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BRIDGING THE GAP BETWEEN SEIZURE CONTROL AND QUALITY OF LIFE: STIRIPENTOL AND FENFLURAMINE IN DRAVET SYNDROME

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ABSTRACT

Dravet syndrome is a severe, early childhood epileptic encephalopathy, most often associated with a mutation in the SCN1a gene characterized by drug resistance and high neurological burden. For many years treatment was limited to non-specific antiepileptic drugs, but recently new, targeted therapies have appeared, which have significantly improved the prognosis of patients. Stiripentol, modulating GABAergic transmission, has been approved as an adjuctive treatment in the treatment of Dravet syndrome, showing a significant reduction in the frequency of seizures in combination with clobazam and valproic acid. In turn, fenfluramine, acting on serotonin receptors, among others, has proven also effective. Both drugs have been approved by the FDA and EMA, constitiuting a breakthrough in the treatment of Dravet syndrome Their introduction has significantly improved the quality of life of patients and opened up new perspectives in the treatment of developmental epilepsies.

KEYWORDS

Dravet Syndrome, Treatment- Resistant Epilepsy, Epileptic Encephalopathy, Severe Myoclonic Epilepsy of Infancy, Stiripentol, Fenfluramine

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1. Introduction

Dravet Syndrome (DS), also known as Severe Myoclonic Epilepsy of Infancy (SMEI), is a severe genetically determined epilepsy syndrome characterized by drug-resistant seizures and progressive psychomotor developmental disorders[1]. In most cases, the disease is caused by a loss-of-function mutation in the SCN1A gene encoding the α1 subunit of voltage-gated sodium channels NaV1.1[2]. Impaired production of this protein leads to hyperexcitability of the neuronal network, as the NaV1.1 sodium channel is highly expressed in GABAergic neurons of the Central Nervous System [3]. A characteristic feature of Dravet syndrome is the occurrence of epileptic seizures already in the first year of life. The type of seizures evolves over time and becomes increasingly complex. Observed seizure types include hemiclonic seizures, myoclonic seizures, generalized tonic-clonic seizures, atypical absence seizures and other focal and generalized seizure types. Beyond seizures, the disease significantly impacts the child's cognitive, motor and behavioral development. It also manifests with psychomotor developmental delay and an increased risk of sudden death [4]. Standard antiepileptic treatment based on the use of antiepileptic drugs such as valproic acid, topiramate or clobazam is rarely able to provide seizure control. It has even been noted that some medications, especially medications acting on sodium channels such as carbamazepine, lamotrigine, can worsen the patient's condition [1].

In recent years, new therapeutic options have been introduced for the treatment of Dravet syndrome. Two drugs in particular- stiripentol and fenfluramine deserve special attention, as their effectiveness in reducing the frequency of epileptic seizures has been confirmed in clinical trials and multicenter studies [5, 6]. The mechanisms of action of these drugs differ significantly. Stiripentol enhances the GABA-ergic activity and has been approved for use in DS in combination with valproate and clobazam. Fenfluramine, previously used in the treatment of obesity, has demonstrated antiepileptic effects through mehcanism including modulation of the serotonergic system and influence on neuronal pathways [7]. Both substances contribute to a reduction in seizure frequency, which can be considered a breakthrough in the DS treatment due to the associated improvement in patients' quality of life.

The aim of this paper is to present the mechanisms of action, clinical efficacy and safety of stiripentol and fenfluramine as modern therapeutic methods used in patients with Dravet syndrome

2. Current therapeutic challenges in the treatment of Dravet syndrome

Dravet syndrome is primarily a clinical diagnosis, but it is often confirmed by the identification of the previously described SCN1A gene mutation, as the vast majority of affected children carry this mutation [8]. DS is a severe epileptic syndrome characterized by the onset of generalized seizures within the first year of life. During the second and third years of life, patients typically begin to experience additional types of seizures [9]. In the following years of life, behavioral disorders, motor difficulties and cognitive impairments commonly emerge. In late childhood or early adolescence, the frequency of seizures usually decreases [2]. However, drug resistance to standard antiepileptic medications is typically present at every stage of development. Therefore, despite advances in diagnostics and treatment, optimal management of Dravet Syndrome remains a significant clinical challenge [10].

First-line treatment usually involves the use of valproic acid or clobazam. If one drug alone provides suboptimal seizure control, both medications are used in combination. Valproic acid has several mechanisms of action, it enhances GABAergic function, exerts an inhibitory effect on voltage-dependent sodium channels, and antagonizes NMDA receptor-mediated neural excitation. Clobazam, on the other hand, is a benzodiazepine and acts on the γ-aminobutyric acid type A (GABAA) receptor[11]. In the treatment of patients with Dravet syndrome, sodium channel blockers such as carbamazepine, oxcarbazepine, lamotrigine, or phenytoin [12] should be avoided. Vigabatrin, eslicarbazepine, pregabalin, gabapentin, rufinamide, and lacosamide [1] should also be avoided. As a next-line anticonvulsant treatment, it is possible to consider using known antiepileptic drugs, such as levetiracetam, topiramate, zonisamide, ethosuximide [13]. In the event of status epilepticus, standard emergency treatment is recommended. If other medications fail, intravenous phenytoin may be used as a last resort [12]. In addition, rectal diazepam and nasal or buccal midazolam have shown good effectiveness for rescue treatment [14]. In the managment of Dravet syndrome, it is important to avoid seizure-provoking factors, such as exposure to flashing lights, hot baths, or excessive physical exertion [15]. As previously mentioned, Dravet syndrome is resistant to treatment, which often necessitates polytherapy and stepwise escalation to successive lines of treatment. Therefore, a stepwise approach is used in DS, starting with first-line drugs and, if the effect is not satisfactory, using subsequent lines of therapy [11]. A detailed analysis of the mechanism of action, clinical efficacy, and safety profiles of stiripentol and fenfluramine in the treatment of DS allows a better understanding of their roles in therapy, as well as a broader perspective on the complexity of the disease. Many aspects of Dravet syndrome remain incompletely understood, highlighting the ongoing need for further research into therapeutic strategies for this condition.

3. Mechanism of action, safety profile, clinical efficacy of stiripentol

The mechanism of action of stiripentol, like many other antiepileptic drugs, is multifaceted. It is a positive allosteric modulator of ligand-gated GABAA receptors [16]. Dysregulation of GABAergic signaling is associated with the occurrence of seizures, as γ-aminobutyric acid is the primary inhibitory neurotransmitter in the cortex [17]. Stiripentol binds to the GABAA receptor, prolonging the opening time of channel, thereby enhancing inhibitory signaling in the presence of GABA. Stiripentol acts most effectively on GABAA receptors containing α3 or δ subunits, which may explain why this drug is effective in the treatment of childhood epilepsy. Animal models have shown that mRNA encoding the α3 subunit is strongly expressed in the rat brain during embryonic and early postnatal period, and is reduced in adulthood. Stiripentol has an additive effect in combination with benzodiazepines, because it binds to GABAA receptors containing the γ subunit at a different site than benzodiazepines, and in contrast to them, it also binds to GABAA receptors containing the δ subunit [18]. The enhancement of the inhibitory effect of γ-aminobutyric acid after the use of stiripentol is also possible due to the increase in GABA concentration in the brain, probably due to the inhibition of γ-aminobutyric acid reuptake and/or by inhibiting its degradation [19]. In addition to enhancing GABAergic transmission, stiripentol has a number of other mechanisms of action. It has been shown to inhibit T-type voltage-dependent calcium channels, which may contribute to the reduction of status epilepticus and atypical absence seizures observed in patients with Dravet Syndrome [18]. This drug also inhibits lactate dehydrogenase (LDH), leading to reduced neuronal excitability and seizure activity [20]. This is a mechanism similar to the efects of the ketogenic diet. Furthermore, stiripentol inhibits cytochrome P450 enzymes, influencing the metabolism of other drugs. On the one hand, this may increase the effectiveness of therapy, especially in combination with clobazam, but on the other hand it may be associated with an increased risk of adverse effects [21, 22]. In experimental models, stiripentol has demonstrated neuroprotective properties, which could be beneficial in epilepsy treatment [23]. These described mechanisms of action suggest that the

effectiveness of stiripentol arises from its multidirectional effect on the nervous system, rather than a single isolated mechanism. A simplified diagram of the mechanism action of stiripentol is presented in Figure 1.

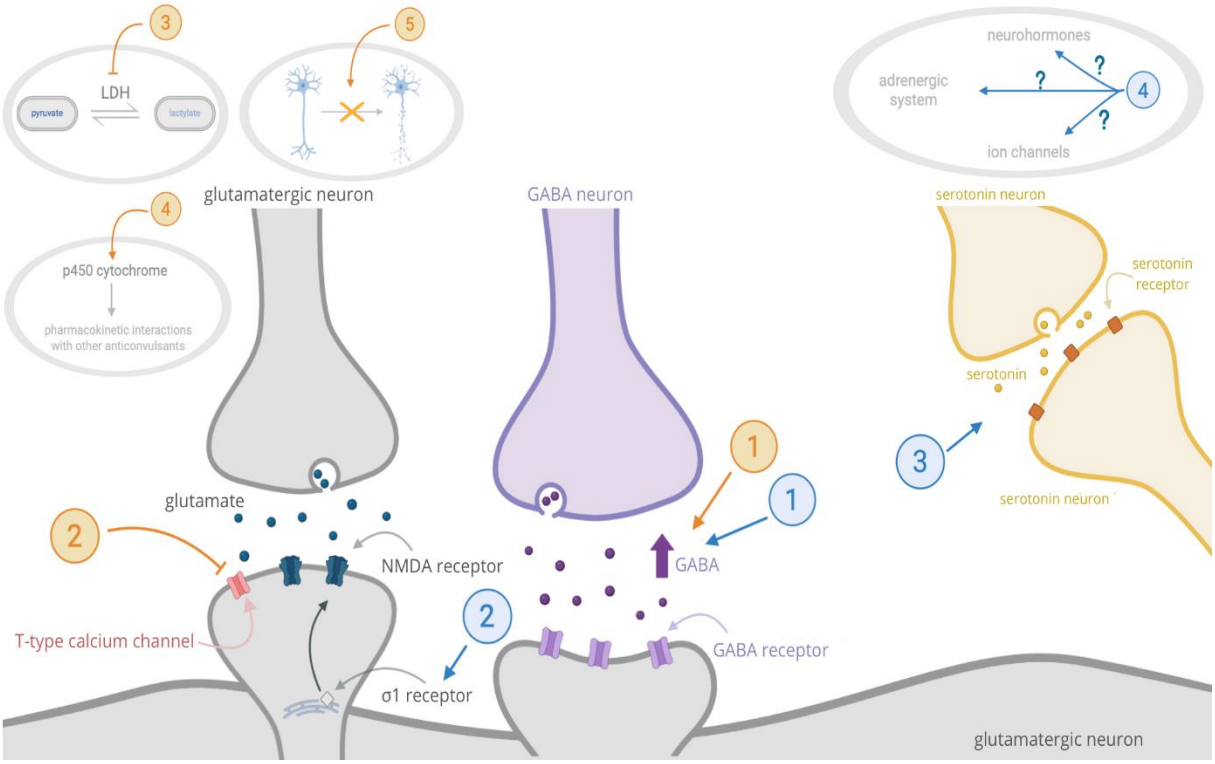

Fig. 1. *Mechanisms of action of stiripentol in the treatment of Dravet syndrome are marked with yellow arrows and assigned numbers. (1) Stiripentol enhances GABAergic signaling. (2) Inhibits T-type calcium channels. (3) Inhibits lactate dehydrogenase activity. (4) Due to its effect on cytochrome p450, stiripentol exhibits pharmacokinetic interactions with other anticonvulsants, such as clobazam. (5) Stiripentol exhibits a general neuroprotective effect. Mechanisms of action of fenfluramine in the treatment of Dravet syndrome are marked with blue arrows and assigned numbers. (1) Increased serotonergic transmission. (2) Acts as a positive modulator of the σ1 receptor, which regulates the activity of NMDA receptors. (3) Enhanced GABAergic transmission. (4) Fenfluramine may have anticonvulsant effects by affecting ion channels, neurohormones, and the adrenergic system. Figure created using BioRender.com*

The anticonvulsant effect of stiripentol was confirmed 45 years ago in preclinical studies, and its efficacy has since been confirmed in numerous animal models and clinical trials [24]. The first clinical data showed high effectiveness in patients with Dravet syndrome, especially when used in combination with clobazam.

Stiripentol was first approved by the European Medicines Agency (EMA) in 2007. As an adjunctive therapy in the treatment of epileptic seizures in patients with Dravet Syndrome in combination with clobazam and sodium valproate [25]. The U.S. Food and Drug Administration (FDA) approved it in 2018 for use in patients aged 6 months and older with DS [15]. The FDA approval was based on two key randomized clinical trials conducted in France and Italy. These studies showed that stiripentol, when used with clobazam, and valproic acid, led to significant reduction in seizures, with some children achieving complete seizure control [18]. In comparative analyses, stiripentol showed greater effectiveness (odds ratio, OR 47.5) in seizure reduction than fenfluramine (OR 17.4) and cannabidiol (OR 2.36) in the comparative analysis of different therapies [26]. The efficacy of stiripentol has been confirmed not only in clinical trials, but also in real- word studies. An important aspect of stiripentol therapy is also its effect on reducing status epilepticus. In real-wrold data, up to 77% of patients did not experience an episode of status epilepticus during long-term treatment. Initiating therapy before the age of 2 was associated with better treatment results, and the benefits of treatment were maintained in adulthood. Randomized controlled trials have shown that the most common side effects of stiripentol were drowsiness (67%), decreased appetite (46%), agitation (27%), weight loss (27%),

hypotonia, nausea, tremor, dysarthria and insomnia. It is possible to reduce the frequency of side effects by reducing the doses of stiripentol or concomitantly used drugs [18].

4. Mechanism of action, safety profile, clinical efficacy of fenfluramine

Fenfluramine (FFA, 3-trifluoromethyl-N-ethylamphetamine) was initially used at high doses in the treatment of obesity, as a drug reducing appetite through the activation of serotonergic systems in the hypothalamus. Following the discovery of its antiepileptic effects at low doses, fenfluramine began to be used as an antiepileptic drug [27, 28]. Fenfluramine is a racemic mixture of the enantiomers levofenfluramine and dextrofenfluramine , both metabolized to the active norfenfluramine [29]. Dextrofenfluramine increases serotonergic transmission by inhibiting serotonin reuptake and stimulating its release. Some of the serotonergic receptors activated in this process are associated with the antiepileptic effects of this drug. Fenfluramine acts as an agonist of several serotoninergic receptors: 5-HT1D, 5-HT2A, 5-HT2B, 5-HT2C, and 5-HT4 and as an antagonist of 5-HT1A. More recent studies suggest its activity also at the 5-HT7 receptor as well. Its anticonvulsant effects are primarily attributed to action on the 5-HT1D, 5-HT2A and/or 5-HT2C, 5-HT4 receptors. In animal models, blocking these receptors eliminated fenfluramine's anticonvulsant effects [30]. High doses of FFA, mainly through activation of 5-HT2B receptors, are associated with an increased risk of cardiovascular diseases, while the doses used in antiepileptic treatment are much lower and considered safe [31]. Fenfluramine also most likely acts as a positive modulator of the σ1 receptor. Through their action on the σ1 receptor, they regulate the activity of NMDA receptors by reducing calcium influx and glutamatergic synaptic activity, which restores GABAergic balance and reduces epileptic seizures [32]. Further studies are needed to determine which second messenger pathways are responsible for the anticonvulsant action of FFA via the σ1 receptor. Fenfluramine also acts on other ion channels, which may contribute to its potential antidepressant effects. It has been suggested that FFA may improve synaptic inhibition by protecting the structure of GABA neurons and increasing their activity. Fenfluramine enhances GABAergic transmission by releasing serotonin and stimulating 5-HT2A and 5-HT2C receptors. In animal models of Dravet syndrome, it has been shown to restore the dendritic branching in GABAergic neurons [30]. Fenfluramine, particularly levofenfluramine, may exert a mild influence on dopaminergic transmission, though this effect is weak, dose-dependent, and not central to its anticonvulsant action. However, it may contribute to its appetite-suppressing effects [33]. Some data suggest that FFA may affect noradrenergic transmission, but the effect on adrenergic receptors is poorly documented [34]. Fenfluramine may affect the levels of hormones such as ACTH, prolactin, oxytocin, vasopressin, and neuroactive steroids, which could be relevant to its anticonvulsant effect. These mechanisms are not fully understood and warrant further research. A simplified diagram of the mechanism action of fenfluramine is presented in Figure 1.

Fenfluramine was first approved by the FDA and EMA in 2020 for the treatment of Dravet Syndrome in children aged 2 years and older [15]. Clinical and preclinical data indicate that fenfluramine improves seizure control and has a beneficial effect on other symptoms of developmental and epileptic encephalopathies, including Dravet syndrome [30]. Clinical trials have also shown a reduction in mortality due to sudden unexpected death in epilepsy (SUDEP) – from 11.7/100 person-years before treatment to 1.7/100 person-years with fenfluramine therapy [35]. In animal models, fenfluramine reduced the incidence of respiratory arrest following seizures [36]. Moreover, FFA has been associated with improvements in daily functioning, emotion regulation, attention and cognitive functions in patients with Dravet syndrome. These benefits may be related to modulation of the σ1 and 5-HT4 receptors, though further research is required [30, 37]. In randomized clinical trials, the most commonly reported adverse events of fenfluramine were decreased appetite (20–44%), diarrhea (18–31%), drowsiness and lethargy (10–26%), fever, and rhinitis. Minor echocardiographic findings such as trace mitral or aortic valve insufficiency were observed in some patients [38]. Analysis of data from the Expanded Access Program (EAP) for Dravet Syndrome patients revealed that adverse events occurred in 31.5% of patients, with no reported cardiac complications or deaths [39].

5. Other therapeutic options for Dravet syndrome and future treatment possibilities

Stiripentol and fenfluramine represent an important breakthrough in the treatment of Dravet syndrome; however, there are several other alternative and experimental therapeutic approaches for DS that are worth mentioning. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved cannabidiol, a non-psychoactive compound derived from cannabis, which acts by influencing the endocannabinoid system, a key regulator of various physiological processes [17]. In randomized clinical trials, cannabidiol demonstrated significant effectiveness in reducing seizure frequency, particularly when used in

combination with clobazam. It has a favorable safety profile, although some adverse effects may occur, such as drowsiness, diarrhea, or increased liver enzyme activity [40]. The ketogenic diet, which is high-fat and low-carbohydrate, has been used for years in the treatment of drug-resistant epilepsies, including Dravet syndrome [41]. The antiepileptic mechanism is not fully understood, but it is believed that the production of ketone bodies affects neuronal metabolism and ion channel function [15]. Vagus nerve stimulation is another method of treating drug-resistant epilepsy. It involves implanting a device that generates impulses into the vagus nerve, which affects the activity of neurons responsible for generating seizures. A meta-analysis demonstrated a reduction in seizure frequency up to 45% [42]. Long-term studies have shown progressive improvement, with hoarseneness being the most commonly reported side effect [43]. Currently, drugs such as clemizole, lorcaserin, trazodone, LP352, soticlestat are being studied in the context of the treatment of Dravet syndrome with promising results in the context of reducing epileptic seizures and improving the neurophysiological condition, although further studies are needed to assess their safety and efficacy. Considering the genetic background of Dravet syndrome associated with mutations in the SCN1A gene, an important aspect of treatment is to target the cause of DS, and not only to prevent the occurrence of symptoms. Gene and molecular therapies such as the use of antisense oligonucleotides, transcription modulation, or transfer using viral genes are still at an early stage of research, although preliminary results are promising [15]. Due to the severe course of the disease, the heterogeneity in treatment response, and frequent drug resistance, it is necessary to individualize therapy and combine various treatment approaches. As previously mentioned, combination therapies are increasingly being used. This approach enables better seizure control and improves the quality of life for both patients and their families.

6. Conclusions

Dravet syndrome is a severe genetic epilepsy syndrome characterized by early onset, treatment resistance, and a significant impact on the quality of life of both patients and their families. Effective management requires a multidisciplinary approach, and previously used antiepileptic drugs often do not bring satisfactory results [1]. Stiripentol and fenfluramine constitute a significant advancement in the treatment of Dravet syndrome. Both drugs are effective in reducing the frequency of epileptic seizures. Importantly, their mechanisms of action differ, allowing them to be used together in combination therapy [7]. The use of these medications improves seizure control, which may have a beneficial effect on the child's development and their cognitive and social functioning. Therefore, stiripentol and fenfluramine can be considered breakthrough therapies in the treatment of Dravet syndrome, and their introduction into clinical practice has significantly expanded the therapeutic possibilities in this disease entity. However, further studies is needed to assess the long-term safety of these drugs and their potential impact on patient development, as well as to ensure accesss to treatment across different health care systems. Although stiripentol and fenfluramine represent significant progress in the treatment of Dravet syndrome, it is worth emphasizing that personalization of therapy should remain a key element in the treatment of patients with Dravet syndrome. Other therapeutic approaches such as the use of cannabinoids, ketogenic diet or gene therapy are playing an increasingly important role. The therapeutic paradigm for Dravet Syndrome is expected to evolve substantially in the future, incorporating combination strategies and disease-modifying approaches; however, the adoption of these interventions will require further research and validation.

Disclosure

Authors' contribution:

Conceptualization: K.Ko, K.Kr
Methodology: P.F
Software: A.G
Check: A.B
Formal analysis: P.P, K.Ko
Investigation: K.N and M.S
Resources: K.H
Data curation: M.S
Writing -rough preparation: P.A and K.H
Writing -review and editing: K.Ko, A.G
Visualization: K.Kr, P.F
Supervision: A.B, K.N
Project administration: P.P

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