacute sclerosing panencephalitis and paraneoplastic syndromes. Generally, startle epilepsy and reflex myoclonus are generally treated with antiepileptics as shown in Fig. 2.The choice of antiepileptic drug (AED) prescribed would depend on various factors including AED effectiveness in the type startle epilepsy or myoclonus, adverse effects of the AED such as sedation from clonazepam or rashes from carbamazepine in patients with HLA-B*1502, affordability of the AED, availability of the AED and potential interaction of the AED with other medications.

The hemiparetic form of startle epilepsy has been reported to be responsive to carbamazepine while valproic acid and clonazepam are effective for generalised form and Lennox-Gastaut syndrome [6]. Observational case series of subjects with uncontrolled seizures showed that lamotrigine as an adjunctive therapy to valproic acid, clobazam, phenytoin and zonisamide reduced episodes of startle epilepsy [17,18]. Levetiracetam, a synaptic vesicle protein 2A (SV2A) modulator is effective in the treatment of startle epilepsy as an add-on therapy [19]. Perampanel, a high-selective, non-competitive antagonist of AMPA receptors has been shown in a case report to be effective in treating startle-induced epilepsy [20]. Despite its effectiveness in treating startle-induced myoclonus, extreme caution of the psychiatric side effects in patients treated with perampanel, principally, irritability and aggression is warranted. Surgical treatment on the other hand is only effective if there is an identifiable structural lesion.

Cortical myoclonus, often focal multifocal is commonly action-induced, sensitive to tactile stimulus and prominent in the hands and face. Subcortical myoclonus, commonly generalised and affects both arms, synchronous flexor response and sensitive to auditory stimulus. Reticular reflex myoclonus resembles hyperekplexia. Reticular reflex myoclonus originates in the lower brainstem. Reticular myoclonus more often presents with stimulus sensitivity over the limbs while propriospinal myoclonus presents with stimulus sensitivity over the abdomen. Antiepileptics are the mainstay of treatment in cortical-subcortical myoclonus. Piracetam at a dose of 7–24 g daily has been shown to be effective in cortical myoclonus in a double blind placebo controlled trial [21]. On the other hand, reticular reflex myoclonus only respond partially to clonazepam. There is lack of evidence to support the other treatments in reticular reflex myoclonus. Alternatively, levetiracetam which exerts antimyoclonic effect has been proven effective for treatment of cortical myoclonus in open-label trials [22]. Observational retrospective series showed that propriospinal myoclonus was ameliorated by the use of zonisamide, levetiracetam and clonazepam [23,24].

Startle-induced stiffness, typically seen in stiff-person syndrome is characterised by progressive intermittent spasms of the legs and lumbar region lasting seconds to minutes. Immunotherapy and symptomatic treatments remain the mainstay in the management of stiff-person syndrome. Intravenous immune globulin was efficacious in reducing spasms and activities of daily living [25]. A randomized, double blind, placebo-controlled crossover study done by Dalakas showed that the use of intravenous immunoglobulin was effective in reducing stiffness scores of patients with stiff person syndrome [26,27]. Though case reports and case series suggest that corticosteroids, azathioprine and rituximab are beneficial, a placebo-controlled randomised trial of rituximab in stiff-person syndrome showed no significant difference in stiffness, heightened sensitivity and quality of life between rituximab and placebo [28]. The heightened sensitivity scale comprises of several startle-induced stiffness and cramps namely noise-induced stiffness and cramps, somatosensory- induced stiffness and cramps [29]. There were mixed

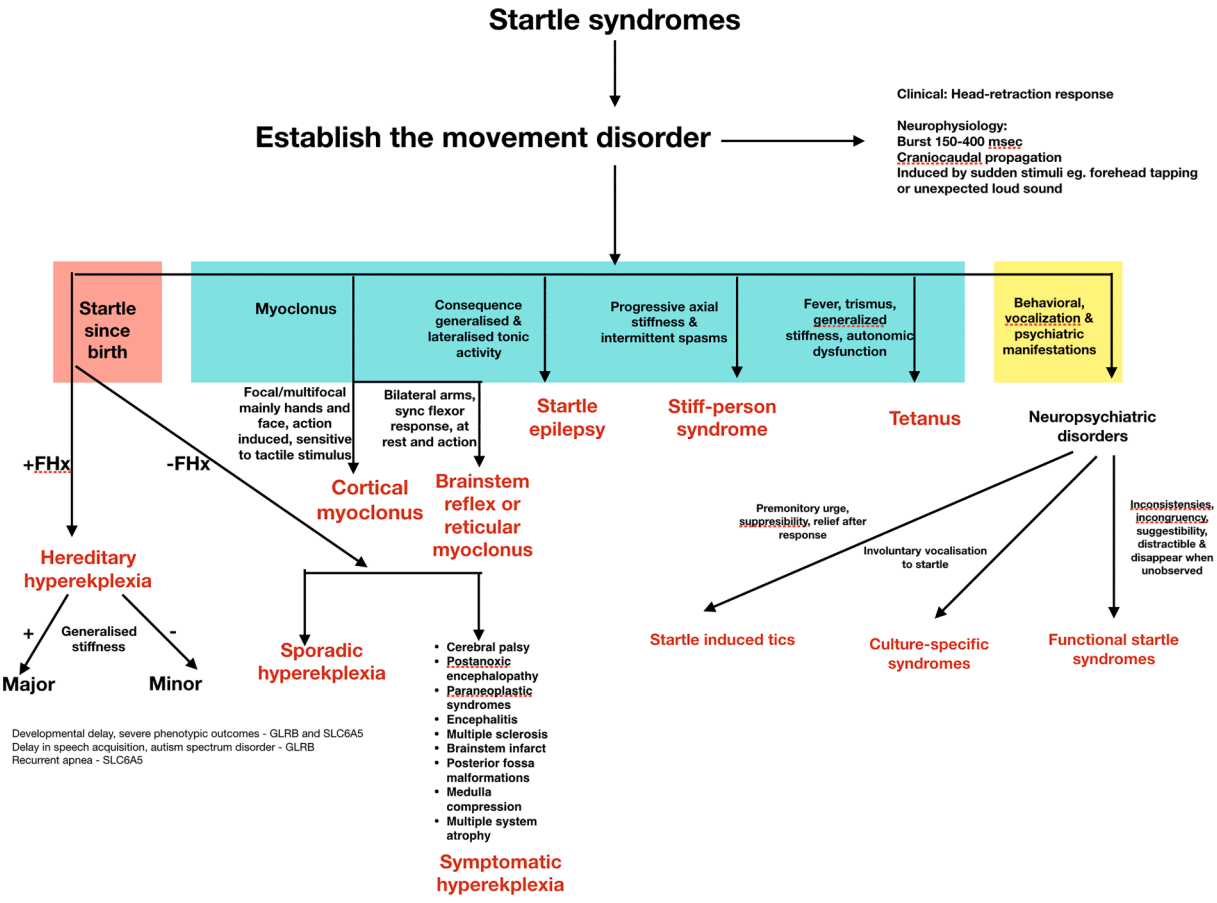

Fig. 3. Algorithm of the clinical approach to the diagnosis of startle and related disorders.

Table 1
Summary of clinical studies on pharmacological treatment for startle syndrome and related disorders.

First Author & Year of Publication	Study Design, Intervention and Sample Size	Study Outcomes
Hyperekplexia (comprehensively including all clinical trial, meta analysis, randomized controlled trial, and systematic review – total 7 results, with subsequent review of their respective references for quoted papers i.e. relevant case series**)**		
Jun Mine, 2014	Observational / retrospective series of 17 patients with variable follow-up duration up to 5 years	13 of 17 subjects were treated with clonazepam: Muscle stiffness disappearance was reported in 9 of the 13 subjects; Remission or disappearance of motor startle responses was reported in 10 of the 13 subjects.
M.A.J. Tijssena, 1997	Double-blind, placebo-controlled, cross-over trial with a washout period of two weeks involving 4 adult males. Study medications were identical capsules containing 1 mg of clonazepam or 1000 mg of vigabatrin or placebo	Clonazepam reduced the magnitude of motor startle responses in patients with hereditary hyperekplexia, while no significant changes for vigabatrin and placebo; The average visual analogue scores for the three treatments showed no significant changes in each of the 4 scores: observer-scored stiffness, patient-scored stiffness, observer-scored drowsiness, and patient-scored drowsiness.
Ryan SG, 1992	Observational cohort with variable follow-up duration (up to 36 months) involving 16 patients with relatively severe symptoms being treated with clonazepam	Total daily dose of clonazepam did not exceed 3.0 mg (1.5 mg for children) in any patient. All experienced dramatic improvement of the symptoms of stiffness, startling, and nocturnal muscle jerks, and no patient had startle-induced falls.
Michael A. Nigro, 1992	Observational / retrospective case series of 15 patients	Clonazepam (0.1–0.2 mg/kg/day) was efficacious in preventing the apneic episodes in infancy and diminishing the startle response. In older patients, a dose of 2–6 mg/day was effective in preventing startle reactions with drop attacks and rigidity.
Frederick Andermann, 1980	Observational / retrospective case series of 3 patients	Case 1 – Treatment with clonazepam 2 mg BD abolished the falling attacks and the prolonged episodes of generalized jerking. The startle response was improved. Case 2 – Treatment with clonazepam 1 mg BD led to striking improvement in her gait, which became more secure and firm; her falling attacks ceased and her startle reactions, though still abnormal, were much diminished. Case 3 - Response to clonazepam was also very similar and pronounced with stable gait and no falls.
Startle Epilepsy (comprehensively including all clinical trial, meta analysis, randomized controlled trial, and systematic review – total 4 results, with subsequent review of their respective references for quoted papers i.e. relevant case series**)**		
Hiroko Ikeda, 2011	Observational / retrospective case series of 3 patients with uncontrolled seizures. Lamotrigine was initiated as add-on / adjunctive therapy to other anti-seizure medications.	Case 1, 19yo male – lamotrigine 225 mg/day was added to valproate and clobazam, subsequently seizure frequency reduced from few episodes daily to once a month. Case 2, 51yo female – lamotrigine 150 mg/day was added to clobazam, zonisamide, and phenytoin, subsequently seizure frequency reduced from 5 to 15 episodes daily to less than once a month. Case 3, 6yo, female – lamotrigine 20 mg/day was added to valproate, subsequently severity of startle-induced seizures was attenuated to a degree that injury was avoided, even though decrease in seizure frequency was not significant.
Candan Gürses, 2007	Observational / retrospective series of 10 adults with uncontrolled seizures treated with levetiracetam as adjunct to other anti-seizure medications, with a maximum dose of 3000 mg daily. Seizure control was subsequently observed for 12–28 months with an average follow-up period was 22.66 ± 5.50 (12–28) months.	Average dose of levetiracetam was 1916.66 ± 861.20 (500–3000) mg. Six of the 10 patients demonstrated good response:3 (30%) were seizure free, 3 (30%) had 50–90% seizure reduction, 1 (10%) had 25–50% seizure reduction, and 3 (30%) had seizure increment.
Edward Faught, 1999	Observational / retrospective case series of 4 patients with uncontrolled seizures. Lamotrigine was initiated as add-on / adjunctive therapy to other anti-seizure medications.	Case 1, 18yo female – lamotrigine 100 mg/day was added to valproate, subsequently her seizure frequency improved from daily seizure to seizure free for 1 year. Case 2, 24yo female – lamotrigine 250 mg/day was added to valproate, subsequently she improved with no further seizure and no falls / drop attacks for 3 years. Case 3, 26yo female – lamotrigine 75 mg/day was added to valproate and clobazam, subsequently resulted in immediate improvement in her seizure frequency with no further falls / drop attacks. Case 4, 62yo female – lamotrigine 100 mg/day was added to gabapentin and topiramate, subsequently her frequency of falls / drop attacks decreased from 2 to 5 weekly to none within 2 weeks of initiating lamotrigine.
P. Tinuper, 1986	Observational / retrospective series of 16 patients with uncontrolled seizure on anti-seizure medications.	One week after the introduction of clobazam, 10 of the 13 patients showed a complete or almost complete control of the induced seizures.

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Table 1 (*continued*)

First Author & Year of Publication	Study Design, Intervention and Sample Size	Study Outcomes
	Clobazam was added to the previous ineffective treatments in 13 patients, at doses of 0.5 to 1.3 mg/kg/day (average 0.8 mg/kg/day)	Eight of the 13 patients were on long follow-up - six patients maintained complete seizure control (100% reduction in seizures) for a mean of 24.2 months; meanwhile two patients showed a partial reduction in the initial complete control (60% and 70% reduction in frequency respectively) for a mean of 18.5 months.
E. Shenz-Lope, 1984	Observational / retrospective series of 14 patients observed over an average of 8 years (range, 2 to I4 years).	Two patients with Lennox-Gastaut syndrome were brought under satisfactory control with clonazepam Four patients had a 70% to 100% reduction in seizure frequency with valproate treatment. Carbamazepine caused improvement in eight patients with five of them being seizure free. However, eight of these 14 patients did not respond to clonazepam.
S. Gimenez-Roldan, 1979	Observational / retrospective case series of 5 children and adolescents with cerebral palsy who suffered from uncontrolled epilepsy despite being on antiseizure medications. Clonazepam was initiated as adjunct to other antiseizure medications, at a mean daily dosage of 3.4 mg/day, range of 1.5—–8 mg/day	Dramatic reductions in the frequency of startle-induced seizures was recorded: Four patients became seizure free after the first month of clonazepam; Another one patient recorded seizures reduction from a mean of 21 per week to 1 per week.
Reflex Myoclonus – cortical myoclonus (27 results)		
Pasquale Striano, 2005	Short, open-label, add-on trial involving 16 subjects to evaluate the antimyoclonic effect and tolerability of orally administrated levetiracetam in patients with chronic refractory cortical myoclonus of various degrees of severity and of different causes. Levetiracetam was orally administered at a starting dose of 500 mg twice daily for 1 week followed by increments of 500 mg twice daily each week up to the target dose of 50 mg/kg/day (titration phase).	Levetiracetam dose reached was between 3,000 and 4,000 mg/day (mean dose, 3,214 mg/day. In all 14 patients who completed the trial, add-on levetiracetam was associated with clinical improvement of myoclonus and a significant lowering of the mean scores of all Unified Myoclonus Rating Scale sections, except the negative myoclonus section. Effect of levetiracetam was not related to disease duration, cause or severity of myoclonus. Levetiracetam was well tolerated and there were no changes in the plasma level of concomitant antiepileptic drugs during trial.
M. Koskiniemi, 1998	Multicentre, randomised, double blind, crossover study comparing the efficacy and safety of three dosages of oral piracetam with placebo in relieving symptoms in progressive myoclonus epilepsy. Twenty subjects (12 men, eight women) , aged 17–43 years were recruited. Effects of daily doses of 9.6 g, 16.8 g, and 24 g piracetam, given in two divided doses, were compared with placebo. Primary outcome measure was a sum score representing the adjusted total of the ratings of six components of a myoclonus rating scale in which stimulus sensitivity, motor impairment, functional disability, handwriting, and global assessments by investigators and patients were scored	Treatment with 24 g/day piracetam produced significant and clinically relevant improvement in the Unified Myoclonus Rating Scale mean sum score and in the means of its subtests: motor impairment, functional disability, and in global assessments by both investigator and patient. Significant improvement in functional disability was also found with daily doses of 9.6 g and 16.8 g. Dose-effect relation was linear and significant: more patients showed clinically relevant improvement with the highest dosage and, in individual patients, increasing the dose improved response. A dose of 24 g is highly beneficial, more effective than lower doses and that a dose–effect relation exists.
P. Brown, 1993	Placebo-controlled, double-blind, crossover trial over 2 years. 21 subjects (8 males and 13 females; median age 33 years, range 21–72 years) were recruited: All 21 had action myoclonus; 9 had spontaneous myoclonus; 9 also had stimulus-sensitive myoclonus No washout period between each course of treatment. Median duration of the course of piracetam was 14 (range 9–15) days; median duration of treatment with placebo was 9 (range 1–24) days.	In 10 subjects, the relapse in their condition occurred during treatment with placebo, and not piracetam; frequency of relapse during the placebo phase did not differ significantly whether placebo formed the first (four patients relapsed) or second (six patients relapsed) course of treatment in the crossover trial. Each of the individual and total test scores of Unified Myoclonus Rating Scale improved significantly during treatment with piracetam, with exception of the stimulus sensitivity score. 15 of 21 subjects showed significant positive change (improvement) in total myoclonus score.
Reflex Myoclonus – propriospinal myoclonus (all filters – 24 results)		
E. Roze, 2009	Observational / retrospective series of 10 patients aged 17–70.	Three patients improved with zonisamide at daily dose of 100–200 mg. Four patients improved with clonazepam (dose not stated) .
S C Keswani, 2002	Observational / retrospective case series of 3 patients.	Case 1, 62yo female with spinal epidural compression: levetiracetam 500 mg/day resulted in marked reduction in myoclonic jerk frequency and amplitude. Case 2, 85yo female with zoster myelitis: levetiracetam 1000 mg/day resulted in ceasation of myoclonus. Case 3, 12yo male with transverse myelitis: levetiracetam 1250 mg/day resulted in ceasation of myoclonus.
Stiff Person Syndrome (pubmed search: 'stiff person syndrome' + 'clinical trials' = 21 results)		

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Table 1 (*continued*)

First Author & Year of Publication	Study Design, Intervention and Sample Size	Study Outcomes
Albahra, 2019	Retrospective analyses of therapeutic plasma exchange (TPE) in patients with anti-GAD65 positive SPS (n = 10)	Out of 4 patients who underwent acute hospitalized course of TPE, one had complete resolution of symptoms, one had partial response while two experienced no improvement. Out of 6 patients who had TPE as maintenance treatment, two had transient improvements with further disease progression while four had relapse of symptoms when interval between exchanges was increased. Adverse events were not reported.
Dalakas, 2001	Randomized, double-blind, placebo-controlled crossover study of intravenous immunoglobulin 2 g per kg of body weight per month over 3 months vs. placebo with a one month-washout treatment before cross-over (n = 16) in patients with anti-GAD65 positive SPS.	Among patients who received immune globulin first, Stiffness Index scores decreased significantly and Heightened-Sensitivity scores decreased substantially during immune globulin therapy but rebounded during placebo administration. Among patient who received placebo first, stiffness scores remained constant during initial phase, and decreased significantly during IV immune globulin administration. No major adverse effects were observed.
Dalakas, 2017	Randomized, double-blind, placebo-controlled study of two bi-weekly cycles of intravenous rituximab 1gm (n = 12) vs. placebo (n = 12) with follow-up duration of 6 months	No significant difference in Stiffness Index and Heightened-Sensitivity scores between two groups at month 6. Quality of life improved in both groups at month 3 but not at month 6, indicating an early placebo effect. No major adverse effects were observed.
Burt, 2021	Prospective open-label cohort study (n = 23) of hematopoietic stem cell transplantation (HSCT) in patients with SPS.	Of the 74% of participants who responded, 47% have stayed in remission for a mean of 3.5 years; 26% did not respond. There was no treatment-related mortality. One participant died 1 year after transplantation of disease progression.
Gershlager, 2002	Retrospective case series of 6 patients with SPS who received intravenous immunoglobulin at 0.4 g/kg per day for 5 days. Oral medications (differed among subjects) remained unchanged for 3 months in all subjects.	Significant improvement ($p < 0.05$) in the medical outcomes study short form health survey (SF-36) subscores for pain, social functioning, general mental health, and energy–vitality with treatment. The visual analogue scale (VAS) also improved significantly ($p = 0.03$)
Stayer, 1997	Retrospective case series of on eight patients with SPS (n = 3) and PERM (n = 5) receiving intrathecal baclofen via pump.	General mobility increased, and spasms and rigidity were reduced; however, no complete remissions were observed. Several adverse events observed: spasm-induced rupture of the catheter, catheter dislocation causing radicular symptoms, and pump malfunction resulting in inaccurate dosage administration. Patients suffered fewer side effects with intrathecal baclofen than with oral medication, but overdose resulted in a transient, comalike state in one patient and sudden dosage reduction due to pump failure was fatal in another.
Dalakas, 2005	Randomized, double-blind, placebo-controlled study of 2 g/kg intravenous immunoglobulin, divided into two daily doses or placebo consisting of half-normal saline every month for 3 months with one month washout period before crossing over to the alternative therapy for another 3 months (n = 16)	The stiffness scores (distribution of stiffness index and the heightened sensitivity scores) in the IVIG-randomised patients declined significantly from month 1 through 4, but rebounded when they crossed to placebo. In contrast, the scores in the placebo-randomised group remained constant from month 1–4 but dropped significantly after crossing to IVIg. Anti- GAD_{65} antibody titres declined after IVIg, but not after placebo. None of the subjects had side effects to IVIg.
PERM (pubmed search: 'progressive encephalomyelitis with rigidity and myoclonus' = 102 results)		
Balint, 2014	Retrospective case series in patients with PERM (n = 3) associated with antibodies directed against dipeptidyl peptidase-like protein 6 (DPPX).	**Case 1:** Treatment with IVIg 2 cycles at 2 g/kg per day divided over 2–3 days did not improve condition. 5 sessions of plasma exchange transiently reduced both hyperekplexia and the hand and voice tremor. IV rituximab (4 cycles every 3 months, each 375 mg/m^2) starting 42 months after symptom onset resulted in gradual improvement as substantiated by the Scale for the Assessment and Rating of Ataxia, his handwriting, and the EOG recordings. **Case 2**: Oral treatment with low-dose oral methylprednisolone and clonazepam resulted in stable clinical course for 2 years. No noticeable effect seen after a course of IVIg. **Case 3**: High dose steroid and IVIg (2 g/kg body weight per day over 5 days) only resulted in initial response but effects did not last. Cyclophosphamide and plasma exchange (5 sessions) treatment did not result in treatment response.
Mas 2010	A case series of PERM associated with positive Glycine receptor antibodies (GlyR-ab), n = 3	**Case 1**: A progressive complete recovery (limb rigidity with spasms and involuntary jerks) was obtained initially with corticosteroids, diazepam and baclofen. Relapsed was treated successfully (asymptomatic for 8 years) with a course of intravenous immunoglobulin (IVIG) (0.4 g/kg/ day for 5 days) and restarted with symptomatic therapy. **Case 2**: no treatment was administered. Patient had cardiac arrest 7 days after admission and remained in persistent vegetative state and ventilator dependent.

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Table 1 (*continued*)

First Author & Year of Publication	Study Design, Intervention and Sample Size	Study Outcomes
		Case 3: Treatment with diazepam and gabapentin provided an immediate complete relief of the spasms. 10 monthly courses of IVIG and oral corticosteroids resulted in a partial improvement with resolution of his leg rigidity but persistence of the pruritus, dysgeusia, hypersomnia, masseter spasms with yawn, and behavioural changes.
Shugaiv 2013	A case series of 3 patients with PERM	**Case 1:** Did not respond to 7 pulse steroid and intravenous immuno- globulin (IVIg) treatment courses **Case 2** (concurrent renal cell carcinoma): Symptoms (cerebellar symptoms, myoclonic jerks, rigidity, startle response) disappeared following pulse steroid treatment (5 × 1 g i.v. methylprednisolone) and left nephrectomy mRS remained at 3 in a follow-up period of 2 years under azathioprine maintenance. **Case 3**: Myoclonic jerks, generalized rigidity, dysphagia responded favourably to anticonvulsants, pulse steroid (5 × 1 g i.v. methylprednisolone) and IVIg (2 g/ kg every 4 weeks) treatments. No new symptoms in a follow-up period of 3 years.
Lewis Kass-Iliyya 2021	Retrospective cross sectional study looking into outcomes of autologous haematopoietic stem cell transplant in patients who had refractory SPS/PERM (n = 4; SPS = 3, PERM = 1) *Refractory = failure of at least 1 immunotherapy*	All 4 patients had marked symptoms improvement (all had troublesome muscle spams and stiffness) and managed to stop IVIG and other forms of immunotherapy with sustained symptomatic and clinical improvement.
Hinson 2018	Retrospective case-control study examining seropositivity of Glycine receptor alpha-1 subunit (GlyRa1) IgG in stiff person syndrome spectrum. Treatment outcome information was available in 19 patients (n = 18 for immunotherapy, n = 1 for benzodiazepines).	Objective improvements in SPS neurologic symptoms (measured by the modified rankin scale) were recorded in 16 of 18 patients who received first-line immunotherapy (89%, 9/10 treated with corticosteroids, 8/10 treated with IVIg, 3/4 treated with plasma exchange, and 1 treated with rituximab). Treatment-sparing maintenance strategies were successful in 4 of 7 patients (rituximab [2/3], azathioprine [1/1], and myco-phenolate [1/3]).
McKeon 2012	Observational studies looking into the characteristics of a cohort of patients with stiff-man syndrome (n = 99). 34 patients received immunotherapy (n = 18 in GAD65 antibody-seropositive patients with classic SMS; n = 8 in GAD65 antibody-seropositive patients with partial SMS; n = 8 in GAD65 antibody negative patients)	For the GAD65 antibody-seropositive with classic SPS group, Rankin scores were not significantly different in those treated with immunotherapy vs those not treated at base- line (P =.87) or at the last follow-up visit (P =.79).
Bernardo 2020	Retrospective case series of 3 patients	**Case 1** (PERM): 5 days IV methylprednisolone 1 g per day followed by oral corticosteroids (slow taper from 1 mg/kg/day for one year), two courses of five days of IVIg (2 g/kg in total per course). Progressive clinical improvement noted with partial recovery of MMSE from 3 to 17. **Case 2** (SPS): treatment was not administered. Patient's symptoms dramatically evolved with marked generalized rigidity and encephalopathy and eventually succumbed to death a few days after admission. **Case 3** (SPS with anti-Zic4 ab): 5 days IV MTP (1 g per day) + 5 days IVIG (2 g/kg in total) followed by oral corticosteroids (slow taper from 1 mg/kg/day for 1 year) and azathioprine (2 mg/kg/day). Remission achieved (no details)
Mckeon 2013	Retrospective case-control study (n = 81 with SPS phenotype). Seropositive cases (12% of cases) included 9 with stiff-man syndrome (4 classic; 5 variant; 66% were glutamic acid decarboxylase 65–IgG positive) and 1 with progressive encephalomyelitis with rigidity and myoclonus.	Immunotherapy responses were noted more frequently in GlyRα1-IgG–positive cases (6 of 7 improved) than in seronegative cases (7 of 25 improved; P =.02). Illustrated symptoms which responded included muscle spasms, stiffness and blurring of vision with optic atrophy.
Meinck 1994	Retrospective case series on SPS (n = 8)	Benzodiazepines (diazepam/ clonazepam) proved most effective. 5/8 patients had good or satisfactory functional capabilities. 2/8 patients had grand mal seizure while on clonazepam.
Startle-induced tics (pubmed search: 'STARTLE' AND 'TICS' = 31 RESULTS) ** (pubmed search: 'startle-induced tics = 2 results)		
Tijssen, 1999	Retrospective case series (n = 3)	No treatment was mentioned in 2 cases and 1 case reported by the author to be ineffectively treated by clonazepam.

*Case series and clinical trials with ≥ 3 study subjects/patients were included.

outcomes in the use of therapeutic plasma exchange in the treatment of stiff person syndrome as depicted in a retrospective analyses done by Albahra [30]. Haematopoietic stem cell transplantation may play a role in the treatment of stiff person syndrome as shown in a prospective cohort label study conducted by Burt [31]. Comparatively, the use of intrathecal baclofen led to several adverse side effects including catheter dislocation causing radicular symptoms, spasm induced rupture of catheter and inaccurate dosing secondary to pump malfunction, leaving it a less desired option in treating stiff person syndrome [32]. The use of intravenous immunoglobulin and steroids seems to yield inconsistent

results as shown in several retrospective case series with some showing partial or no improvement in symptoms in patients with PERM [33–36]. However, there may be a role in the use of immunotherapy in GlyRalpha-1-IgG positive cases as seen in a retrospective case-control study [37]. Autologous haematopoietic stem cell transplant in contrast may play a role in treatment of refractory of PERM as shown in a retrospective cross sectional study [38].

4. Neuropsychiatric Startle syndromes

Startle-induced ticsStartle-induced tics are unexpected startling following a stimulus and may occur as part of Tourette's syndrome. The first choice for startle-induced tics is an alpha-2- agonist (eg. clonidine and guanfacine) [39]. Though antipsychotics are an effective option for startle-induced rites, however due to unfavourable side effects such as tardive dyskinesia, it is often not recommended as a first choice treatment.

Aside from medication, behavioural therapy is also an established evidence-based management for tics and is recommended as a first-line intervention as an adjunct to medication [40]. These therapies include habit reversal (HR), exposure and response prevention, operant conditioning models (rewarding tic suppression and discouraging disruptive tics) and massed practice (repeated, voluntarily performance of a tic until fatigue occurs) [41].

Other therapies which may play a role in managing tics include Deep Brain Stimulation (DBS) and repetitive Transcranial Magnetic Stimulation (rTMS). In particular, growing evidence suggests that DBS may have a role in the treatment of medication-refractory tics. Potential DBS targets for startle-induced tics include bilateral centro- median parafascicular and ventral orals complex (central nuclei) of the thalamus, globes pallidus internal and nucleus accumbens/anterior limb of the internal capsule [42–51].

Although the initial studies with repetitive Transcranial Magnetic Stimulation (rTMS) targeting motor and premotor sites have had no success in treating tics [52], rTMS targeting bilateral supplementary motor areas are effective in improving tic symptoms in a *meta*-analysis [53]. Moreover, rTMS has significant effect on improving obsessive–compulsive symptoms in Tourette syndrome. Nevertheless, to date, there are no studies on usage of rTMS in startle-induced tics and therefore more studies are needed in the area of interest.

5. Culture-specific syndromes

Culture-specific syndromes occur in many parts of the world and are often overlooked as they may be considered as part of a cultural behaviour [54]. Examples of theses syndromes include Jumping Frenchmen of Maine [55] (seen among males of French Canadian background in certain rural areas in Maine & Quebec), myriachit (seen in Siberia), Ragin' Cajuns (seen in southwestern Louisiana) [56] lapp panic (seen in the Sami of northernmost Europe), Imu (seen among Ainu people of (Hokkaido) Japan), Mali-mali or Silok (seen among Filipinos), Bah-tsche ('tickle-crazy', seen among Thais), Yaun ('ticklish', seen in Burma-Myanmar) and Latah ('nervous, ticklish', seen in Malaysia and Indonesia) [57]. These culture-specific syndromes cause significant psychosocial impacts on the sufferer thus it is important for the people around them to understand the characteristics so they are able to provide appropriate support. In addition, some sufferers may benefit from medical and psychosocial treatment.

To date, there are lack of studies on the treatment of culture-specific startle syndromes [58]. While treatment of latah is generally unsuccessful, the consequences on overall health are minimal [59]. Therefore, treatment of culture- specific startle syndromes have been understudied, especially as many do not consider culture-specific startle syndromes as a disease itself. In fact, many people who have this condition learn to accept it and do not seek treatment.

In terms of pharmacotherapy, the benzodiazepines such as clonazepam, that modulate GABAergic neurotransmission may be of potential benefit, although there are lack of studies for their use in culture-specific startle syndromes [60].

However, we should emphasize that not all these subjects need to be treated. In terms of non-pharmacological treatments, various behavioral techniques are of possible interest and worth studying. First, 'relaxation therapy'could possibly help these individuals as many may have underlying stressors. Another treatment option could be an 'operant technique' where startle free periods are positively reinforced and startle behaviours are negatively reinforced [61]. Desensitization via an exposure-based treatment to address the startle triggering phenomenon could also be a useful technique to investigate. Finally, subjects could be encouraged and trained to not respond to the triggers of startle. Habit reversal training, whereby the subject learns to detect their startle habit, identify high-risk situations and then trained to isometrically contract certain muscles in response to startle stimulus may also be of worth. However, huge mental effort is required to comply with habit reversal training. Perhaps, culture-specific startle syndromes are best managed in a multidisciplinary approach with the support from a neurologist, psychiatrist, psychologist, caregiver and nurse.

6. Functional startle syndromes

Functional startle syndromes as in functional movement disorders are commonly sudden in onset with inconsistency, incongruity, suggestibility, distractibility and disappearance of symptoms when unobserved. It may be stimulus sensitive mimicking other startle syndromes. Neurophysiological testing helps differentiates functional startle syndromes from organic causes. There are variable latencies to onset of stimulus-induced jerks and generally longer latencies in functional startle syndromes.

The treatment of functional startle syndromes remain challenging. Firstly, the patient needs to be explained on the diagnosis and the rationale behind it. Trust between patient and doctor is important in order for the treatment to be successful. Treatment of functional startle syndromes consists of a multidisciplinary approach involving psychotherapy, rehabilitation, physical therapy, occupational therapy and psychology [58]. Various types of psychological therapy has been promising including cognitive behaviour therapy, psychotherapy and psychodynamic interpersonal therapy.

The main role of physical therapy in functional startle syndromes is motor retraining, enabling patients to regain control over their movements. Treatment should address illness beliefs, self-directed attention and abnormal habitual movement patterns through a process of education, movement retraining and self-management strategies within a positive and non-judgemental context [62].

Occupational therapy (OT) can be potentially useful, where patients can relearn normal movement patterns and suppress unwanted movements while training to perform activities of daily living [63]. OT helps integrate specific treatment techniques into function and guide the patient to carry these independently. Initial intervention strategies include identification of prejerk cognitions and movement such as signs of anxiety, frustration and breath-holding and addressing them through relaxation techniques and progressive muscle relaxation [64]. Aside from that, sensory grounding and cognitive distractors are also some of the strategies used by OT to help patients with functional startle disorders. In addition, slow movement activities such as yoga, tai chi and mindful breathing exercises can help patients regain movement control and redirect attention away from the symptom.

Cognitive behavioural therapy (CBT) is a psychotherapy that is intended to change cognitive distortions to improve emotions and behaviours. The effectiveness of CBT as an adjunct to standard care in functional movement disorders such as psychogenic non epileptic seizures (PNES) has been consistently reported in multiple randomized controlled trials. In particular, the CODES trial has shown that the addition of CBT to standard medical care provided longer seizure free

periods and improvement in psychosocial functioning [65]. Similarly, reduction of functional tremor has been reported in 73% of patients who underwent 12-weekly treatment sessions [66]. Though the use of CBT in functional startle disorders is not well studied, its effectiveness in the treatment of functional movement disorders suggest that it may play a role in the multidisciplinary treatment of functional startle disorders.

7. Conclusion

The treatment of startle and related disorders are often overlooked and under diagnosed although it may cause significant physical, psychological and social impact to the patients. Moreover, the treatment of startle and related disorders remained understudied. This review article hopes to increase the awareness of physicians and neurologists on the treatment of startle and related disorders and enhance the interest in this topic.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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