

Vigabatrin and Newer Interventions in Succinic Semialdehyde Dehydrogenase Deficiency

Andrea Gropman, MD

Succinic semialdehyde dehydrogenase (SSADH) deficiency is a rare disorder characterized by an inborn error of the catabolism of the inhibitory neurotransmitter GABA. Because of the deficiency of SSADH, the final enzyme of the GABA degradation pathway, the substrate, succinic semialdehyde, is shunted towards production of 4-hydroxybutyric acid (γ -hydroxybutyric acid). Elevations of γ -hydroxybutyric acid can be detected in the physiologic fluids of patients with SSADH deficiency, and forms the mainstay of diagnosis. The clinical features of SSADH deficiency include nonspecific neurologic manifestations such as mental retardation/developmental delay, absent speech, hypotonia, nonprogressive ataxia, features of autism or pervasive developmental delay, developmental language delay (dyspraxia, receptive, and expressive delays), and occasionally, seizures. Although the metabolic pathway has been established, it is not known whether insufficient GABA and/or excess γ -hydroxybutyric acid contribute to the disease phenotype. Pharmacological therapy in patients with this disorder has been limited to vigabatrin, an anticonvulsant that blocks GABA transaminase. This review will discuss therapeutic options in SSADH deficiency, on the basis of patient experience, and preliminary work using a murine model. Finally, a discussion of adjunctive therapies will be included.

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Succinic semialdehyde dehydrogenase (SSADH) deficiency is a rare autosomal-recessive disorder characterized by an inborn error in GABA catabolism.¹ SSADH works with the enzyme GABA transaminase to convert GABA to succinic acid (Fig 1). Succinic acid can subsequently be utilized for energy production via its entry into the Krebs cycle (Fig 2). In the absence of the enzyme SSADH, the substrate, succinic semialdehyde, accumulates and cannot be oxidized to succinic acid, and it is therefore reduced to 4-hydroxybutyric acid (γ -hydroxybutyrate, GHB) by 4-hydroxybutyric dehydrogenase (see Fig 1). GHB elevations can be detected in the physiologic fluids of patients with SSADH deficiency and forms the biochemical hallmark of this disorder.²

GABA is the major inhibitory neurotransmitter in the central nervous system, and it is formed from glutamate by the action of glutamic acid decarboxylase (see Fig 1). GABA acts at the presynaptic neuron to inhibit its further release, or at the postsynaptic membrane, leading to both fast and inhibitory neurotransmission. These effects are mediated by GABA_A and

GABA_B receptors, respectively. The first patient with SSADH was described by Jakobs and colleagues³ in a boy presenting with nonprogressive ataxia, mild mental retardation, and hypotonia. Subsequently, over 350 additional patients have been described (Gibson, personal communication). Deficiency of the enzyme in lysates of lymphocytes in patients with SSADH deficiency was demonstrated by Gibson and colleagues,^{4,5} and analysis of urine by isotope dilution gas chromatography-mass spectrometry revealing elevation of GHB in physiologic fluids (blood, urine, cerebrospinal fluid) in affected individuals is the mainstay of diagnosis.⁶ Prenatal diagnosis for SSADH is possible by analysis of chorionic villus sampling or amniocentesis.^{7–9}

The clinical features of SSADH deficiency are mainly neurological. Moreover, they are nonspecific, and include mental retardation/developmental delay; absent speech; hypotonia; nonprogressive ataxia; features of autism or pervasive developmental delay; developmental language delay (dyspraxia, receptive, and expressive delays); and occasionally seizures.^{10–12} Patients with SSADH deficiency may also experience hal-

From the Neurogenetics Branch, Section on Neuronal Migration, National Institutes of Health, Bethesda, MD; Neurogenetics Clinic, Children's National Medical Center, Washington, DC.

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Address correspondence to Dr Andrea Gropman, Neurogenetics Branch, Section on Neuronal Migration, National Institutes of Health, 10 Center Drive, Building 10, Room 3B04, Bethesda, MD 20892. E-mail: gropmana@ninds.nih.gov

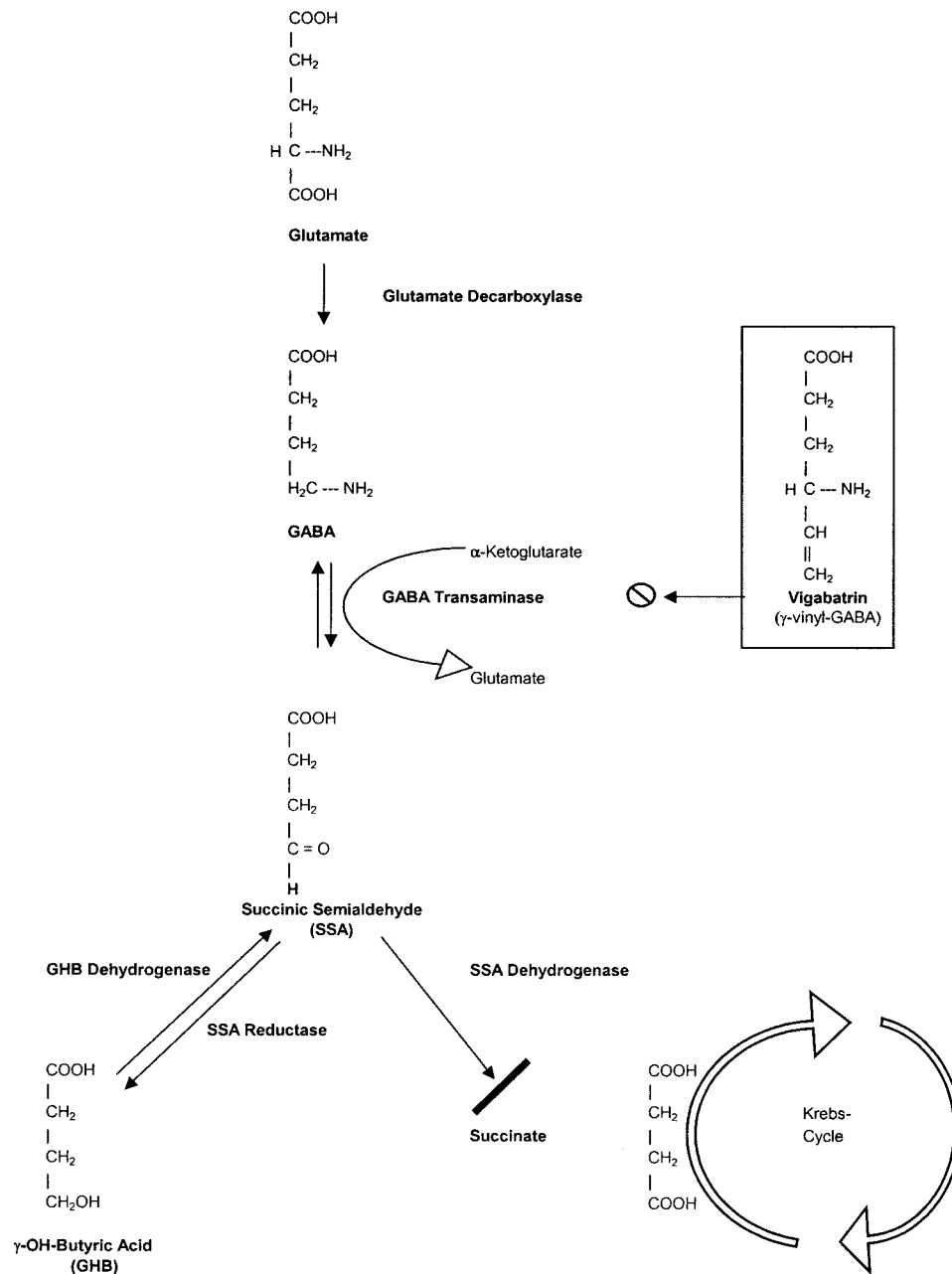


Fig 1. GABA metabolism as it relates to SSADH deficiency. Vigabatrin acts as an irreversible inhibitor of GABA transaminase. ⊙ = irreversible inhibition.

lucinations, anxiety, and hostility. Abnormalities in the electroencephalogram (EEG), even in the absence of clinical seizures, occur in about half of patients,^{11,12} including diffuse background slowing and multifocal spike discharges. It is unclear whether decreased GABA and/or elevations of GHB account for the clinical phenotype, although there are several lines of evidence that implicate elevations of GHB as playing a role in the clinical manifestations of SSADH.¹³ Unlike other in-born errors of metabolism, in SSADH deficiency there is no metabolic decompensation or exacerbation of

symptoms with acute stress and/or illness (ie, no vomiting, acidosis, or hypoglycemia), nor do patients typically present in the throes of acute illness. Because of the lack of a specific phenotype, it is likely that this disorder remains underdiagnosed.

The biochemical hallmarks of SSADH deficiency include the elevation of both total GABA and GHB in physiologic fluids. Isotope dilution gas chromatography-mass spectrometry remains the gold standard method for detecting elevations of GHB in physiological fluids, using deuterium and ¹³C-labeled internal standards.

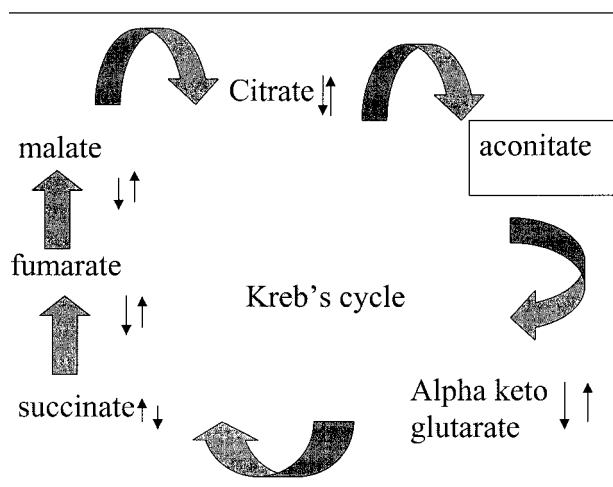


Fig 2. The Krebs cycle: Succinate, produced as a result of breakdown of succinic semialdehyde (see Fig 1) can enter into the Krebs cycle to be further metabolized to yield energy.

Once an elevation of GHB is determined, enzyme analysis from leukocytes will confirm the diagnosis.⁴ Many patients possess some limited residual enzyme activity. The gene has been identified, on chromosome 6p22. More than 47 disease-causing mutations have been identified, all of which lead to absence of functional protein (splice-site mutations, missense mutations, and frameshift mutations), and mutational analysis is available.¹⁴

GHB is a short-chain fatty acid and has a wide variety of actions in the central nervous system (CNS). It occurs naturally in brain and may function as a putative neurotransmitter. It is transmitted into and out of the CNS via a carrier-mediated system. It is believed that GHB is excreted intact, or alternatively, is degraded via the fatty-acid oxidation pathway.¹⁵ GHB has been shown to induce a spike-and-wave activity similar to that seen in generalized absence epilepsy in animal models.¹⁶⁻¹⁸

Currently, therapeutic intervention in humans with SSADH deficiency has been limited to the antiepileptic agent, vigabatrin (Sabril), a drug that has not been uniformly effective in this patient population. Vigabatrin was developed as a structural analogue of GABA to inhibit GABA transaminase activity, which leads to increased CSF GABA concentration. Vigabatrin, by virtue of its mechanism of action, would appear the intuitive treatment of choice, because it acts pharmacologically as an irreversible inhibitor of GABA transaminase. The effect of this inhibition should be increased free and total GABA concentration in brain with concomitant decreases in semialdehyde and GHB levels. Clinical uses and reports of the effect of vigabatrin in SSADH deficiency have been limited to anecdotal experience, because controlled studies have not been undertaken.¹⁹⁻²⁶ Therapy has been encouraging

in a few patients, and of little efficacy in others. Doses similar to those used for infantile spasms, childhood epilepsy, and adult epilepsy (Table) have been reported in humans. In the few instances in which vigabatrin appeared to be associated with a positive response, improvements in behavior with increased socialization, alertness, attention span, and general manageability, as well as improvement in ataxia, have been reported. Treatment with vigabatrin leads to the expected rise in both the free and total GABA levels in CSF, with a concomitant small decrease in GHB levels. Reduction of intracellular concentrations of succinic semialdehyde should lead to a significant decrease in GHB production. However, in the majority of patients in whom this was measured, the reduction in CSF GHB levels was not significant (see Table). In one patient reported by Jaeken and colleagues,¹⁹ CSF GHB levels fell 70% from pretreatment levels; however, this is not a consistent observation. At least two patients developed new onset seizures and worsening of the EEG (slowing of the background into the delta frequency) during vigabatrin treatment, despite clinical improvements in socialization and alertness. However, when vigabatrin was administered at lower dosages, the EEG normalized and the behavioral benefits were noted.²⁶ In other patients, no significant changes were noted. In all patients treated with vigabatrin, in whom CSF levels of GHB were measured, there was no change in the GHB levels in brain, leading to the theory of a peripheral resupply due to nonspecific activation of other enzymes.²¹

The side-effects of vigabatrin include manifestations of gastrointestinal discomfort, such as abdominal pain and constipation, as well as neurological effects, such as abnormal coordination, agitation, anxiety, clumsiness, confusion, mental depression, drowsiness, diplopia, fatigue, and tremor. More important, and perhaps limiting the widespread use of vigabatrin for epilepsy, is the report of irreversible constriction of the visual fields.²⁷⁻²⁹ While retinal changes and visual-field disorders are associated with other antiepileptic drugs, the pattern of visual-field loss appears unique to vigabatrin. Currently, it is recommended that patient visual fields be tested both before and during vigabatrin therapy. This is difficult in patients with cognitive difficulties as would be seen in certain subclasses of epilepsy patients, as well as those with SSADH deficiency. Because of the mixed efficacy of vigabatrin in patients with SSADH deficiency, and the potential for irreversible visual field deficits, other agents are being actively investigated in experimental models.

What would constitute the ideal treatment strategy for SSADH deficiency? Ideally, the agent should lead to improvement or correction of the metabolic defect and demonstrate clinical efficacy via a measurable clinical parameter. The drug should be easily absorbed, readily available with minimal side-effects, easy to ad-

Table. Clinical Trials with Vigabatrin

Author	Type of Study	Pretreatment Symptoms	Duration of Treatment	Dosage	Cerebrospinal (CSF), Plasma and/or Urine GHB Levels, Percent Change	Pretreatment Electroencephalogram (EEG)	Posttreatment Improvements
Howelis et al., 1992	Single patient, double-blind crossover with placebo	10-year-old boy with autistic features, hypotonia, hyporeflexia, moderate mental retardation, hyperactive, behavior problems	2 months	75mg/kg/day	CSF: 19% reduction, Urine: no change	No information	Improved concentration, less distractible, improved ataxia, IQ, speech and motor, no change in behavior and hyperactivity.
Gibson et al., 1989	Single patient, unblinded	2-9/12-year-old girl with choreoathetosis, nystagmus, mental retardation	4 months	20-100mg/kg/day	CSF: 14% reduction, Urine: no change	No information	Improved ataxia, IQ, speech and motor, no change in behavior and hyperactivity. After initial improvement, vegetative, dystonia, irritability, encephalopathy
Jaeken et al., 1989	Single patient, unblinded	2-year-old with ataxia and moderate mental retardation	16 months	75mg/kg/day	CSF: 70% reduction	Sharp waves	Improvements in ataxia and EEG
Dietz et al., 1994	Single patient, unblinded	7-year-old boy with mental retardation, aggressive behavior, hyperactivity	No information	50-100mg/kg/day	No information	No information	Improvements in fine motor skills, socialization on, receptive language, and predominant improvements in expressive language
Gibson et al., 1995	Six patients, unblinded	ataxia, mental retardation, hypotonia, language deficits, behavior problems	1 month-1 year	40-100mg/kg/day	CSF: measured in four patients with 26%, 27%, 36%, and 47% reductions	No information	Decreased ataxia: improved concentration, agility, speech, behavior, and alertness; and decreased hyperactive behavior. One patient developed absence-like seizures and then generalized tonic clonic seizures with slowing on the EEG
Uziel et al., 1993	Single patient, unblinded	7-5/12-year-old boy with severe mental retardation, hypotonia, hyporeflexia, autistic features. MRI demonstrating bilateral increased T2 signal in the globus pallidus	11 months	50mg/kg/day	Urine: 60% reduction	Slow background	Increased alertness, decreased hypotonia, improvements in language
Jakobs et al., 1992	Single patient, unblinded	12-year-old girl with hypotonia, mental retardation, speech delay, autistic features, behavioral problems, incontinent	No information	20-100mg/kg/day	CSF: decrease Plasma: 66% decreased	No information	Within 2 weeks, improvements in locomotion with decreased ataxia; improved speech, self-help skills, and bladder control; slight improvement in autistic behaviors
Matern et al., 1996	Single patient, unblinded	12-year-old male with mental retardation, nonprogressive ataxia, hypotonia, MRI demonstrating bilateral increased T2 signal in the globus pallidus	22 months	75mg/kg/day 25mg/kg/day	Urine: no change	Normal	Within 2 weeks, improvements seen in concentration, social interaction, and motor skills, associated with slowing of EEG consistent with encephalopathy. After 8 weeks, patient had a new-onset generalized tonic-clonic seizure. With low dosage, EEG improved and patient maintained some improvements

minister, and be of nonprohibitive cost. Given the clinical heterogeneity and nonspecific neurological features of SSADH deficiency, one would need to establish clear endpoints. What effects may be ameliorated by treatment: cognitive, behavioral, and motor (hypotonia, ataxia) effects, as well as seizures? What is the best

measure of efficacy? Is there a biochemical marker for improvement, in the sense that elevated GABA and decreased GHB are the biochemical markers in SSADH deficiency? These are questions that should be kept in mind when investigating potential preclinical agents.

In SSADH deficiency, the metabolic pathway is

known. However, it is not known how the enzyme deficiency and accumulation of GABA and GHB contribute to the clinical phenotype. Certainly, it would be important to know whether deficiency of GABA and/or elevation of GHB account for the clinical features seen, so that the correct metabolic mechanism could be targeted. Several hypotheses favor a toxic effect of GHB as contributing to the neurological features seen in SSADH. There is an association between high levels of GHB, seizures, and EEG patterns. For example, in animal studies, GHB has been associated with 3Hz spike-and-wave patterns, similar to those seen in patients with absence epilepsy. Concentrations of GHB that induce anesthesia in rat brain are associated with catalepsy. However, because the animals are exposed to GHB over the short term, and because humans with SSADH deficiency are exposed to high brain concentrations of GHB during periods of early brain development, it is difficult to directly compare these findings. At present, current treatment strategies should focus on both decreasing the total production of GHB and also increasing the total concentration of GABA. Antagonists such as 6,7,8,9-tetrahydro-5-[H]benzocycloheptene-5-ol-4-ylideneacetic acid (NCS-382) and the various GABA_B receptor antagonists such as 3-aminopropyl(diethoxymethyl)phosphinic acid (CGP 35348) are plausible agents. At this point, controlled clinical trials have not been undertaken. Another potential antiepileptic agent that may prove useful is lamotrigine, an antiepileptic that inhibits the release of excitatory amino acids including glutamate, which is the major precursor of GABA via inhibition of glutamic acid dehydrogenase. Lamotrigine has been successfully used and tolerated in several patients with SSADH deficiency. Valproate would be relatively contraindicated in SSADH deficiency because of inhibition of residual SSADH enzymatic activity.

Animal Model of SSADH Deficiency

For the study preclinical treatments in human diseases, a model system is invaluable. This may be a cell culture model or (more ideally) an animal model. Animal models have been used to provide novel insights into the mechanism of human disease, as well as to assist with the development of pharmacological treatments. Ideally, the animal model should have a similar clinical phenotype as well as measurable biochemical parameters. A murine model of SSADH (*Aldh5a1*^{-/-}) was developed by typical gene targeting methodology using a cre-lox homologous recombination leading to deletion of the gene.³⁰ The mice are born at the expected Mendelian frequencies for an autosomal-recessive disorder. These mice demonstrate a uniform absence of SSADH enzyme activity in all tissues studied, along with accumulations of GHB and GABA in tissues and physiological fluids.

The neurological phenotype of the mice is quite distinctive. These mice exhibit hypotonia, truncal ataxia, generalized tonic-clonic seizures associated with 100% mortality, and a postnatal onset of failure to thrive. In addition, the murine model of SSADH deficiency shows neurologic deterioration coincident with weaning. The mice uniformly die at 3 to 4 postnatal weeks. Preliminary histopathological findings include hippocampal gliosis. Metabolic profiling³¹ has shown significant elevations of GHB and total GABA levels in urine, brain, and liver. The mice uniformly lack SSADH enzyme activity. In addition, there appear to be normal levels of succinic acid and succinic semialdehyde. Thus, although the phenotype of the murine model is much more severe than that seen in humans, at present, the murine model has been regarded as a valid metabolic model to study potential therapeutic interventions, with survival used as the endpoint.

Gibson's group has utilized the *Aldh5a1*^{-/-} mice to test a number of antiepileptic drugs (AEDs) (for more details, please refer to the accompanying manuscript by K. Michael Gibson). The AEDs that have been investigated include phenytoin, phenobarbital, and vigabatrin. The general study design involved the application of the AED to the drinking water. Subsequent measurements of GABA and GHB were performed in tissue extracts of liver, brain, and kidney. All AEDs were associated with enhanced survival, yet with no improvements in weight gain or the failure-to-thrive phenotype.³² Additionally, vigabatrin treatment prevented generalized tonic-clonic seizures and led to enhanced survival. Measurement of GABA levels revealed elevations in brain, yet no decrease in GHB levels was seen.

Based upon the observation that neurological deterioration occurred after weaning in the *Aldh5a1*^{-/-} mice, it was hypothesized that a substance in breast milk was important.³² The nonprotein amino acid, taurine, is present in very high concentrations in breast milk and is considered an essential amino acid in the newborn. Taurine is thought to play a role in development and survival of neurons, and high concentrations are found in the hippocampus. Additional functions include that of a cell-volume regulator, and possibly has a role in neurotransmission (activation of glycine receptors, protects against glutamate toxicity, and acts as a putative agonist at cortical glycine receptors).³³ Taurine improves symptoms of epilepsy in both animals and humans and interacts with both GABA_A and GABA_B receptors, and thus may play a neuroprotective role in the brain. Treatment of *Aldh5a1*^{-/-} with taurine provided rescue during the critical period.

Because GHB appears to possess several potential receptor interactions, Gibson's group assessed the efficacy of the specific GHB receptor antagonists NCS-382 and CGP 35348 as potential preclinical agents.³² GHB binds to GABA_B receptors and may be a weak antag-

onist of the GABA_B receptor.^{34,35} Gibson's group also investigated neurometabolic levels in mice that were receiving moderate and high dosages of vigabatrin, so that the investigators could elucidate possible reasons as to why this agent shows poor clinical effect in humans.

Gibson's group compared the ability of oral versus peritoneal administration of these agents to rescue the *Aldh5a1*^{-/-} mice from an early death. All interventions were associated with significant extension of the lifespan with NCS-382 being the most effective, leading to a 50 to 61% survival rate. Their studies further allowed them to conclude that GHB and GABA_B receptors are involved in the pathophysiology of SSADH deficiency.

In the absence of specific clinical treatment guidelines for SSADH deficiency, much of the therapy remains individualized to the patient. For example, benzodiazepines have been found to be helpful in some patients with anxiety, and one patient responded to treatment with a selective serotonin reuptake inhibitor.

Adjunctive Therapies in SSADH

Despite the current lack of specific pharmacological therapies for SSADH deficiency, the impact of adjunctive physical, occupational, and speech therapies cannot be overlooked. The therapies should be tailored to the individual patient. The goal of physical therapy is to build strength, endurance, and balance in a safe environment. Occupational therapy should focus on development of fine motor skills and address concurrent feeding issues. Sensory integration therapy delivered by neurodevelopmentally trained therapists has benefited many families whose children demonstrated severe tactile aversions that interfered with advancement of feeding skills and fine motor development and aggravated daily family-coping skills. Speech and language services should be offered to address lack of expressive speech. Development of alternative communication strategies, such as sign language, computer-assisted technologies, and a picture-exchange system, need to be considered. Because of the dyspraxia present in this syndrome, it is likely that sign language will not be an option for the majority of patients. Because many of the patients with SSADH deficiency have experienced delay in diagnosis, it is not known to what extent earlier intervention of services may alter the clinical course.

Conclusion

The repertoire of pharmacological agents available to treat SSADH deficiency appears limited as compared to the other categories of pediatric neurotransmitter disorders. The one drug that would appear to be the obvious candidate (vigabatrin) has not shown consistent results. The inconsistent efficacy of vigabatrin may be due to its inability to decrease brain GHB concentrations. Furthermore, its association with irreversible

visual-field changes, and its lack of approval by the U.S. Food and Drug Administration, makes it unlikely that this agent will receive further consideration. With the development of the *Aldh5a1*^{-/-} mice, promising preclinical agents are being investigated, with the caveat that the mouse phenotype is more severe than the human disease model. Out of the murine work, however, taurine and NCS-382 might be clinically relevant agents and amenable to carefully designed and controlled clinical trials in patients. Because of the number of potential receptor interactions for GHB, and in light of results from animal studies, it is possible that combined modalities may prove more beneficial than the use of a single pharmacological agent. Heterogeneity of clinical phenotype will likely complicate the analysis of outcome, a problem that has complicated the design of clinical trials for another metabolic disorder, the mitochondrial cytopathies. Early identification and diagnosis of SSADH deficiency with timely initiation of therapy is needed. It is likely to improve the clinical outcome by decreasing the period of time the brain is exposed to elevations of GHB. Nonetheless, carefully designed clinical trials are needed if the best clinical management for this group of patients is to be determined.

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