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Editorial

Raising the bar: Fenfluramine sets new treatment standards for Dravet syndrome

Treatment and diagnosis of developmental and epileptic encephalopathies have entered a new era [1]. In this new environment, widespread availability of genetic testing speeds time to precise diagnosis; networked epilepsy centers offer improved access to appropriate medical care in the USA and in the EU; new medications are demonstrating unprecedented treatment outcomes; and targeted gene therapy approaches are on the horizon. Overall, newly available treatment options are advancing patient care from symptomatic treatment to disease modification [2].

In many ways, aspects of the management of Dravet syndrome have pioneered this emergent paradigm shift. Dravet syndrome is a treatment-resistant developmental and epileptic encephalopathy characterized by a high burden of seizures and debilitating outcomes in motor, cognitive, and behavioral domains [3]. Until recently, treatment options were limited, and most patients retained a high seizure burden even with polypharmacy, with little positive impact on non-seizure-related outcomes [4]. Stiripentol and cannabidiol became the first drugs approved for Dravet syndrome in the USA (both in 2018) and in the EU (2007 and 2019, respectively) [5]. In 2020, fenfluramine was approved for Dravet syndrome by both agencies based on the results of 3 independent pivotal trials, each of which demonstrated monthly convulsive seizure frequency reductions of 54% to 65% in comparison to placebo, even in patients who were concurrently receiving stiripentol [6–8]. For the first time, it became possible for a large percentage of patients to achieve profound reductions in convulsive seizure frequency; ≥75% reduction in monthly convulsive seizure frequency (MCSF) was achieved by 48% to 50% of patients on stiripentol-free regimens versus 2% to 4% of those receiving placebo (Studies 1 and 3), and in 35% of patients on stiripentol-inclusive regimens versus 2% of patients taking placebo (Study 2). The longest mean seizure-free interval was between 29.7 and 32.9 days for the most effective fenfluramine dose compared with 10.6 to 13.4 days for placebo [7,8].

Compared to other therapies, fenfluramine appears to be achieving responder rates at the ≥75% level that were previously observed at the ≥50% level. In pivotal studies for cannabidiol, for example, the proportion of patients who achieved ≥50% reduction in MCSF was 43% to 49% compared with placebo response rates of 26% to 27% [9,10]. The number needed to treat (NNT) with fenfluramine to achieve either ≥50% or ≥75% reduction in MCSF was between 2 and 3, compared with NNTs of 4 to 6 to achieve ≥50% levels in comparable Class I level-of-evidence clinical trials of antiseizure medications for Dravet syndrome (e.g., cannabidiol), and NNTs of 8 to 20 in a meta-analysis of antiepileptic drugs for treatment-refractory partial epilepsy [10–14]. Unlike the pharmacodynamic tolerance or tachyphylaxis exhibited by some antiepileptic drugs (e.g., some benzodiazepines) [15], long-term open-label extension studies up to 3 years demonstrate that fenfluramine provided sustained reductions in convulsive seizure frequency [16,17]. Fenfluramine not only showed a clinical response that was unprecedented in the pediatric clinical trial target patient population (ages 2–18 years), it also showed continued efficacy in patients who reached their 18th birthday during the clinical trials and in those who were adults when treated as part of early access programs [9,18]. Fenfluramine has demonstrated a positive benefit-risk profile in Dravet syndrome and has been generally well tolerated in clinical trials. The most common adverse events were reported as decreased appetite, fatigue, diarrhea, and pyrexia. Fenfluramine treatment for developmental and epileptic encephalopathies has not resulted in any cases of pulmonary arterial hypertension (PAH) or valvular heart disease (VHD), which had previously led to withdrawal from the market when fenfluramine was used at higher doses as an anorectic agent to treat obese adult patients [19]. The long-term safety profile continues to be investigated in patients with Dravet syndrome and other developmental and epileptic encephalopathies. Ongoing open-label long-term extension studies to 3 years of daily fenfluramine treatment have reported no observations of PAH or VHD in any patient at any time (N = 330; median treatment duration: ~631 days; range: 81–1086 days; dose range: 0.2–0.7 mg/kg/day; maximum: 26 mg/day for patients on stiripentol-free regimens, 17 mg/day max for patients on stiripentol-containing regimens) [17]. Treatment of a small number of patients for 6–27 years (N = 12; mean treatment duration: 16.1 years) also did not result in clinically significant echocardiographic findings [20]. However, solely based on historical reports from the use of higher doses of fenfluramine for treatment of adult obesity, the recent approval of fenfluramine by the FDA includes a Risk Evaluation and Mitigation (REMS) program, with a requirement for serial echocardiogram monitoring every 6 months and medical providers must be enrolled in the program to prescribe [21].

Fenfluramine has also set new standards for achieving clinically important results in patient-reported outcomes. A recent study

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highlighted that the unpredictability of seizures, along with their frequency and severity, was a key concern of caregivers [22]. Improving the interval between seizures improves quality of life not only for the patient but also for the entire family unit, including parents and siblings [22–24]. Further, reducing the frequency of prolonged acute convulsive seizures has the potential to improve quality of life by preventing episodes of status epilepticus and associated long-term, irreversible neurological sequelae [25]. Beyond seizures, a survey study of caregivers reported that cognitive impairment is one of their top 3 concerns [23]; later interview-based studies confirmed that cognitive and behavioral functioning had global impact on the child [26,27]. Some of these aspects are captured quantitatively by the Clinical Global Impression of Improvement (CGI-I), a metric that assesses patients across all aspects of clinical presentation. When considering a new treatment option, clinicians counsel patients on possible side effects, including lethargy, somnolence, and other negative cognitive outcomes known to be caused by antiepileptic drugs [28]. Fenfluramine did not worsen cognitive outcomes in safety assessments but, surprisingly, in analyses prespecified in the protocol, appeared to improve measures of executive functioning, a construct of cognition, in the short term (14 weeks) [8]. Furthermore, another, post hoc analysis recently evaluated the longest assessment of executive function in the largest number of patients with Dravet syndrome published to date (N = 58; 1 year). Improvements in aspects of executive function at 1 year were reported, as measured by the Behavior Rating Inventory of Executive Function 2 (BRIEF®2) instrument [29].

The mechanisms of action of fenfluramine in reducing convulsive seizure activity are the subject of active investigation. Although fenfluramine has long been recognized as a potent serotonin-releasing agent with agonist activity at 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors, recent evidence supports activity at 5-HT_7 and 5-HT_4 receptors and positive modulatory activity at σ_1 receptors [30–32]. Reports in a zebrafish model of Dravet syndrome demonstrate that fenfluramine restores dendritic arborization, suggesting its potential for disease modification [33]. Serotonergic and/or σ_1 receptor-related mechanisms may mediate not only seizure frequency reduction but also non-seizure outcomes, including cognitive outcomes and prevention of sudden unexpected death in epilepsy (SUDEP) [31,32,34]. It is unclear whether these mechanisms are specific to the unique *SCN1A* genetic etiology of Dravet syndrome or to the neuropathophysiology inherent in specific convulsive seizure subtypes. Early evidence in Lennox-Gastaut syndrome, for example, suggests that fenfluramine is uniquely effective in controlling convulsive seizures (e.g., generalized tonic-clonic seizures) in patients with this diagnosis [35].

These novel aspects of fenfluramine treatment for both clinical and patient-centered outcomes have effectively raised the bar for assessment of future therapies. Definitions of minimally effective and optimal seizure control in patients with Dravet syndrome will need to be re-evaluated when future treatment paradigms are discussed. New standards may be set for reduction in seizure burden and patient-centered outcomes that will guide conversations between clinicians and patients and their families in clinical decision-making. As treatment algorithms are developed [36,37], these newer treatments are likely to be considered as early second-line treatment [38]. Fenfluramine is currently labeled for treatment at a minimum age of 2 years [21], with pivotal trials conducted in patients at a mean age of ~9 years [8]. However, disease onset most often occurs before 1 year of age, and minimizing seizure burden from an early stage in the disease could result in a better long-term prognosis for cognitive outcomes and other non-seizure comorbidities (1) as a direct result of seizure control [8,29,39–43], (2) as the result of better engagement in other early intervention and education programs to support cognitive and social development [23,26,27], and (3) due to the inherent pharmacological activity of fenfluramine [30,31,33]. As Dravet is diagnosed earlier and earlier, the question arises as to whether fenfluramine could be utilized in younger patients (before the age of 2 years). Although developmental delay has been considered to be associated with seizure burden, evidence now suggests that mutations in *SCN1A* encoding the α_1 subunit of $Na_v1.1$ likely contribute to cognitive outcomes independently of seizures [5,44]. As highlighted above, ongoing studies are evaluating the pharmacological role of serotonergic and/or σ_1 receptor targets in the antiseizure and neuroprotective mechanisms of fenfluramine [30,31]. Assessing how cognitive outcomes are affected by seizure burden versus non-seizure effects of the underlying *SCN1A* mutations will be necessary when clinicians consider how patients respond to future treatments [44].

As our understanding of disease pathogenesis for developmental and epileptic encephalopathies with defined genetic etiology improves, precision medicine and targeted gene therapy approaches offer the possibility of reaching even higher levels of therapeutic efficacy. Treatment efficacy of fenfluramine in patients with Dravet syndrome may be attributable to the high proportion of patients who share a common genetic etiology, given that 70% to 85% of patients with Dravet syndrome present with mutations in the *SCN1A* gene [5]. In the new genomic era, targeted gene therapy approaches that augment or restore gene function show the most promise for greatest efficacy. Targeted Augmentation of Nuclear Gene Output (TANGO) technology and CRISPR-Cas9 gene activation approaches have shown efficacy in seizure reduction and SUDEP prevention in mouse models [45,46]. Stoke Therapeutics has initiated trials in patients with Dravet syndrome using the TANGO technology platform (http://stoketherapeutics.com). Whereas CRISPR technology is a powerful tool for gene editing, TANGO and other strategies aim to increase expression of the functional copy of the *SCN1A* gene. Encoded Therapeutics is exploring upregulation of *SCN1A* expression in GABAergic inhibitory neurons via an adeno-associated viral vector delivery system that has been shown to reverse key phenotypes in a mouse model of Dravet syndrome (EX101; http://encoded.com) [47]. Tevard Biosciences has developed an mRNA stabilization approach using a viral vector to enhance expression of the functional *SCN1A* gene copy (http://tevard.com). As new antiepileptic drugs and gene therapies come onto the market and into the therapeutic pipeline, these treatments should be evaluated against the demonstrated efficacy of fenfluramine. These expectations will continue to set standards for all future therapies, including targeted and gene therapies.

1. Conclusions

Fenfluramine has raised the bar for evaluating the efficacy of future therapies in Dravet syndrome, both for seizures and for critically important patient-centered outcomes. Not only does the unprecedented level of seizure control demonstrated with fenfluramine treatment set a new standard for what can be achieved in Dravet syndrome, it also provides important insights into treatment for other developmental and epileptic encephalopathies. The convergence of genomic and precision medicine, diagnostics, and treatment strategies in recent years has led to re-envisioned achievable efficacy for various epilepsy syndromes. There is still a long way to go before the ultimate goal of seizure freedom and normal cognitive functioning becomes a reality, but recent advances will have important implications for research, diagnosis, and treatment of epilepsy syndromes moving forward.

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