ACETYL LEUCINE FOR TREATING SYNGAP1-RELATED DISORDERS

BACKGROUND

Field

[0001] The present disclosure provides methods of treating a SYNGAP1-related disorder in a subject by administering a therapeutically effective amount of N-acetyl leucine.

Background

[0002] SYNGAP1-related disorders are neurological disorders characterized by moderate to severe intellectual disability that is evident in early childhood. SYNGAP1-related disorders are caused by mutations in the *SYNGAP1* gene. The protein produced from this gene, called SynGAP, plays an important role in nerve cells in the brain. It is found at the junctions between nerve cells (synapses) and helps regulate changes in synapses that are critical for learning and memory. Mutations involved in this condition prevent the production of functional SynGAP protein from one copy of the gene, reducing the protein's activity in cells. Studies show that a reduction of SynGAP activity can have multiple effects in nerve cells, including pushing synapses to develop too early. The resulting abnormalities disrupt the synaptic changes in the brain that underlie learning and memory, leading to cognitive impairment and other neurological problems characteristic of SYNGAP1-related disorders.

[0003] The earliest features of a SYNGAP1-related disorder are typically delayed development of speech and motor skills, such as sitting, standing, and walking. Many people with this condition have weak muscle tone (hypotonia), which contributes to the difficulty with motor skills. Some affected individuals lose skills they had already acquired (developmental regression). Other features of a SYNGAP1-related disorder include recurrent seizures (epilepsy), hyperactivity, and autism spectrum disorder, which is characterized by impaired communication and social interaction. Almost everyone with SYNGAP1-related disorder develops epilepsy, and about half have autism spectrum disorder.

[0004] There is currently no cure or specific treatment for the underlying condition that causes SYNGAP1-related disorders. There exists a need in the art for pharmaceutical agents to treat SYNGAP1-related disorders and/or the symptoms thereof.

BRIEF SUMMARY

[0005] In one aspect, the present disclosure provides methods of treating a SYNGAP1-related disorder, or a symptom thereof, in a subject in need thereof, the method comprising administering a therapeutically effective amount of N-acetyl leucine, e.g., N-acetyl-DL-leucine or N-acetyl-L-leucine, to the subject.

[0006] In another aspect, the present disclosure provides N-acetyl leucine, or a pharmaceutical composition thereof, for use in treating a SYNGAP1-related disorder, or a symptom thereof, in a subject in need thereof.

[0007] In another aspect, the present disclosure provides the use of N-acetyl leucine for the manufacture of a medicament for treating a SYNGAP1-related disorder, or a symptom thereof, in a subject in need thereof.

[0008] SYNGAP1-related disorders, or a symptom thereof include, but are not limited to, mild to severe intellectual disability, hypotonia, global development delay, epilepsy, sensory processing disorder, gross and fine motor skill delays, dyspraxia, mild to severe speech delay/apraxia, autism spectrum disorder, sleep disorder, behavior disorder, or visual abnormality, or a combination thereof.

[0009] It is to be understood that both the foregoing summary and the following detailed description are exemplary and explanatory only, and are not restrictive of the invention as claimed.

BRIEF SUMMARY OF THE DRAWINGS

[0010] Fig. 1A is a line graph showing the morning dose and cumulative daily dose of N-acetyl-DL-leucine in Case Report # 2 after 8 weeks.

[0011] Fig. 1B is a line graph showing daily quality of life (QOL) ratings for the subject and the caregivers in Case Report # 2 after 8 weeks. QOL ratings were reported from +5 (great day) to -5 (terrible day).

[0012] Fig. 1C is a line graph showing sleep quality recorded as the number of hours asleep and awake during the normal nighttime sleeping period in Case Report # 2 after 8 weeks.

[0013] Fig. 2A is a line graph showing the cumulative weekly ratings over time from caregivers for changes in various features of seizures, sleep, communication, behaviors, and physical activities for the subject in Case Report # 2 after 8 weeks. Ratings were reported on a scale from +5 (really improved) to -5 (much worse).

[0014] Fig. 2B is a bar graph showing the longitudinal ratings for specific features for various categories demonstrating the change over time for the subject of Case Report # 2 after 8 weeks.

[0015] Fig. 3A is a line graph showing the morning dose and cumulative daily dose of N-acetyl-DL-leucine in Case Report # 3 after 6 weeks.

[0016] Fig. 3B is a line graph showing daily quality of life (QOL) ratings for the subject and the caregivers in Case Report # 3 after 6 weeks. QOL ratings were reported from +5 (great day) to -5 (terrible day).

[0017] Fig. 3C is a line graph showing sleep quality recorded as the number of hours asleep and awake during the normal nighttime sleeping period in Case Report # 3 after 6 weeks.

[0018] Fig. 4A is a line graph showing the cumulative weekly ratings over time from caregivers for changes in various features of seizures, sleep, communication, behaviors, and physical activities for the subject in Case Report # 3 after 6 weeks. Ratings were reported on a scale from +5 (really improved) to -5 (much worse).

[0019] Fig. 4B is a bar graph showing the longitudinal ratings for specific features for various categories demonstrating the change over time for the subject of Case Report # 3.

[0020] Fig. 5A is a line graph showing the morning dose and cumulative daily dose of N-acetyl-DL-leucine in Case Report # 4.

[0021] Fig. 5B is a line graph showing sleep quality recorded as the number of hours asleep and awake during the normal nighttime sleeping period in Case Report # 4.

[0022] Fig. 6A is a line graph showing the cumulative weekly ratings over time from caregivers for changes in various features of seizures, sleep, communication, behaviors, and physical activities for the subject in Case Report # 4. Ratings were reported on a scale from +5 (really improved) to -5 (much worse).

[0023] Fig. 6B is a bar graph showing the longitudinal ratings for specific features for various categories demonstrating the change over time for the subject of Case Report # 4.

[0024] Fig. 7A is a line graph showing the morning dose and cumulative daily dose of N-acetyl-DL-leucine in Case Report # 5 after 6 weeks.

[0025] Fig. 7B is a line graph showing daily quality of life (QOL) ratings for the subject and the caregivers in Case Report # 5 after 6 weeks. QOL ratings were reported from +5 (great day) to -5 (terrible day).

[0026] Fig. 7C is a line graph showing sleep quality recorded as the number of hours asleep and awake during the normal nighttime sleeping period in Case Report # 5 after 6 weeks.

[0027] Fig. 8A is a line graph showing the cumulative weekly ratings over time from caregivers for changes in various features of seizures, sleep, communication, behaviors, and physical activities for the subject in Case Report # 5 after 6 weeks. Ratings were reported on a scale from +5 (really improved) to -5 (much worse).

[0028] Fig. 8B is a bar graph showing the longitudinal ratings for specific features for various categories demonstrating the change over time for the subject of Case Report # 5 after 6 weeks.

[0029] Fig. 9A is a line graph showing the morning dose and cumulative daily dose of N-acetyl-DL-leucine in Case Report # 6 after 6 weeks.

[0030] Fig. 9B is a line graph showing daily quality of life (QOL) ratings for the subject and the caregivers in Case Report # 6 after 6 weeks. QOL ratings were reported from +5 (great day) to -5 (terrible day).

[0031] Fig. 9C is a line graph showing sleep quality recorded as the number of hours asleep and awake during the normal nighttime sleeping period in Case Report # 6 after 6 weeks.

[0032] Fig. 10 is a bar graph showing the longitudinal ratings at week 6 for specific features for various categories (seizures, sleep, communication, behaviors, and physical activities) demonstrating the change over time for the subject of Case Report # 6 after 6 weeks.

[0033] Fig. 11A is a line graph showing the morning dose and cumulative daily dose of N-acetyl-DL-leucine in Case Report # 7.

[0034] Fig. 11B is a line graph showing daily quality of life (QOL) ratings for the subject and the caregivers in Case Report # 7. QOL ratings were reported from +5 (great day) to -5 (terrible day).

[0035] Fig. 11C is a line graph showing sleep quality recorded as the number of hours asleep and awake during the normal nighttime sleeping period in Case Report # 7.

[0036] Fig. 12A is a line graph showing the cumulative weekly ratings over time from caregivers for changes in various features of seizures, sleep, communication, behaviors, and physical activities for the subject in Case Report # 7. Ratings were reported on a scale from +5 (really improved) to -5 (much worse).

[0037] Fig. 12B is a bar graph showing the longitudinal ratings for specific features for various categories demonstrating the change over time for the subject of Case Report # 7.

[0038] Fig. 13 is a table providing an overview of the subjects and treatment outcomes described in Case Report #s 2-7 of EXAMPLE 2. The initial case listed in the table is not provided in the example. The effects of acetyl-leucine (NAL) are shown as a range from worse (--) to better (++) for each category. No change is indicated by (.); not observed is indicated by NO. Individuals that stopped taking acetyl–leucine are highlighted under the "weeks on NAL" column.

[0039] Fig. 14A is a line graph showing the morning dose and cumulative daily dose of N-acetyl-DL-leucine in Case Report # 2 after 17 weeks.

[0040] Fig. 14B is a line graph showing daily quality of life (QOL) ratings for the subject and the caregivers in Case Report # 2 after 17 weeks. QOL ratings were reported from +5 (great day) to -5 (terrible day).

[0041] Fig. 14C is a line graph showing sleep quality recorded as the number of hours asleep and awake during the normal nighttime sleeping period in Case Report # 2 after 17 weeks.

[0042] Fig. 14D is a line graph showing number of seizures for the subject in Case Report # 2 after 17 weeks.

[0043] Fig. 15A is a line graph showing the morning dose and cumulative daily dose of N-acetyl-DL-leucine in Case Report # 3 after 17 weeks.

[0044] Fig. 15B is a line graph showing daily quality of life (QOL) ratings for the subject and the caregivers in Case Report # 3 after 17 weeks. QOL ratings were reported from +5 (great day) to -5 (terrible day).

[0045] Fig. 15C is an updated line graph showing sleep quality recorded as the number of hours asleep and awake during the normal nighttime sleeping period in Case Report # 3 after 17 weeks.

[0046] Fig. 15D is an updated line graph recording the number of seizures for the subject of Case Report # 3 after 17 weeks.

[0047] Fig. 15E is a bar graph showing the results of standardized assessment taken before (green) and 3 months after (purple) initiation of N-acetyl-DL-leucine treatment: Nisonger Child Behavior Rating form for the subject in Case Report # 3 after 17 weeks.

[0048] Fig. 15F is a bar graph showing the results of standardized assessment taken before (green) and 3 months after (purple) initiation of N-acetyl-DL-leucine treatment: NICHQ Vanderbilt Assessment Scale for the subject in Case Report # 3 after 17 weeks.

[0049] Fig. 15G is a graph showing results of standardized assessment taken before (green) and 3 months after (purple) initiation of N-acetyl-DL-leucine treatment: the relative changes in overall positive and problem behaviors between these two assessments in Case Report # 3.

[0050] Fig. 16A is an udpated line graph showing the morning dose and cumulative daily dose of N-acetyl-DL-leucine in Case Report # 5 after 9 weeks.

[0051] Fig. 16B is an updated line graph showing daily quality of life (QOL) ratings for the subject and the caregivers in Case Report # 5 after 9 weeks. QOL ratings were reported from +5 (great day) to -5 (terrible day).

[0052] Fig. 16C is an updated line graph showing sleep quality recorded as the number of hours asleep and awake during the normal nighttime sleeping period in Case Report # 5 after 9 weeks.

[0053] Fig. 16D is an updated line graph showing the number of seizures for the subject of Case Report # 5 after 9 weeks.

[0054] Fig. 16E is an updated line graph showing the cumulative weekly ratings over time from caregivers for changes in various features of seizures, sleep, communication, behaviors, and physical activities for the subject in Case Report # 5 after 9 weeks. Ratings were reported on a scale from +5 (really improved) to -5 (much worse).

[0055] Fig. 16F is an updated bar graph showing the longitudinal ratings for specific features for various categories demonstrating the change over time for the subject of Case Report # 5 after 9 weeks.

[0056] Fig. 17A is a line graph showing the morning dose and cumulative daily dose of N-acetyl-DL-leucine in Case Report # 6 after 7 weeks.

[0057] Fig. 17B is an updated line graph showing the number of seizures for the subject of Case Report # 6 after 7 weeks.

[0058] Fig. 17C is an updatd line graph showing sleep quality recorded as the number of hours asleep and awake during the normal nighttime sleeping period in Case Report # 6 after 7 weeks.

[0059] Fig. 18 is a bar graph showing Quality of life (QOL) impact of N-acetyl-DL-leucine treatment. Caregivers rated QOL changes at a single time point in various features of seizures, sleep, communication, behaviors, physical activities, and cognitive improvements after initiating Acetyl Leucine treatment for the subject in Case Report # 8.

[0060] Fig. 19A is a line graph showing the morning dose and cumulative daily dose of N-acetyl-DL-leucine in Case Report # 9.

[0061] Fig. 19B is a line graph showing the number of seizures for the subject of Case Report # 9.

[0062] Fig. 19C is a line graph showing sleep quality recorded as the number of hours asleep and awake during the normal nighttime sleeping period in Case Report # 9.

[0063] Fig. 19D is a line graph showing daily quality of life (QOL) ratings for the subject and the caregivers in Case Report # 9. QOL ratings were reported from +5 (great day) to -5 (terrible day).

[0064] Fig. 19E is a line graph showing the cumulative weekly ratings over time from caregivers for changes in various features of seizures, sleep, communication, behaviors, and physical activities for the subject in Case Report # 9. Ratings were reported on a scale from +5 (really improved) to -5 (much worse).

[0065] Fig. 19F is a bar graph showing the longitudinal ratings for specific features for various categories demonstrating the change over time for the subject of Case Report # 9.

[0066] Fig. 20A is a line graph showing the morning dose and cumulative daily dose of N-acetyl-DL-leucine in Case Report # 10.

[0067] Fig. 20B is a line graph showing the number of seizures for the subject of Case Report # 10.

[0068] Fig. 20C is a line graph showing sleep quality recorded as the number of hours asleep and awake during the normal nighttime sleeping period in Case Report # 10.

[0069] Fig. 20D is a line graph showing daily quality of life (QOL) ratings for the subject and the caregivers in Case Report # 10. QOL ratings were reported from +5 (great day) to -5 (terrible day).

[0070] Fig. 20E is a bar graph showing the longitudinal ratings for specific features for various categories demonstrating the change over time for the subject of Case Report # 10.

[0071] Fig. 21A is a line graph showing the morning dose and cumulative daily dose of N-acetyl-DL-leucine in Case Report # 11.

[0072] Fig. 21B is a line graph showing the number of seizures for the subject of Case Report # 11.

[0073] Fig. 21C is a line graph showing sleep quality recorded as the number of hours asleep and awake during the normal nighttime sleeping period in Case Report # 11.

[0074] Fig. 21D is a line graph showing daily quality of life (QOL) ratings for the subject and the caregivers in Case Report # 11. QOL ratings were reported from +5 (great day) to -5 (terrible day).

[0075] Fig. 21E is a bar graph showing the longitudinal ratings for specific features for various categories demonstrating the change over time for the subject of Case Report # 11.

[0076] Fig. 22A is a line graph showing the morning dose and cumulative daily dose of N-acetyl-DL-leucine in Case Report # 12.

[0077] Fig. 22B is a line graph showing the number of seizures for the subject of Case Report # 12.

[0078] Fig. 22C is a line graph showing sleep quality recorded as the number of hours asleep and awake during the normal nighttime sleeping period in Case Report # 12.

[0079] Fig. 22D is a line graph showing daily quality of life (QOL) ratings for the subject and the caregivers in Case Report # 12. QOL ratings were reported from +5 (great day) to -5 (terrible day).

[0080] Fig. 23 is a bar graph showing Quality of life (QOL) impact of N-acetyl-DL-leucine treatment. Caregivers rated QOL changes at a single time point in various features of seizures, sleep, communication, behaviors, physical activities, and cognitive improvements after initiating N-acetyl-DL-leucine treatment for the subject in Case Report # 13.

[0081] Fig. 24 is a bar graph showing Quality of life (QOL) impact of N-acetyl-DL-leucine treatment. Caregivers rated QOL changes at a single time point in various features of

seizures, sleep, communication, behaviors, physical activities, and cognitive improvements after initiating N-acetyl-DL-leucine treatment for the subject in Case Report # 14.

[0082] Fig. 25A is a line graph showing the morning dose and cumulative daily dose of N-acetyl-DL-leucine in Case Report # 15.

[0083] Fig. 25B is a line graph showing the number of seizures for the subject of Case Report # 15.

[0084] Fig. 25C is a line graph showing sleep quality recorded as the number of hours asleep and awake during the normal nighttime sleeping period in Case Report # 15.

[0085] Fig. 25D is a line graph showing daily quality of life (QOL) ratings for the subject and the caregivers in Case Report # 15. QOL ratings were reported from +5 (great day) to -5 (terrible day).

[0086] Fig. 26A is a line graph showing the morning dose and cumulative daily dose of N-acetyl-DL-leucine in Case Report # 16.

[0087] Fig. 26B is a line graph showing the number of seizures for the subject of Case Report # 16.

[0088] Fig. 26C is a line graph showing sleep quality recorded as the number of hours asleep and awake during the normal nighttime sleeping period in Case Report # 16.

[0089] Fig. 26D is a line graph showing daily quality of life (QOL) ratings for the subject and the caregivers in Case Report # 16. QOL ratings were reported from +5 (great day) to -5 (terrible day).

[0090] Fig. 27A is a line graph showing the morning dose and cumulative daily dose of N-acetyl-DL-leucine in Case Report # 17.

[0091] Fig. 27B is a line graph showing the number of seizures for the subject of Case Report # 17.

[0092] Fig. 27C is a line graph showing sleep quality recorded as the number of hours asleep and awake during the normal nighttime sleeping period in Case Report # 17.

[0093] Fig. 27D is a line graph showing daily quality of life (QOL) ratings for the subject and the caregivers in Case Report # 17. QOL ratings were reported from +5 (great day) to -5 (terrible day).

[0094] Fig. 27E is a line graph showing the cumulative weekly ratings over time from caregivers for changes in various features of seizures, sleep, communication, behaviors,

and physical activities for the subject in Case Report # 17. Ratings were reported on a scale from +5 (really improved) to -5 (much worse).

[0095] Fig. 27F is a bar graph showing the longitudinal ratings for specific features for various categories demonstrating the change over time for the subject of Case Report # 17.

[0096] Fig. 28A is a line graph showing the morning dose and cumulative daily dose of N-acetyl-DL-leucine in Case Report # 18.

[0097] Fig. 28B is a line graph showing the number of seizures for the subject of Case Report # 18.

[0098] Fig. 28C is a line graph showing sleep quality recorded as the number of hours asleep and awake during the normal nighttime sleeping period in Case Report # 18.

[0099] Fig. 28D is a line graph showing daily quality of life (QOL) ratings for the subject and the caregivers in Case Report # 18. QOL ratings were reported from +5 (great day) to -5 (terrible day).

[0100] Fig. 28E is a line graph showing the cumulative weekly ratings over time from caregivers for changes in various features of seizures, sleep, communication, behaviors, and physical activities for the subject in Case Report # 18. Ratings were reported on a scale from +5 (really improved) to -5 (much worse).

[0101] Fig. 28F is a bar graph showing the longitudinal ratings for specific features for various categories demonstrating the change over time for the subject of Case Report # 18.

[0102] Fig. 29A is a line graph showing the morning dose and cumulative daily dose of N-acetyl-DL-leucine in Case Report # 19.

[0103] Fig. 29B is a line graph showing the number of seizures for the subject of Case Report # 19.

[0104] Fig. 29C is a line graph showing sleep quality recorded as the number of hours asleep and awake during the normal nighttime sleeping period in Case Report # 19.

[0105] Fig. 29D is a line graph showing daily quality of life (QOL) ratings for the subject and the caregivers in Case Report # 19. QOL ratings were reported from +5 (great day) to -5 (terrible day).

[0106] Fig. 30A is a bar graph showing the results of standardized assessment taken before (green) and 3 months after (purple) initiation of N-acetyl-DL-leucine treatment: Nisonger Child Behavior Rating form for the subject in Case Report # 20.

[0107] Fig. 30B is a bar graph showing the results of standardized assessment taken before (green) and 3 months after (purple) initiation of N-acetyl-DL-leucine treatment: NICHQ Vanderbilt Assessment Scale for the subject in Case Report # 20.

[0108] Fig. 30C is results of standardized assessment taken before (green) and 3 months after (purple) initiation of N-acetyl-DL-leucine treatment in Case Report # 20: the relative changes in overall positive and problem behaviors between these two assessments.

DETAILED DESCRIPTION

[0109] A "subject," as used herein, may be a vertebrate, mammal or domestic animal. Hence, compositions according to the disclosure may be used to treat any mammal, for example livestock, e.g. a horse, cow, sheep or pig, pets, e.g. a cat, dog, rabbit or guinea pig, a laboratory animal, e.g. a mouse or rat, or may be used in other veterinary applications. In one embodiment, the subject is a human being. "Subject" and "patient" are used interchangeably.

[0110] As used herein, the singular forms "a," "an," and "the" include plural reference.

[0111] As used herein, the term "about" should be generally understood to encompass ± 10% of a specified amount, frequency or value. Numerical quantities given herein are approximate unless stated otherwise, meaning that term "about" can be inferred when not expressly stated.

[0112] The terms "administer," "administration," or "administering" as used herein refer to (1) providing, giving, dosing and/or prescribing by either a health practitioner or his authorized agent or under his direction, N-acetyl leucine; and (2) putting into, taking or consuming by the patient or person himself or herself, N-acetyl leucine.

[0113] The term "N-acetyl leucine" refers to N-acetyl-DL-leucine, N-acetyl-D-leucine, and/or N-acetyl-L-leucine. Any reference to N-acetyl leucine includes pharmaceutically acceptable salts of the same, even if not expressly stated.

[0114] In one embodiment, the term N-acetyl leucine refers to N-acetyl-DL-leucine.

[0115] In one embodiment, the term N-acetyl leucine refers to N-acetyl-L-leucine. Studies have shown that the therapeutic effects of N-acetyl-DL-leucine are due to the L-entantiomer. *See, e.g.*, Churchill et al., (2020) PLoS ONE 15(2): e0229585. https://doi.org/10.1371/journal.pone.0229585. N-Acetyl-L-leucine (AQNEURSA™) is FDA-approved for the treatment of neurological manifestations of Niemann-Pick disease

type C (NPC) in adults and pediatric patients weighing ≥15 kg. AQNEURSA™ Presribing Information; https://aqneursa.com/.

[0116] A "pharmaceutically acceptable salt" as referred to herein, is any salt preparation that is appropriate for use in a pharmaceutical application. Pharmaceutically acceptable salts include, but are not limited to, amine salts, such as N,N'-dibenzylethylenediamine, chloroprocaine, choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, N-methylglucamine, procaine, N-benzylphenethylamine, 1-para-chloro-benzyl-2-pyrrolidin-1'-ylmethylbenzimidazole, diethylamine and other alkylamines, piperazine, tris(hydroxymethyl)aminomethane and the like; alkali metal salts, such as lithium, potassium, sodium and the like; alkali earth metal salts, such as barium, calcium, magnesium and the like; transition metal salts, such as zinc, aluminum and the like; other metal salts, such as sodium hydrogen phosphate, disodium phosphate and the like; mineral acids, such as hydrochlorides, sulfates and the like; and salts of organic acids, such as acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates, fumarates and the like.

[0117] N-acetyl leucine may be formulated and administered to a subject in accordance with known teachings in the art. For example, N-acetyl leucine may be formulated as a pharmaceutical composition. The pharmaceutical composition may comprise N-acetyl-DL-leucine and a pharmaceutically acceptable carrier, N-acetyl-L-leucine and a pharmaceutically acceptable carrier, or N-acetyl-D-leucine and a pharmaceutically acceptable carrier.

[0118] The pharmaceutical composition may take any of a number of different forms depending, in particular, on the manner in which it is to be used. Thus, for example, it may be in the form of a powder, tablet, capsule, liquid, ointment, cream, gel, hydrogel, aerosol, spray, micellar solution, transdermal patch, liposome suspension or any other suitable form that may be administered to a person or animal in need of treatment.

[0119] A "pharmaceutically acceptable carrier" as referred to herein, is any known compound or combination of known compounds, e.g., excipients, carriers, etc., that are known to those skilled in the art to be useful in formulating pharmaceutical compositions. It will be appreciated that the carrier of the pharmaceutical composition should be one which is tolerated by the subject to whom it is given.

[0120] In one embodiment, the pharmaceutically acceptable carrier may be a solid, and the composition may be in the form of a powder or tablet. A solid pharmaceutically acceptable carrier may include, but is not limited to, one or more substances which may also act as flavouring agents, buffers, lubricants, stabilisers, solubilisers, suspending agents, wetting agents, emulsifiers, dyes, fillers, glidants, compression aids, inert binders, sweeteners, preservatives, dyes, coatings, or tablet-disintegrating agents. The carrier may also be an encapsulating material. In powders, the carrier may be a finely divided solid that is in admixture with the finely divided active agents according to the disclosure. In tablets, the active agent may be mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets may, for example, contain up to 99% of the active agents. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins. In another embodiment, the pharmaceutically acceptable carrier may be a gel and the composition may be in the form of a cream or the like.

[0121] The carrier may include, but is not limited to, one or more excipients or diluents. Examples of such excipients are gelatin, gum arabicum, lactose, microcrystalline cellulose, starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like.

[0122] In another embodiment, the pharmaceutically acceptable carrier may be a liquid. In one embodiment, the pharmaceutical composition is in the form of a solution. Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. N-acetyl leucine may be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier may contain other suitable pharmaceutical additives such as solubilisers, emulsifiers, buffers, preservatives, sweeteners, flavouring agents, suspending agents, thickening agents, colours, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (partially containing additives as above, e.g. cellulose derivatives, such as sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the

carrier may also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are useful in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurised compositions may be a halogenated hydrocarbon or other pharmaceutically acceptable propellant.

[0123] Liquid pharmaceutical compositions, which are sterile solutions or suspensions, may be utilised by, for example, intramuscular, intrathecal, epidural, intraperitoneal, intravenous and subcutaneous injection. The active agent may be prepared as a sterile solid composition that may be dissolved or suspended at the time of administration using sterile water, saline, or other appropriate sterile injectable medium.

[0124] The compositions may be administered orally in the form of a sterile solution or suspension optionally containing other solutes or suspending agents (for example, enough saline or glucose to make the solution isotonic), bile salts, acacia, gelatin, sorbitan monoleate, polysorbate 80 (oleate esters of sorbitol and its anhydrides copolymerized with ethylene oxide) and the like. The compositions may also be administered orally either in liquid or solid composition form. Compositions suitable for oral administration include solid forms, such as pills, capsules, granules, tablets, and powders, and liquid forms, such as solutions, syrups, elixirs, and suspensions. Forms useful for parenteral administration include sterile solutions, emulsions, and suspensions.

[0125] Compositions may alternatively be administered by inhalation, e.g. intranasally. Compositions may also be formulated for topical use. For instance, creams or ointments may be applied to the skin.

[0126] N-acetyl leucine may be incorporated within a slow- or delayed-release device. Such devices may, for example, be inserted on or under the skin, and the medicament may be released over weeks or even months. Such devices may be advantageous when long-term treatment with N-acetyl leucine according to the present disclosure is required and which may require frequent administration, e.g. at least daily administration.

[0127] In one embodiment, the pharmaceutical composition is a solid oral dosage form, such as a tablet. In tablets, the active agent may be mixed with a vehicle, such as a pharmaceutically acceptable carrier, having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The tablets may contain up to 99% by weight of the N-acetyl leucine.

[0128] Pharmaceutical compositions in solid oral dosage form, such as tablets, may be prepared by any method known in the art of pharmacy. Pharmaceutical compositions are usually prepared by mixing the active agent with conventional pharmaceutically acceptable carriers.

[0129] A tablet may be formulated as is known in the art. Tanganil®, for example, includes wheat starch, pregelatinised maize (corn) starch, calcium carbonate and magnesium stearate as excipients. The same, or similar, excipients, for example, may be employed with the present disclosure.

[0130] The composition of each 700 mg Tanganil® tablet is as follows: 500 mg acetyl-DL-leucine, 88 mg wheat starch, 88 mg pregelatinised maize (corn) starch, 13 mg calcium carbonate and 11 mg magnesium stearate. The same tablets, for example, may be employed in the methods of the present disclosure.

[0131] In one embodiment, N-acetyl-L-leucine is formulated as granules for oral suspension in sachet. The granules for oral suspension may also comprise isomalt and/or hypromellose. Each sachet with 1000 mg of N-acetyl-L-leucine may be formulated, for example, to be suspended in 40 mL water.

[0132] As discussed above, N-acetyl leucine may be formulated and administered as a pharmaceutical composition taking any number of different forms. For example, N-acetyl leucine may be formulated as a pharmaceutical composition to facilitate its delivery across the blood-brain barrier. As a further example, N-acetyl leucine may be formulated as a pharmaceutical composition for bypassing the blood-brain barrier. Formulations that facilitate delivery across the blood-brain barrier or that are suitable for administration in a manner that bypasses the blood-brain barrier may be used to prepare and administer N-acetyl leucine.

[0133] In one embodiment, the pharmaceutical composition, e.g., a pharmaceutical composition comprising N-acetyl-L-leucine, or salt thereof, is formulated for nanodelivery, e.g., colloidal drug-carrier systems. Suitable examples include but are not limited to liposomes, nanoparticles (e.g., polymeric, lipid and inorganic nanoparticles), nanogels, dendrimers, micelles, nanoemulsions, polymersomes, exosomes, and quantum dots. See, e.g., Patel et al., "Crossing the Blood-Brain Barrier: Recent Advances in Drug Delivery to the Brain," CNS Drugs 31:109-133 (2017); Kabanov et al., "New Technologies for Drug Delivery across the Blood Brain Barrier," Curr Pharm Des., 10(12):1355-1363 (2004);

Cheng et al., "Highly Stabilized Curcumin Nanoparticles Tested in an In Vitro Blood–Brain Barrier Model and in Alzheimer's Disease Tg2576 Mice," The AAPS Journal, vol. 15, no. 2, pp. 324-336 (2013); Lähde et al. "Production of L-Leucine Nanoparticles under Various Conditions Using an Aerosol Flow Reactor Method," Journal of Nanomaterials, vol. 2008, article ID 680897 (2008).

[0134] In one embodiment, the pharmaceutical composition, e.g., a pharmaceutical composition comprising acetyl-L-leucine, or salt thereof, is formulated for direct delivery to the central nervous system (CNS), such as by injection or infusion. Formulations for and methods of direct delivery to the CNS are known in the art. *See, e.g.*, U.S. Patent No. 9,283,181. Examples of such administration include but are not limited to intranasal, intraventricular, intrathecal, intracranial, and delivery via nasal mucosal grafting.

[0135] In one embodiment, the pharmaceutical composition is formulated for (and administered by) intranasal delivery. See, e.g., Hanson et al., "Intranasal delivery bypasses the blood-brain barrier to target therapeutic agents to the central nervous system and treat neurodegenerative disease," *BMC Neurosci. 9(Suppl 3)*:S5 (2008). In one embodiment, the pharmaceutical composition is formulated for (and administered by) delivery via a nasal mucosal graft. In one embodiment, the pharmaceutical composition is formulated for (and administered by) intracerebroventricular injection or infusion. In another embodiment, the pharmaceutical composition is formulated for (and administered by) intrathecal intracisternal injection or infusion. In one embodiment, the pharmaceutical composition is formulated for (and administered by) intrathecal lumbar injection or infusion.

[0136] Various techniques may be used including, without limitation, injection through a burrhole or cisternal or lumbar puncture or the like as known in the art. Various devices, whether internal (e.g., implanted) or external, may be used for delivery as known in the art, such as pumps, catheters, reservoirs, etc. In one embodiment, the administration interval is once every two weeks.

[0137] In one embodiment, the administration interval is once every month. In one embodiment, the administration interval is once every two months. In one embodiment, the administration interval is twice per month. In one embodiment, the administration interval is once every week. In one embodiment, the administration interval is twice or several times per week. In one embodiment, the administration interval is daily. In one embodiment, the administration is continuous, such as continuous infusion.

[0138] In one embodiment, the dose or amount equivalent of N-acetyl leucine may adjusted to account for either its direct delivery to the CNS or its delivery across the blood-brain barrier.

[0139] In one embodiment, the present disclosure provides N-acetyl leucine, or a pharmaceutical composition thereof, for treating a SYNGAP1-related disorder in a subject in need thereof.

[0140] In another embodiment, the present disclosure provides N-acetyl leucine, or a pharmaceutical composition thereof, for treating a symptom of a SYNGAP1-related disorder in a subject in need thereof.

[0141] A "subject in need thereof" as used herein may be any subject who has a SYNGAP1-related disorder or a symptom thereof.

[0142] As used herein, "SYNGAP1-related disorder" refers to a disorder that is traced back to a pathogenic variant, i.e., a mutation, in the *SYNGAP1* gene. SYNGAP1-related disorders include a spectrum of neurodevelopmental disorders that can include, but are not limited to childhood-onset epilepsy, developmental delays, movement disorders, features of autism spectrum disorder, and intellectual disabilities. In children with SYNGAP1-related disorders, delays in achieving developmental milestones during infancy or early childhood may be the first indication of the condition. In other children, seizures are the first sign of the condition. In most individuals with SYNGAP1-related disorders, seizures begin in early childhood, usually around age 2. However, the age of onset varies widely between individuals, ranging from around 4 months to later in childhood.

[0143] Epilepsy is a common feature of SYNGAP1-related disorders, and is present in more than 95% of children with this condition. Children with SYNGAP1-related disorders may develop different types of seizures, which are often difficult to control with anti-seizure medications. Common seizure types may include: absence seizures, eyelid myoclonia, generalized tonic-clonic seizures (also called grand mal seizures), or atonic (drop) seizures. Many children with SYNGAP1-related disorders also have: decreased muscle tone (hypotonia), movement disorders, e.g., ataxia or tremor, behavior disorders, e.g., aggression, hyperactivity or features of autism spectrum disorder, high pain thresholds, eating difficulties, or sleeping problems.

[0144] Exemplary non-limiting features or symptoms of a SYNGAP1-related disorder include mild to severe intellectual disability, hypotonia (low muscle tone), global

development delay, epilepsy, e.g., subtle eyelid flutters, brief jerks, staring seizures and drop seizures, sensory processing disorder, gross and fine motor skill delays, dyspraxia (coordination disorder), mild to severe speech delay/apraxia, autism spectrum disorder, sleep disorders, behavior disorders, and visual abnormalities, or a combination thereof.

[0145] In some embodiments, the subject has been diagnosed with a SYNGAP1-related disorder by genetic testing prior to administration of N-acetyl leucine.

[0146] A "therapeutically effective amount" of N-acetyl leucine is any amount which, when administered to a subject, is the amount that is needed to produce the desired effect, which, for the present disclosure, can be therapeutic and/or prophylactic. The dose may be determined according to various parameters, such as the N-acetyl leucine used, e.g., N-acetyl-DL-leucine or N-acetyl-L-leucine; the age, weight and condition of the patient to be treated; the route of administration; and the required regimen. A physician will be able to determine the required route of administration and dosage for any particular patient. For example, a daily dose may be from about 0.1 g to about 30 g, from about 1 g to about 15 g, or from about 3 g to about 10 g of N-acetyl leucine may be administered, e.g., as a tablet or an oral suspension.

[0147] As used herein, "treating" or "treatment" refers to any indicia of success in preventing, arresting, or ameliorating a SYNGAP1-related disorder, in a subject, and/or preventing, arresting, or ameliorating any one or more symptoms of a SYNGAP1-related disorder in a subject, including any objective or subjective parameter such as abatement; remission; diminishing, inhibiting, preventing, or eliminating one or more symptoms; making the SYNGAP1-related disorder more tolerable to the subject; slowing in the worsening of the SYNGAP1-related disorder; or improving the physical or mental well-being of the subject in need thereof.

[0148] The terms "treating" or "treatment" also encompasses, e.g., inducing inhibition, regression, rescue, or stasis of a SYNGAP1-related disorder. For example, treatment of a subject in need of treatment for a SYNGAP1-related disorder includes preventing or reducing a symptom of the SYNGAP1-related disorder in the subject, inducing clinical response, preventing, inhibiting or reducing progression of a SYNGAP1-related disorder, or preventing, inhibiting or reducing a complication of a SYNGAP1-related disorder.

[0149] Preventing, arresting, or ameliorating a SYNGAP1-related disorder, such as preventing, diminishing, inhibiting, or eliminating one or more symptoms of a

SYNGAP1-related disorder can be based on objective and/or subjective parameters, including, e.g., the results of genetic testing, physical examination(s), neurological examination(s), and/or psychiatric evaluation(s). The success of treatment for a SYNGAP1-related disorder may be measured or evaluated by, for example, comparing the severity of the SYNGAP1-related disorder, or symptom thereof, before treatment with N-acetyl leucine is initiated, with the severity of the SYNGAP1-related disorder, or symptom thereof, following treatment with N-acetyl leucine. For example, the severity of a SYNGAP1-related disorder, or symptom thereof, may be assessed using a scale, index, rating, or score. In one embodiment, the treatment described herein improves such an assessment from a value or degree characteristic of a symptomatic subject to a value or degree characteristic of a non-symptomatic subject. In one embodiment, the treatment described herein improves such an assessment compared to a baseline. The baseline may be, for example, the subject's condition before initiating any treatment for the SYNGAP1-related disorder, or symptom thereof, or before initiating treatment for the SYNGAP1-related disorder, or symptom thereof, with N-acetyl leucine. Alternatively, the baseline may be, for example, the subject's condition after a certain time period on treatment for the disease. In one embodiment, treatment with N-acetyl leucine as described herein improves the subject's assessment, e.g., scale, index, rating, or score of objective and/or subjective parameters, compared to a baseline by at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, or at least 50%. In one embodiment, assessment is improved by at least 60%, at least 70%, at least 80%, at least 90%, or 100%.

[0150] A "symptom" of a SYNGAP1-related disorder includes any clinical or laboratory manifestation associated with the SYNGAP1-related disorder and is not limited to what the subject can feel or observe. Symptoms of a SYNGAP1-related disorder include, but are not limited to, mild to severe intellectual disability, hypotonia, global development delay, epilepsy, sensory processing disorder, gross and fine motor skill delays, dyspraxia, mild to severe speech delay/apraxia, autism spectrum disorder, sleep disorder, behavior disorder, or visual abnormality, or a combination thereof.

[0151] In another embodiment, the disclosure provides procedures of personalized medicine for subjects having a SYNGAP1-related disorder that encompasses the selection of treatment options with the highest likelihood of successful outcome for individual subjects. In another aspect, the disclosure relates to the use of a genetic testing to predict

treatment outcome, e.g., the likelihood of favorable responses or treatment success, in subjects having SYNGAP1-related disorder.

[0152] In another embodiment, the disclosure provides a method of selecting a subject for treatment of a SYNGAP1-related disorder with N-acetyl leucine, comprising obtaining a biological sample, e.g., a blood or saliva sample, from the subject, and testing the biological sample from the subject for the presence of a pathogenic variant, i.e., a mutation, in the *SYNGAP1* gene. Mutations in the *SYNGAP1* gene can be determined by genetic testing, e.g., chromosomal microarray analysis (CMA), single gene sequencing, multigene panel testing, and/or exome sequencing. The diagnosis of a SYNGAP1-related disorder is confirmed by identification of either a heterozygous pathogenic variant in SYNGAP1 or a deletion of the chromosome 6. This selection method may further comprise administering a therapeutically effective amount of N-acetyl leucine to the subject if the biological sample contains the biomarker a pathogenic variant in the *SYNGAP1* gene.

[0153] In another embodiment, the disclosure provides methods for predicting treatment outcomes in a subject having a SYNGAP1-related disorder, comprising obtaining a biological sample from the subject, testing the biological sample from the subject for the presence of a pathogenic variant in the *SYNGAP1* gene, wherein the detection of the pathogenic variant in the *SYNGAP1* gene indicates the subject will respond favorably to administration of a therapeutically effective amount of N-acetyl leucine. Favorable responses include, but are not limited to, preventing or delaying the onset of symptoms that would normally be expected in a subject afflicted with a SYNGAP1-related disorder.

[0154] In another embodiment, the disclosure provides methods of treating a SYNGAP1-related disorder in a subject, comprising administering a therapeutically effective amount of N-acetyl leucine to the subject wherein the subject's cells contain a pathogenic variant in the *SYNGAP1* gene. In one embodiment, the subject is selected for treatment with N-acetyl leucine after the subject's cells have been determined to contain a pathogenic variant in the *SYNGAP1* gene.

[0155] In another embodiment, the method of treating a subject having SYNGAP1-related disorder comprises obtaining a biological sample from the subject, determining whether the biological sample contains a pathogenic variant in the *SYNGAP1* gene, and administering to the subject a therapeutically effective amount of N-acetyl leucine if the biological sample contains an elevated level or decreased level of the biomarker.

[0156] The term "biological sample" as used herein refers to any tissue or fluid from a subject that is suitable for detecting a pathogenic variant in the *SYNGAP1* gene. Examples of useful biological samples include, but are not limited to, blood, plasma, serous fluid, cerebrospinal fluid, saliva, urine, lymph, cerebral spinal fluid, and the like. Other suitable biological samples will be familiar to those of ordinary skill in the relevant arts. A biological sample can be analyzed for biomarker expression and/or mutation using any technique known in the art and can be obtained using techniques that are well within the scope of ordinary knowledge of a clinical practitioner. In one embodiment of the disclosure, the biological sample comprises blood cells.

[0157] The present disclosure provides the following particular embodiments with respect to personalized medicine for subjects having a SYNGAP1-related disorder:

[0158] Embodiment I: A method of treating a subject having a SYNGAP1-related disorder, the method comprising administering a therapeutically effective amount of N-acetyl leucine to the subject, wherein cells of the subject contain a pathogenic variant in the *SYNGAP1* gene.

[0159] Embodiment II: A method of treating a subject having a SYNGAP1-related disorder, the method comprising:

[0160] (a) determining whether a pathogenic variant in the *SYNGAP1* gene is present or absent in a biological sample taken from the subject; and

[0161] (b) administering a therapeutically effective amount of N-acetyl leucine to the subject if a pathogenic variant in the *SYNGAP1* gene is present in the biological sample.

[0162] Embodiment III: A method for treating a SYNGAP1-related disorder in a subject having a pathogenic variant in the *SYNGAP1* gene, the method comprising administering to the subject a therapeutically effective amount of N-acetyl leucine.

[0163] Embodiment IV: A method of treating a subject having mild to severe intellectual disability, hypotonia, global development delay, epilepsy, sensory processing disorder, gross and fine motor skill delays, dyspraxia, mild to severe speech delay/apraxia, autism spectrum disorder, sleep disorder, behavior disorder, or visual abnormality, or a combination thereof, the method comprising:

[0164] (a) determining whether a pathogenic variant in the *SYNGAP1* gene is present or absent in a biological sample taken from the subject; and

[0165] (b) administering a therapeutically effective amount of N-acetyl leucine to the subject if a pathogenic variant in the *SYNGAP1* gene is present in the biological sample.

[0166] Embodiment V: A method comprising administering a therapeutically effective amount of N-acetyl leucine to a subject in need thereof, wherein:

[0167] (a) the subject has mild to severe intellectual disability, hypotonia, global development delay, epilepsy, sensory processing disorder, gross and fine motor skill delays, dyspraxia, mild to severe speech delay/apraxia, autism spectrum disorder, sleep disorder, behavior disorder, or visual abnormality, or a combination thereof; and

[0168] (b) a pathogenic variant in the *SYNGAP1* gene is present in a biological sample taken from the subject.

[0169] Embodiment VI. The method of any one of Embodiments I-V, wherein the subject has a missense mutation in the *SYNGAP1* gene.

[0170] Embodiment VII. The method of any one of Embodiments I-V, wherein the subject has a protein truncating mutation in the *SYNGAP1* gene.

[0171] Embodiment VIII. The method of any one of Embodiments I-VII, wherein the N-acetyl leucine is N-acetyl-L-leucine.

[0172] In one embodiment, N-acetyl leucine may be administered, for example, at a dose ranging from about 500 mg to about 30 g per day or ranging from about 500 mg to about 15 g per day, such as ranging from about 1.5 g to about 10 g per day, optionally by solid oral or liquid oral route, e.g, as an oral suspension. N-acetyl leucine, may be administered, for example, in a dose according to that of Tanganil®, which is prescribed to adults in a dose of 1.5 g to 2 g per day, 3-4 tablets in two doses, morning and evening.

[0173] If a single enantiomer, i.e., N-acetyl-D-leucine or N-acetyl-L-leucine, is administered the doses may be adjusted accordingly. For instance if N-acetyl-L-leucine is administered, the dose may range from about 250 mg to about 30 g per day, range from about 250 mg to about 15 g per day, range from about 1 mg to about 10 g per day, or range from about 1 g to about 5 g per day.

[0174] In one embodiment, the administered total daily dose ranges of N-acetyl leucine, e.g., N-acetyl-DL-leucine or N-acetyl-L-leucine, are from about 1 g to about 30 g per day, from about 1 g to about 15 g per day, from about 1 g to about 10 g per day, or from about 1.5 g to about 7 g per day, from 15.1 g to about 30 g per day, 16 g to about 30 g per day, 17 g to about 30 g per day, 18 g to about 30 g per day, 19 g to about 30 g per day, or 20 g

to about 30 g per day. It may be from about 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 g to about 15 g per day. It may be from about 2, 3, 4, 5, 6, 7, 8 or 9 g to about 10 g per day. It may be from 15.1, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 25, 27, 28, or 29 g to about 30 g per day. It may be more than about 1.5 g per day, but less than about 15, 14, 13, 12, 11, 10, 9, 8, 7, 6 or 5 g per day. In one embodiment, the dose ranges from about 4 g to about 6 g per day. In one embodiment, the dose ranges from about 4 g to about 5 g per day. In one embodiment, the dose is about 4.5 g per day. In one embodiment, the dose is about 5 g per day. In one embodiment, the dose is about 1 g per day, about 2 g per day, about 3 g per day, about 4 g per day, about 5 g per day, about 6 g per day, about 7 g per day, about 8 g per day, about 9 g per day, about 10 g per day, about 11 g per day, about 12 g per day, about 13 g per day, about 14 g per day, or about 15 g per day. In another embodiment, the dose is about 16 g per day, about 17 g per day, about 18 g per day, about 19 g per day, or about 20 g per day. In another embodiment, the dose is about 21 g per day, about 22 g per day, about 23 g per day, about 24 g per day, about 25 g per day, about 26 g per day, about 27 g per day, about 28 g per day, about 29 g per day, or about 30 g per day. In one embodiment, these doses are administered in a solid oral dosage form, notably tablets, or as an oral suspension. In another embodiment, these doses are for N-acetyl leucine when in its racemic form. Doses for N-acetyl leucine when an enantiomeric excess is present may or may not be lower, for example, around 50% lower. The above recited dose-ranges when halved are thus also explicitly encompassed by the present disclosure.

[0175] In one embodiment, the total daily dose of N-acetyl leucine may be spread across multiple administrations, i.e., administration of N-acetyl leucine may occur two, three, or more times a day to achieve the total daily dose. As an example, the required number of tablets or amount of an oral suspension to provide the total daily dose of N-acetyl leucine may be split across two administrations (for example, in the morning and evening) or three administrations (for example, in the morning, noon, and evening). Each dose may be administered with or without food. For example, N-acetyl-L-leucine or N-acetyl-DL-leucine may be dosed by about 1 or about 2 hours before meals, such as at least about 20 minutes, at least about 30 minutes, at least about 40 minutes, or at least about 1 hour before meals, or may be dosed by about 1, about 2, or about 3 hours after meals, such as waiting at least about 20 minutes, at least about 30 minutes, at least about 1 hour, at least about 1.5 hours, at least about 2 hours, or at least about 2.5 hours after meals. For example, a total

daily dose of 4.5 g acetyl-DL-leucine may be administered as three Tanganil® (or equivalent) tablets before, with, or after breakfast, three further tablets before, with, or after lunch and three further tablets before, with, or after dinner.

[0176] Treatment duration may be, for example, about seven days or more, about two weeks or more, about three weeks or more, about one month or more, about six weeks or more, about seven weeks or more, or about two months or more. In one embodiment, it is about three months or more, about four months or more, about five months or more or about six months or more. The treatment duration may be about 1 year or more, about 2 years or more, about 4 years or more, about 5 years or more, or about 10 years or more. The treatment duration may be the life-time of the subject.

[0177] Any and all combinations of dosage form, dose amount, dosing schedule and treatment duration are envisaged and encompassed by the disclosure. In one embodiment, the dose of N-acetyl leucine is from about 4 g to about 15 g per day, taken across one, two, or three administrations per day, for a treatment duration of about two months or more. In another embodiment, the dose is more than 4 g but no more than 5 g per day, taken across one, two, or three administrations per day, for a treatment duration of about six months or more. The dosage form may be a solid oral dosage form, notably tablets. The dosage may also be in the form of an oral suspension.

[0178] N-acetyl leucine may be used as a monotherapy for treating or preventing a SYNGAP1-related disorder, or a symptom thereof, in a subject. Alternatively, N-acetyl leucine may be used as an adjunct to, or in combination with, other therapies for treating or preventing a SYNGAP1-related disorder, or a symptom thereof, in a subject. For example, N-acetyl leucine may be used in combination with anti-seizure medications, e.g., valproate and lamotrigine, to treat a SYNGAP1-related disorder.

[0179] In another embodiment, N-acetyl leucine is used as an adjunct to, or in combination with, other therapies for treating or preventing a SYNGAP1-related disorder, or a symptom thereof, in a subject, wherein the other therapies do not comprise administration of valproate, e.g., sodium valproate, or valproic acid to the subject.

[0180] In another embodiment, the disclosure provides a kit comprising N-acetyl-DL-leucine, or a pharmaceutically acceptable, and instructions for administering N-acetyl-DL-leucine, or a pharmaceutically acceptable to a subject having SYNGAP1-related disorder, or a symptom thereof.

[0181] In another embodiment, the disclosure provides a kit comprising N-acetyl-L-leucine, or a pharmaceutically acceptable, and instructions for administering N-acetyl-L-leucine, or a pharmaceutically acceptable to a subject having SYNGAP1-related disorder, or a symptom thereof.

[0182] All of the features described herein (including any accompanying claims, abstract and drawings), and/or all of the steps of any method so disclosed, may be combined with any of the above aspects in any combination, except combinations where at least some of such features and/or steps are mutually exclusive.

[0183] In another embodiment, the present disclosure provides a method of treating or preventing a SYNGAP1-related disorder, in a subject in need thereof, or treating or preventing a symptom of a SYNGAP1-related disorder in a subject in need thereof, the method comprising administering about 1 g to about 30 g of N-acetyl-DL-leucine to the subject per day. In another embodiment, about 2 g to about 15 g of N-acetyl-DL-leucine is administered to the subject per day. In another embodiment, about 3 g to about 10 g of N-acetyl-DL-leucine is administered is administered to the subject per day. In another embodiment, about 4 g to about 8 g of N-acetyl-DL-leucine is administered to the subject per day. In another embodiment, about 4 g to about 5 g of N-acetyl-DL-leucine is administered to the subject per day. In another embodiment, about 15 g to about 30 g of N-acetyl-DL-leucine is administered to the subject per day. In another embodiment, about 5 g of N-acetyl-DL-leucine is administered to the subject per day.

[0184] In another embodiment, the present disclosure provides a method of treating or preventing a SYNGAP1-related disorder, in a subject in need thereof, or treating or preventing a symptom of a SYNGAP1-related disorder in a subject in need thereof, the method comprising administering about 1 g to about 30 g of N-acetyl-L-leucine to the subject per day. In another embodiment, about 2 g to about 15 g of N-acetyl-L-leucine is administered to the subject per day. In another embodiment, about 3 g to about 10 g of N-acetyl-L-leucine is administered is administered to the subject per day. In another embodiment, about 4 g to about 8 g of N-acetyl-DL-leucine is administered to the subject per day. In another embodiment, about 4 g to about 5 g of N-acetyl-L-leucine is administered to the subject per day. In another embodiment, about 15 g to about 30 g of N-acetyl-L-leucine is administered to the subject per day. In another embodiment, about 5 g of N-acetyl-L-leucine is administered to the subject per day

[0185] The disclosure also provides the following particular method of treatment embodiments.

[0186] Embodiment 1. A method of treating a SYNGAP1-related disorder, or a symptom thereof, in a subject in need thereof, the method comprising administering a therapeutically effective amount of N-acetyl-DL-leucine or N-acetyl-L-leucine to the subject.

[0187] Embodiment 2. The method of Embodiment 1 wherein the subject has been diagnosed with a pathogenic variant in the *SYNGAP1* gene by genetic testing.

[0188] Embodiment 3. The method of Embodiments 1 or 2, wherein the N-acetyl-DL-leucine or N-acetyl-L-leucine is administered to the subject to treat the SYNGAP1-related disorder.

[0189] Embodiment 4. The method of Embodiments 1 or 2, wherein the N-acetyl-DL-leucine or N-acetyl-L-leucine is administered to the subject to treat a symptom of the SYNGAP1-related disorder.

[0190] Embodiment 5. The method of Embodiment 4, wherein the symptom of the SYNGAP1-related disorder is mild to severe intellectual disability, hypotonia, global development delay, epilepsy, sensory processing disorder, gross and fine motor skill delays, dyspraxia, mild to severe speech delay/apraxia, autism spectrum disorder, sleep disorder, behavior disorder, or visual abnormality, or a combination thereof.

[0191] Embodiment 6. The method of any one of Embodiments 1-5, wherein a total dose of about 1 g to about 30 g of N-acetyl-DL-leucine is administered to the subject per day.

[0192] Embodiment 7. The method of Embodiment 6, wherein a total dose of about 2 g to about 15 g of N-acetyl-DL-leucine is administered to the subject per day.

[0193] Embodiment 8. The method of Embodiment 7, wherein a total dose of about 3 g to about 10 g of N-acetyl-DL-leucine is administered to the subject per day.

[0194] Embodiment 9. The method of Embodiment 8, wherein a total dose of about 4 g to about 8 g of N-acetyl-DL-leucine is administered to the subject per day.

[0195] Embodiment 10. The method of any one of Embodiments 6-9, wherein the N-acetyl-DL-leucine is administered once a day, twice a day, or three times a day to the subject to achieve the total daily dose.

[0196] Embodiment 11. The method of any one of Embodiments 6-10, wherein the N-acetyl-DL-leucine is administered to the subject as a tablet or as an oral suspension.

[0197] Embodiment 12. The method of any one of Embodiments 1-5, wherein a total dose of about 1 g to about 30 g of N-acetyl-L-leucine is administered to the subject per day.

[0198] Embodiment 13. The method of Embodiment 12, wherein a total dose of about 2 g to about 15 g of N-acetyl-L-leucine is administered to the subject per day.

[0199] Embodiment 14. The method of Embodiment 13, wherein a total dose of about 3 g to about 10 g of N-acetyl-L-leucine is administered to the subject per day.

[0200] Embodiment 15. The method of Embodiment 14, wherein a total dose of about 4 g to about 8 g of N-acetyl-L-leucine is administered to the subject per day.

[0201] Embodiment 16. The method of any one of Embodiments 12-15, wherein the N-acetyl-L-leucine is administered once a day, twice a day, or three times a day to the subject to achieve the total daily dose.

[0202] Embodiment 17. The method of any one of Embodiments 12-16, wherein the N-acetyl-L-leucine is administered to the subject as a tablet or as an oral suspension.

[0203] Embodiment 18. A kit comprising N-acetyl-DL-leucineand instructions for administering N-acetyl-DL-leucine, or a pharmaceutically acceptable to a subject having SYNGAP1-related disorder, or a symptom thereof.

[0204] Embodiment 19. A kit comprising N-acetyl-L-leucine and instructions for administering N-acetyl-L-leucine, or a pharmaceutically acceptable to a subject having SYNGAP1-related disorder, or a symptom thereof.

[0205] Embodiment 20. The kit of Embodiments 18 or 19, wherein the symptom of the SYNGAP1-related disorder is mild to severe intellectual disability, hypotonia, global development delay, epilepsy, sensory processing disorder, gross and fine motor skill delays, dyspraxia, mild to severe speech delay/apraxia, autism spectrum disorder, sleep disorder, behavior disorder, or visual abnormality, or a combination thereof.

[0206] Embodiment 21. A method of treating a subject having mild to severe intellectual disability, hypotonia, global development delay, epilepsy, sensory processing disorder, gross and fine motor skill delays, dyspraxia, mild to severe speech delay/apraxia, autism spectrum disorder, sleep disorder, behavior disorder, or visual abnormality, or a combination thereof, the method comprising:

[0207] (a) determining whether a pathogenic variant in the *SYNGAP1* gene is present or absent in a biological sample taken from the subject; and

[0208] (b) administering a therapeutically effective amount of N-acetyl leucine to the subject if a pathogenic variant in the *SYNGAP1* gene is present in the biological sample.

[0209] Embodiment 22. A method, comprising administering a therapeutically effective amount of N-acetyl leucine to a subject in need thereof, wherein:

[0210] (a) the subject has mild to severe intellectual disability, hypotonia, global development delay, epilepsy, sensory processing disorder, gross and fine motor skill delays, dyspraxia, mild to severe speech delay/apraxia, autism spectrum disorder, sleep disorder, behavior disorder, or visual abnormality, or a combination thereof; and

[0211] (b) a pathogenic variant in the *SYNGAP1* gene is present in a biological sample taken from the subject.

[0212] Embodiment 23. The method of any one of Embodiments 2-17, 21, or 22, wherein the pathogenic variant in the *SYNGAP1* gene is a protein truncating (PT), c490 C>T; PT, c.1167_1168delAG; PT, C.1760_1792del33; missense (MS), c.662 A>T; PT, c.333del; or PT, c.3233_3236delTCAG mutation.

[0213] Embodiment 24. The method of Embodiment 23, wherein the pathogenic variant in the *SYNGAP1* gene is a PT, c490 C>T mutation.

[0214] The disclosure also provides the following particular use-limited product embodiments.

[0215] Embodiment 1. N-acetyl-DL-leucine or N-acetyl-L-leucine for use in treating a SYNGAP1-related disorder, or a symptom thereof, in a subject in need thereof

[0216] Embodiment 2. The N-acetyl-DL-leucine or N-acetyl-L-leucine of Embodiment 1 wherein the subject has been diagnosed with a pathogenic variant in the SYNGAP1 gene by genetic testing.

[0217] Embodiment 3. The N-acetyl-DL-leucine or N-acetyl-L-leucine of Embodiments 1 or 2, wherein the N-acetyl-DL-leucine or N-acetyl-L-leucine is to be administered to the subject to treat the SYNGAP1-related disorder.

[0218] Embodiment 4. The N-acetyl-DL-leucine or N-acetyl-L-leucine of Embodiments 1 or 2, wherein the N-acetyl-DL-leucine or N-acetyl-L-leucine is to be administered to the subject to treat a symptom of the SYNGAP1-related disorder.

[0219] Embodiment 5. The N-acetyl-DL-leucine or N-acetyl-L-leucine of Embodiment 4, wherein the symptom of the SYNGAP1-related disorder is mild to severe intellectual disability, hypotonia, global development delay, epilepsy, sensory processing disorder, gross and fine motor skill delays, dyspraxia, mild to severe speech delay/apraxia, autism spectrum disorder, sleep disorder, behavior disorder, or visual abnormality, or a combination thereof.

[0220] Embodiment 6. The N-acetyl-DL-leucine of any one of Embodiments 1-5, wherein a total dose of about 1 g to about 30 g of N-acetyl-DL-leucine is to be administered to the subject per day.

[0221] Embodiment 7. The N-acetyl-DL-leucine of Embodiment 6, wherein a total dose of about 2 g to about 15 g of N-acetyl-DL-leucine is to be administered to the subject per day.

[0222] Embodiment 8. The N-acetyl-DL-leucine of Embodiment 7, wherein a total dose of about 3 g to about 10 g of N-acetyl-DL-leucine is to be administered to the subject per day.

[0223] Embodiment 9. The N-acetyl-DL-leucine of Embodiment 8, wherein a total dose of about 4 g to about 8 g of N-acetyl-DL-leucine is to be administered to the subject per day.

[0224] Embodiment 10. The N-acetyl-DL-leucine of any one of Embodiments 6-9, wherein the N-acetyl-DL-leucine is to be administered once a day, twice a day, or three times a day to the subject to achieve the total daily dose.

[0225] Embodiment 11. The N-acetyl-DL-leucine of any one of Embodiments 6-10, wherein the N-acetyl-DL-leucine is to be administered to the subject as a tablet or as an oral suspension.

[0226] Embodiment 12. The N-acetyl-L-leucine of any one of Embodiments 1-5, wherein a total dose of about 1 g to about 30 g of N-acetyl-L-leucine is to be administered to the subject per day.

[0227] Embodiment 13. The N-acetyl-L-leucine of Embodiment 12, wherein a total dose of about 2 g to about 15 g of N-acetyl-L-leucine is to be administered to the subject per day.

[0228] Embodiment 14. The N-acetyl-L-leucine of Embodiment 13, wherein a total dose of about 3 g to about 10 g of N-acetyl-L-leucine is to be administered to the subject per day.

[0229] Embodiment 15. The N-acetyl-L-leucine of Embodiment 14, wherein a total dose of about 4 g to about 8 g of N-acetyl-L-leucine is to be administered to the subject per day.

[0230] Embodiment 16. The N-acetyl-L-leucine of any one of Embodiments 12-15, wherein the N-acetyl-L-leucine is to be administered once a day, twice a day, or three times a day to the subject to achieve the total daily dose.

[0231] Embodiment 17. The N-acetyl-L-leucine of any one of Embodiments 12-16, wherein the N-acetyl-L-leucine is to be administered to the subject as a tablet or as an oral suspension.

[0232] Embodiment 18. The N-acetyl-L-leucine of any one of Embodiments 2-17, wherein the pathogenic variant in the *SYNGAP1* gene is a PT, c490 C>T; PT, c.1167_1168delAG; PT, C.1760_1792del33; MS, c.662 A>T; PT, c.333del; or PT, c.3233_3236delTCAG mutation.

[0233] Embodiment 19. The N-acetyl-L-leucine of Embodiment 18, wherein the pathogenic variant in the *SYNGAP1* gene is a PT, c490 C>T mutation.

[0234] The disclosure also provides the following particular use-limited process embodiments.

[0235] Embodiment 1. Use of N-acetyl-DL-leucine or N-acetyl-L-leucine in the manufacture of a medicament for treating a SYNGAP1-related disorder, or a symptom thereof, in a subject in need thereof

[0236] Embodiment 2. The use of Embodiment 1 wherein the subject has been diagnosed with a pathogenic variant in the SYNGAP1 gene by genetic testing.

[0237] Embodiment 3. The use of Embodiments 1 or 2, wherein the N-acetyl-DL-leucine or N-acetyl-L-leucine is to be administered to the subject to treat the SYNGAP1-related disorder.

[0238] Embodiment 4. The use of Embodiments 1 or 2, wherein the N-acetyl-DL-leucine or N-acetyl-L-leucine is to be administered to the subject to treat a symptom of the SYNGAP1-related disorder.

[0239] Embodiment 5. The use of Embodiment 4, wherein the symptom of the SYNGAP1-related disorder is mild to severe intellectual disability, hypotonia, global development delay, epilepsy, sensory processing disorder, gross and fine motor skill delays, dyspraxia, mild to severe speech delay/apraxia, autism spectrum disorder, sleep disorder, behavior disorder, or visual abnormality, or a combination thereof.

[0240] Embodiment 6. The use of any one of Embodiments 1-5, wherein a total dose of about 1 g to about 30 g of N-acetyl-DL-leucine is to be administered to the subject per day.

[0241] Embodiment 7. The use of Embodiment 6, wherein a total dose of about 2 g to about 15 g of N-acetyl-DL-leucine is to be administered to the subject per day.

[0242] Embodiment 8. The use of Embodiment 7, wherein a total dose of about 3 g to about 10 g of N-acetyl-DL-leucine is to be administered to the subject per day.

[0243] Embodiment 9. The use of Embodiment 8, wherein a total dose of about 4 g to about 8 g of N-acetyl-DL-leucine is to be administered to the subject per day.

[0244] Embodiment 10. The use of any one of Embodiments 6-9, wherein the N-acetyl-DL-leucine is to be administered once a day, twice a day, or three times a day to the subject to achieve the total daily dose.

[0245] Embodiment 11. The use of any one of Embodiments 6-10, wherein the N-acetyl-DL-leucine is to be administered to the subject as a tablet or as an oral suspension.

[0246] Embodiment 12. The use of any one of Embodiments 1-5, wherein a total dose of about 1 g to about 30 g of N-acetyl-L-leucine is to be administered to the subject per day.

[0247] Embodiment 13. The use of Embodiment 12, wherein a total dose of about 2 g to about 15 g of N-acetyl-L-leucine is to be administered to the subject per day.

[0248] Embodiment 14. The use of Embodiment 13, wherein a total dose of about 3 g to about 10 g of N-acetyl-L-leucine is to be administered to the subject per day.

[0249] Embodiment 15. The use of Embodiment 14, wherein a total dose of about 4 g to about 8 g of N-acetyl-L-leucine is to be administered to the subject per day.

[0250] Embodiment 16. The use of any one of Embodiments 12-15, wherein the N-acetyl-L-leucine is to be administered once a day, twice a day, or three times a day to the subject to achieve the total daily dose.

[0251] Embodiment 17. The use of any one of Embodiments 12-16, wherein the N-acetyl-L-leucine is to be administered to the subject as a tablet or as an oral suspension.

[0252] Embodiment 18. The use of any one of Embodiments 2-17, wherein the pathogenic variant in the *SYNGAP1* gene is a PT, c490 C>T; PT, c.1167_1168delAG; PT, C.1760_1792del33; MS, c.662 A>T; PT, c.333del; or PT, c.3233_3236delTCAG mutation.

[0253] Embodiment 19. The use of Embodiment 18, wherein the pathogenic variant in the *SYNGAP1* gene is a PT, c490 C>T mutation.

EXAMPLES

EXAMPLE 1

Behavioral Testing in heterozygous *Syngap1* knockout mice

[0254] Mice with a heterozygous mutation in the *Syngap1* gene (*Syngap1* $^{-/+}$ mice) reproduce symptoms of a SYNGAP1-related disorder in humans, including but not limited to, increased locomotor activity; decreased prepulse inhibition; impaired working and reference spatial memory; decreased sensitivity to painful stimuli; and impaired motor function. Nakajima et al., Neuropsychopharmacol Rep.: 223–237 (2019).

[0255] *Syngap1* $^{-/+}$ mice will be treated with N-acetyl leucine and subjected to well-defined behavioral studies, e.g., rotarod, hot plate, open field, light/dark transition, elevated plus maze, social interaction, prepulse inhibition, Porsolt forced swim, tail suspension, gait analysis, T-maze, Y-maze, Barnes maze, contextual and cued fear conditioning, and home cage locomotor activity, to determine whether N-acetyl leucine treatment improves or rescues the deficits and dysfunctions associated with mutation of the *Syngap1* gene as compared to an untreated control group of *Syngap1* $^{-/+}$ mice. This is a prophetic study.

EXAMPLE 2

Case Reports with N-acetyl-DL-leucine

[0256] N-Acetyl-DL-leucine (Tanganil®) was sourced by families from pharmacies in France. Families voluntarily followed treatment monitoring protocols and provided their results for analysis.

[0257] SynGAP1-related disorder (SynGAP1-RD) symptoms were documented at baseline then at defined intervals. Caregivers completed a daily diary to record medication usage,

adverse events, seizures type and frequency, sleep habits, and quality of life measures, including communication, behavior, coordination, sensory and GI issues. Daily quality of life was scored from +5 (great day) to -5 (terrible day), with 0 being the same as baseline. Caregivers then rated quality of life for the same measures at baseline, weekly for 1 month, then monthly for up to 3 months. These weekly ratings were also reported on a scale from +5 (really improved) to -5 (much worse), with 0 being the same as baseline. *See, e.g.*, Wright et al., J. Neurodev. Disord. 14:34 (2022); Wiltrout et al., Epilepsia (2024) doi:10.1111/epi.17913; Vlaskamp, Neurology 92: e96–e107 (2019). The term "patient" is used to describe the individual with SynGAP1-RD that received treatment with N-acetyl-DL-leucine. The results of Case Report #'s 2-7 are summarized in Fig. 13.

Case Report # 2

[0258] An 8-year-old boy (27 kg) with SynGAP1-RD (protein truncating mutation; PT, c.490 C>T) was treated orally with an adjusting dose of 1 to 1.5 grams of Tanganil® once or twice daily. The patient's baseline medications included guanfacine, sertraline, and CBD patches. No adjustments were made to his existing medications before initiation of treatment.

[0259] Caregivers monitored the effects of drug treatment using the approach outlined above. At the time this case report was prepared, the patient had just completed 8 weeks of N-acetyl-DL-leucine treatment.

[0260] Longitudinal data collected using a daily diary are shown Figs. 1A-C. Caregivers modified the dose of N-acetyl-DL-leucine, escalating to 1.5 grams per day before scaling back to 1 gram per day, due to a delay in the time it took to fall asleep (Fig. 1A). Quality of life was scored from +5 (great day) to -5 (terrible day), with 0 being the same as baseline. Quality of life improved over time for both the patient and the family members (Fig.1B). Sleep quality and seizures were not affected by N-acetyl-DL-leucine treatment; sleep was not originally problematic (Fig. 1C) and no visible seizures were reported prior to treatment. Additionally, no adverse events were reported.

[0261] Caregivers also rated weekly changes in seizures, sleep, communication, behaviors and physical abilities using a multi-question form. These ratings were also reported on a scale from +5 (really improved) to -5 (much worse), with 0 being the same as baseline. Cumulative ratings from each category were generated. Improvements in communication, behaviors and physical abilities were reported (Fig. 2A). Again, no changes were noted for

seizures or sleep. Individual areas of improvement within each category are shown in Fig. 2B. The greatest reported changes were improvements in undesired behaviors, expressive communication, and understanding.

[0262] In addition to monitoring qualitative and quantitative changes over time, the caregivers provided a letter of their observations. The following are statements from the caregivers letter to highlight the effect on N-acetyl-DL-leucine treatment on their son and their families lives.

[0263] "While our son made progress with his behaviors while on Sertraline, nothing compares to the progress we have seen on [N-acetyl-DL-leucine]. Nearly immediately after starting, we began to see changes in every area of his life. He began saying more words, using his iPad more effectively for communication, trying new foods, less restrictive routines, improved transitions."

[0264] "He is very motivated by the things that he enjoys; i.e. the phone or iPad. We haven't been able to give him the phone or iPad much over his last 2-3 years due to the increased behavior that he would display when it was time to transition away from the device. Currently, we are able to let him enjoy screen time multiple times a week for an allotted time because his transitions have become unlike anything I could have ever imagined. He will hand the phone to us at times or simply get distracted and not ask for it back. We can leave our phones on the counters and walk away whereas 6 months ago this would have been absolutely impossible."

[0265] "Since starting [N-acetyl-DL-leucine], our son has had all but less than 5 great days at school based on the option of great/good/okay or a note from the teacher. There was a point last year where he was hitting, kicking friends nearly daily. As his caregivers, we have so much less anxiety about outings with him."

[0266] "Communication has improved drastically since beginning [N-acetyl-DL-leucine]. Prior to [N-acetyl-DL-leucine], our son was doing well at using his iPad to communicate his wants and needs, but the momentum he is gaining now has been outstanding. He is phonetically spelling words on a 1st-2nd grade level and continues to improve weekly. He will also try and say new words and has added approximately 10-15 new verbal words to his vocabulary."

[0267] "Cognition seems to have greatly improved on [N-acetyl-DL-leucine]. He seems so much more aware of what is going on around him and when he is/is not being included. He

has two other siblings and he has become much more interested in side-by-side play with them. From painting, coloring and playing in the playroom, he seems to be so much more involved with them. As a parent, this has truly warmed my heart to see ALL of our children interacting with one another in a positive way."

[0268] "Our son has been making much more eye contact with us and others. He seems to look to us for approval or disapproval on subjects. This seems to be more of an awareness and understanding of the situation that I have never seen before."

[0269] "Our son's most recent IEP meeting was the best meeting we have ever had. Across the board, the entire room agreed that he has made some drastic improvements since the beginning of the year. They agree that his behaviors are night and day, his transitions have become so much smoother and he has improved significantly in his learning. Almost every single one of his goals have been met and updated. This is huge progress and we could not be prouder."

[0270] "Our son was only able to sit and do a non-preferred task for under a few minutes and now he can complete a task and is asking for more. He also seems to genuinely enjoy school more. He has always enjoyed school but he is truly thriving."

[0271] "Overall, the progress that we have seen has been eye opening. While we still have challenging behaviors intermittently, it is nothing like we have seen in the past. He may have a moment of getting upset but they are short lived and he seems to better understand the consequences of his actions. It is still early on but we will not be stopping [N-acetyl-DL-leucine] anytime soon.

[0272] "Case Report # 2 was updated after the patient finished 17 weeks of treatment. The daily dose of N-acetyl-DL-leucine, the scored quality of life, sleep quality, as well as the number of seizures are shown in Figs. 14A-14D. No adverse events were reported.

[0273] In Case Report # 2, N-acetyl-DL-leucine appeared to be safe, well-tolerated, and effective at improving cognition, communication, maladaptive behaviors, and physical abilities. After 8 weeks, quality of life measures declined and treatment was discontinued at week 17.

Case Report # 3

[0274] A 21-year-old woman (61 kg) with SynGAP1-RD (protein truncating mutation; PT, c.1167_116, 8delAG) was treated orally with 0.5-1 gram of Tanganil® daily. The patient's baseline medications included Onfi, Memantine, Clonidine, Lamotrigine, Sertraline,

Bulletproof Brain Octane C8 MCT Oil, and Midazolam rescue spray. No adjustments were made to her existing medications before initiation of treatment. Caregivers monitored the effects of drug treatment using the approach outlined above. At the time this case report was prepared, the patient had just completed 6 weeks of N-acetyl-DL-leucine treatment.

[0275] Longitudinal data collected using a daily diary are shown in Figs. 3A-C. Caregivers used an escalating dose up to 1 gram a day (Fig. 3A). Quality of life was scored from +5 (great day) to -5 (terrible day), with 0 being the same as baseline. Quality of life improved over time for both the patient and the family members (Fig. 3B). Sleep quality trended toward a longer duration of sleeping hours each night (Fig.3C). Seizures were not affected by N-acetyl-DL-leucine treatment; no visible seizures were reported prior to treatment. Additionally, no adverse events were reported.

[0276] Caregivers also rated weekly changes in seizures, sleep, communication, behaviors, and physical abilities. These ratings were also reported on a scale from +5 (really improved) to -5 (much worse), with 0 being the same as baseline. Ratings from each category were added to generate a relative cumulative score for the first 4 weeks of treatment. Improvements in sleep, communication, behaviors and physical abilities were reported (Fig. 4A). Again, no changes were noted for seizures. Individual areas of improvement within each category are shown in Fig. 4B. The greatest reported changes were improvements in undesired behaviors, self-care, and awareness.

[0277] Case Report # 3 was updated after the patient finished 17 weeks of treatment. The daily dose of N-acetyl-DL-leucine, the scored quality of life, sleep quality, as well as the number of seizures are updated in the Figs. 15A-15D.

[0278] Function and behavior changes were rated by caregivers before and 3 months after drug treatment using the Nisonger Child Behavior Rating Form and NICHQ Vanderbilt Assessment Scale (Figure 15E and 15F, respectively). The assessment forms were used to rate positive and problem behaviors, then relative changes in overall behaviors were evaluated (Figure 15G). An overall increase in positive behaviors were observed, most notably an increase in compliant and calm demeanor. A decrease in problem behaviors were observed, most notably a reduction in hyperactivity and inattention. The reduction in problem behaviors was statistically significant (Figure 15G; $p=0.0312$ by Wilcoxon matched-pairs signed rank test).

[0279] Additionally, comments were provided from the patient's ABA therapist:

[0280] "She has shown an increase in independence skills in daily living tasks, such as self-help and daily routines with minimal prompts or assistance. She has also shown progress in feeding and mealtime related skills, toileting, and hygiene skills. Her clarity and focus seem to have enhanced, thus improving her communication abilities. Her receptive and expressive language have strengthened— this tells me that her comprehension has increased. During sleep, she has had a decrease in disruptions. She is maintaining a 6-8 hour sleep schedule and nighttime outbursts have almost disappeared. It is my opinion that the medication [N-acetyl-DL-leucine] has provided an overall effective outcome in her behavior management plan."

[0281] In Case Report # 3, N-acetyl-DL-leucine appeared to be safe, well-tolerated, and effective at improving sleep, cognition, communication, maladaptive behaviors and physical abilities. After 17 weeks, the caregivers were highly satisfied with their child's improvements and continued to include N-acetyl-DL-leucine in their medication regimen.

Case Report # 4

[0282] A 6-year-old girl (25 kg) with SynGAP1-RD (protein truncating mutation; PT, c.1760_17, 92del33) was treated orally with an escalating dose of 1 to 2 grams of Tanganil® twice daily. The patient's baseline medications included lamotrigine and epidiolex. Caregivers monitored the effects of drug treatment using the approach outlined above. At the time this case report was prepared, the patient had just completed 4 weeks of N-acetyl-DL-leucine treatment.

[0283] Longitudinal data collected using a daily diary are shown in Figs. 5A-B. Caregivers used an escalating dose up to 2 grams per day (Fig.5A). Quality of life changes for the patient and family were not rated. Sleep quality was marked by several nights reduced sleeping hours (Fig. 5B). Caregivers noted several short absence seizures per day before treatment and no change in seizure frequency after treatment; exact seizure frequency was not recorded. Additionally, no adverse events were reported.

[0284] Caregivers also rated weekly changes in seizures, sleep, communication, behaviors, and physical abilities using a multi-question form. These ratings were also reported on a scale from +5 (really improved) to -5 (much worse), with 0 being the same as baseline. Cumulative ratings from each category were generated. Improvements in communication, behaviors and physical abilities were reported; disruptions in sleep over the first 3 weeks were also reported (Fig. 6A). Again, no changes were noted for seizures. Individual areas

of improvement and decline within each category are shown in Fig. 6B. The greatest reported changes were improvements in stability, gross motor function, and eating habits. Sleep disruption in the time to bed, time to fall asleep, and sleep duration were noted over the first 3 weeks of treatment. At week 4 disruptions in sleep were not reported and an increase in nighttime restfulness was observed.

[0285] In addition to monitoring qualitative and quantitative changes over time, the caregivers provided a letter of their observations. The following are statements from the caregivers letter to highlight the effect on N-acetyl-DL-leucine treatment on their son and their families lives.

[0286] "Before [N-acetyl-DL-leucine] treatment she would spend almost 100% of time in a stroller on community outings. After treatment, she is willingly getting out of the stroller and walks independently. She walks about 50% of the time given opportunity. She relies on assistance less, is ok with walking without holding hands, and has started running again."

[0287] "Her curiosity level went up again and she is wanting to walk and check everything out on her own."

[0288] "Overall her fine motor skills are more precise, no significant changes but just a little bit more precise and not as chaotic."

[0289] "She still is nonverbal but her willingness to communicate via PECS (Picture Exchange Communication System) has increased and her speed of learning has increased. Interestingly in the first week of treatment she started babbling again after about 10 months of silence. Her communication intent increased."

[0290] "She is mellowed out, transitions are easier, she seems less rigid and stuck on her ideas. She accepts brushing hair without a fight, in the past it was a struggle. It's easier to convince her with 'now this-then that'. She seems to understand the concept better. She did improve her dropping technique though, now she drops and lies on the floor and its harder to pick her up. She seems to be more clear in her wants also."

[0291] Case Report # 4 was updated after the patient finished 17 weeks of treatment. No additional information was provided.

[0292] In Case Report # 4, N-acetyl-DL-leucine appeared to be safe, well-tolerated, and effective at improving cognition, communication, maladaptive behaviors and physical abilities. After 17 weeks, the caregivers were highly satisfied with their child's improvements and continued to include N-acetyl-DL-leucine in their medication regimen.

Case Report # 5

[0293] A 13-year-old girl (36 kg) with SynGAP1-RD (missense mutation; MS, c.662 A>T) was treated orally with an adjusting dose of 0.5 to 2 grams of Tanganil® given twice daily. The patient's baseline medications included Depakote sprinkles, Vitamin D, Miralax, and Melatonin. No adjustments were made to her existing medications before initiation of treatment. Caregivers monitored the effects of drug treatment using the approach outlined above. At the time this case report was prepared, the patient had just completed 6 weeks of N-acetyl-DL-leucine treatment.

[0294] Longitudinal data collected using a daily diary are shown in Figs. 7A-C. Caregivers modified the dose of N-acetyl-DL-leucine, escalating to 2 grams per day before scaling back to 1 gram per day, due to increased behaviors (Fig. 7A). Quality of life was scored from +5 (great day) to -5 (terrible day), with 0 being the same as baseline. Quality of life initially improved over time for both the patient and the family members and then declined to baseline after 3 weeks (Fig. 7B). Duration of nighttime sleep did not change dramatically over time (Fig. 7C). Seizures were not affected by N-acetyl-DL-leucine treatment; no visible seizures were reported prior to treatment. Additionally, no adverse events were reported.

[0295] Caregivers also rated weekly changes in seizures, sleep, communication, behaviors, and physical abilities using a multi-question form. These ratings were also reported on a scale from +5 (really improved) to -5 (much worse), with 0 being the same as baseline. Cumulative ratings from each category were generated. Improvements in sleep, communication, behaviors, and physical abilities were reported within the first 2 weeks and then declined or did not continue to improve (Fig. 8A). No changes were noted for seizures. Individual areas of improvement or decline within each category are shown in Fig. 8B. The greatest reported changes were improvements in expressive communication, awareness, and fine motor skills. Caregivers reported an increase in undesired behaviors and reduced sleep duration at week 4.

[0296] Case Report # 5 was updated after the patient finished 9 weeks of treatment. The daily dose of N-acetyl-DL-leucine, the scored quality of life, sleep quality, as well as the number of seizures are updated in the Figs. 16A-D. Updates in improvements in seizures, sleep, communication, behaviors, and physical abilities are shown in Fig. 16E. Updates of

longitudinal ratings for specific features for each category demonstrating change over time are shown in Fig. 16F.

[0297] In Case Report # 5, N-acetyl-DL-leucine appeared to be safe, but the outcomes appear to be minimal and variable. After 9 weeks, the caregivers discontinued treatment.

Case Report # 6

[0298] A 7-year-old boy (27 kg) with SynGAP1-RD (protein truncating mutation; PT, c.333del) was treated orally with 1 to 3 grams of Tanganil® daily. The patient's baseline medications included sodium valproate, CBD, and Melatonin. No adjustments were made to his existing medications before initiation of treatment. Caregivers monitored the effects of drug treatment using the approach outlined above. At the time this case report was prepared, the patient had just completed 6 weeks of N-acetyl-DL-leucine treatment, however only 2.5 weeks of data were reported.

[0299] Longitudinal data collected using a daily diary are shown Figs. 9A-C. Caregivers used an escalating dose up to 3 grams per day (Fig. 9A). Quality of life was scored from +5 (great day) to -5 (terrible day), with 0 being the same as baseline. Quality of life initially improved for both the patient and the family members and then declined to baseline within the second week of treatment (Fig. 9B). Daily sleep duration was not reported. Absence seizures clusters appeared on day 4, coincident with an increase in N-acetyl-DL-leucine dose to 3 grams per day. After 2 days of dosing 3 grams per day, the dose was lowered to 2 grams per day; seizures resolved by day 8 (Fig. 9C). The cluster seizures were difficult to count; the number of seizures represented in the figures is meant to reflect detection of seizures and not an accurate seizure count. No other adverse events were reported. After completing 7 weeks on treatment, caregivers noted an increase in undersired behaviors and decided to stop using N-acetyl-DL-leucine.

[0300] Caregivers also rated weekly changes in seizures, sleep, communication, behaviors, and physical abilities. These ratings were also reported on a scale from +5 (really improved) to -5 (much worse), with 0 being the same as baseline. Ratings were provided at week 6 only. At that time, improvements in sleep, communication and physical functioning were reported. Increases in seizure number and undesired behaviors also increased (Fig.10).

[0301] Case Report # 6 was updated after the patient finished 7 weeks of treatment. The daily dose of N-acetyl-DL-leucine as well as the number of seizures are shown in Figs. 17A-B. Daily sleep duration was only reported for the first week of treatment (Figure 17C).

[0302] In Case Report # 6, N-acetyl-DL-leucine potentially increased absence seizure cluster and undesired or aggressive behaviors. While improvements in sleep, communication, and physical functioning were observed, the caregivers decided to stop using N-acetyl-DL-leucine due to the increase in undesired outcomes.

Case Report # 7

[0303] A 9-year-old girl (40 kg) with SynGAP1-RD (protein truncating mutation; PT, c.3233_323, 6delTCAG) was treated orally with 1 gram of Tanganil® daily. The patient's baseline medications included Depakote sprinkles, Sertraline, Risparidone, Quetiapine, and Miralax. No adjustments were made to her existing medications before initiation of treatment. A caregiver monitored the effects of drug treatment using the approach outlined above. At the time this case report was prepared, the patient had just completed 3 weeks of N-acetyl-DL-leucine treatment.

[0304] Longitudinal data collected using a daily diary are shown in Figs. 11A-C. Caregivers used a 1 gram per day, initially split between morning and evening doses then changed to morning dose only due to difficulty waking up in the morning. (Fig. 11A). Quality of life was scored from +5 (great day) to -5 (terrible day), with 0 being the same as baseline. Quality of life initially improved for both the patient and the family members and then declined (Fig. 11B). Daily sleep duration was not affected by N-acetyl-DL-leucine treatment, although difficulty waking was reported (Fig. 11C). Seizures were not affected by N-acetyl-DL-leucine treatment; no visible seizures were reported prior to treatment. No other adverse events were reported.

[0305] Caregivers also rated weekly changes in seizures, sleep, communication, behaviors and physical abilities. These ratings were also reported on a scale from +5 (really improved) to -5 (much worse), with 0 being the same as baseline. Initially improvements in sleep, communication, behavior and physical functioning were reported. Improvements in communication persisted through week 3, while sleep and behaviors declined (Fig. 12A). Individual ratings showed modest improvements in understanding and expressive communication. An increase in undesired or aggressive behaviors were noted (Fig. 12B). After 3 weeks of N-acetyl-DL-leucine treatment, the caregivers decided to stop using the acetyl-leucine.

[0306] In Case Report # 7, N-acetyl-DL-leucine potentially affected waking time and increased undesired or aggressive behaviors. While improvements in communication were

observed, the caregivers decided to stop using N-acetyl-DL-leucine due to the increase in undesired outcomes.

Case Report # 8

[0307] A 14-year-old male (93 kg) with SynGAP1-RD (PT, c.698_699 dupGT) was treated orally with 1 gram of Tanganil® daily. The patient's baseline medications included Lamortagine, Guanfacine, Clonazepam, Citalopram, Colace Buyrate, Iron supplement, Magnesium supplement, and supplement multivitamin. No adjustments were made to his existing medications before initiation of treatment. A caregiver monitored the effects of drug treatment using the approach outlined above. The patient stopped using N-acetyl-DL-leucine after 7 weeks on the treatment.

[0308] Caregivers completed a quick assessment after 7 weeks of N-acetyl-DL-leucine treatment. QOL measures, including seizures, sleep, communication, behaviors, physical abilities, and other, were reported. Communication, physical abilities and cognition were reported to have improved. Sleep quality worsened over the course of treatment and the caregivers decided to discontinue N-acetyl-DL-leucine treatment after 7 weeks. Caregivers rated QOL changes at a single time point after intiating treatment (Fig. 18).

Case Report # 9

[0309] A 2-year-old female (13 kg) with SynGAP1-RD (protein truncating mutation) was treated orally with 0.5 gram of Tanganil® daily. The patient's baseline medications included only iron supplement. No adjustments were made to her existing medications before initiation of treatment. A caregiver monitored the effects of drug treatment using the approach outlined above. At the time this case report was prepared, the patient had just completed 11 weeks of N-acetyl-DL-leucine treatment and the study is ongoing.

[0310] Longitudinal data collected using a daily diary are shown in Figs. 19A-C. Caregivers used a dose of 0.5 gram per day given in split doses twice a day (Fig. 19A). No visible seizures were reported prior to or during treatment (Fig. 19B). Sleep quality was unaffected by treatment (Fig. 19C). Quality of life (QOL) was scored from +5 (great day) to -5 (terrible day), with 0 being the same as baseline. Quality of life improved over time for both the patient and the family members (Fig. 19D). Additionally, no adverse events were reported.

[0311] Caregivers rated weekly changes in seizures, sleep, communication, behaviors and physical abilities. Ratings were only provided for the first 2 weeks of treatment. These

ratings were also reported on a scale from +5 (really improved) to -5 (much worse), with 0 being the same as baseline. Improvements in communication, behaviors and physical abilities were reported (Fig. 19E). No changes were noted for seizures or sleep. Individual areas of improvement within each category are shown in Fig. 19F.

[0312] Caregivers provided the following statements in their weekly ratings:

[0313] "Quality of life for her and family has substantially improved in week 1! Notable changes documented by family and blinded teachers and therapists. Overall, marked improvement in energy level and much more age appropriate play."

[0314] "Quality of life for her and family has substantially improved in week 2. She seems to be doing new things and hitting new milestones daily with minimal or no side effects. Only negative thing has been recently head banging when she cannot express what she wants or doesn't get her way, in frustration."

[0315] In Case Report # 9, N-acetyl-DL-leucine was observed to be safe and reported to improve communication, physical abilities, behaviors, and overall quality of life. The caregivers continue to use N-acetyl-DL-leucine after 11 weeks of treatment.

Case Report # 10

[0316] A 4-year-old male (15 kg) with SynGAP1-RD was treated orally with 0.5 gram of Tanganil® daily. The patient's baseline medications included Lamortagine and Onfi. No adjustments were made to his existing medications before initiation of treatment. A caregiver monitored the effects of drug treatment using the approach outlined above. At the time this case report was prepared, the patient had just completed 11 weeks of treatment and the study is ongoing.

[0317] Longitudinal data collected using a daily diary are shown in Figs. 20A-D. Caregivers used an escalating dose up to 0.5 grams per day (Fig.20A). Absence seizures were reported to be notably reduced during the first week of treatment; no other seizure types were reported (Fig.20B). Prior to treatment 40 absence seizures were reported pre day; after week two 10 absence seizures were reported pre day with two exceptions. Sleep was largely unaffected by treatment (Fig.20C). Quality of life was scored from +5 (great day) to -5 (terrible day), with 0 being the same as baseline. Quality of life improved initially and remained high throughout the reported period, with the exception of one day which corresponded to a high seizure burden day (Fig.20D). No adverse events were reported.

[0318] Caregivers rated weekly changes in seizures, sleep, communication, behaviors and physical abilities after 1 week of treatment only. Ratings were also reported on a scale from +5 (really improved) to -5 (much worse). Improvements in communication and behaviors were reported, while worsening of sleep and physical activities were also noted (Fig. 20E). Parents continue to include N-acetyl-DL-leucine in their medication regimen after 11 weeks.

Case Report # 11

[0319] A 15-year-old male (52 kg) with SynGAP1-RD (PT, c.1677 G>C) was treated orally with 1-3 grams of Tanganil® daily. The patient's baseline medications included vitamin D and multivitamin. No adjustments were made to his existing medications before initiation of treatment. A caregiver monitored the effects of drug treatment using the approach outlined above. At the time this case report was prepared, the patient had just completed 10 weeks of N-acetyl-DL-leucine treatment and the study is ongoing.

[0320] Caregivers used an escalating dose up to 3 grams per day (Fig.21A). No seizures were reported prior to or during treatment (Fig.21B). Sleep duration was not recorded but was reported as unaffected (Fig.21C). Quality of life was scored from +5 (great day) to -5 (terrible day), with 0 being the same as baseline. Quality of life improved initially, declined and then returned around baseline (Fig.21D). Reduced QOL associated with increased meltdowns and tantrums. Caregivers reported this may have corresponded to overstimulation during the first 3 weeks of treatment while on vacation; life conditions returned to normal after 3 weeks. No adverse events were reported.

[0321] Caregivers rated weekly changes in seizures, sleep, communication, behaviors and physical abilities at 3 weeks of treatment. Ratings were also reported on a scale from +5 (really improved) to -5 (much worse). Improvements in communication, behaviors and physical abilities were reported (Fig. 21E). Caregivers continue to include N-acetyl-DL-leucine in their medication regimen after 10 weeks.

Case Report # 12

[0322] A 3-year-old male (17 kg) with SynGAP1-RD (PT, c.2970del) was treated orally with 0.25-0.5 gram of Tanganil® daily. The patient's baseline medications included Valporate, Onfi, Zonisade, and Carnitine. No adjustments were made to his existing medications before initiation of treatment. A caregiver monitored the effects of drug

treatment using the approach outlined above. At the time this case report was prepared, the patient had just completed 10 weeks of N-acetyl-DL-leucine treatment and the study is ongoing.

[0323] Caregivers used an escalating dose up to 0.5 grams per day, then reduced dose to 0.25 grams per day after 5 weeks (Fig.22A). Eyelid myoclonus seizures were reported before and throughout treatment (Fig.22B). Sleep duration was variable and heavily disrupted before and during treatment (Fig.22C). Quality of life was scored from +5 (great day) to -5 (terrible day), with 0 being the same as baseline. Quality of life improved after initiating treatment and remained high over 10 weeks (Fig.22D). QOL dipped at week 9 due to an illness. No adverse events were reported.

[0324] Caregiver reports from the daily diary and videos indicate improvements in communication, coordination and mood. No other reports were provided. Caregivers continue to include N-acetyl-DL-leucine in their medication regimen after 10 weeks.

Case Report # 13

[0325] A 6-year-old male (23 kg) with SynGAP1-RD (protein truncating mutation) was treated orally with 1 gram of Tanganil® daily. The patient's baseline medications included Clonidine, Melatonin, and Risparidone. No adjustments were made to his existing medications before initiation of treatment. A caregiver monitored the effects of drug treatment using the approach outlined above. At the time this case report was prepared, the patient had just completed 4 weeks of N-acetyl-DL-leucine treatment and the study is ongoing.

[0326] Caregivers completed a quick assessment after 4 weeks of N-acetyl-DL-leucine treatment. QOL measures, including seizures, sleep, communication, behaviors, physical abilities, and other, were reported. Sleep, communication, and problem behaviors were reported to have improved. Caregivers rated QOL changes at a single time point after initiating N-acetyl-DL-leucine treatment (Fig. 23). No change in seizures or physical abilities were reported; no negative effects were reported. After 4 weeks, the parents were highly satisfied with their child's improvements and continued to include N-acetyl-DL-leucine in their medication regimen.

[0327] Caregivers provided the following statement:

[0328] "He's much more alert. He is more patient and watches processes unfold step by step with interest now whereas before he didn't have the attention span, for example

watching patiently while we make his breakfast. Teacher reports he is following class routines much better this term even though she is unaware of the trial. He is more affectionate and his receptive language or obedience (not sure which one) has improved a lot."

Case Report # 14

[0329] A 6-year-old female (20 kg) with SynGAP1-RD (PT, p.Gly1126V, alfsTer4) was treated orally with 1.5 grams of Tanganil® daily. The patient's baseline medications included Valporate and Butyrate. No adjustments were made to her existing medications before initiation of treatment. A caregiver monitored the effects of drug treatment using the approach outlined above. At the time this case report was prepared, the patient had just completed 12 weeks of N-acetyl-DL-leucine treatment and the study is ongoing.

[0330] Caregivers completed a quick assessment after 12 weeks of N-acetyl-DL-leucine treatment. QOL measures, including seizures, sleep, communication, behaviors, physical abilities, and other, were reported. Physical abilities, focus and understanding were reported to have improved. Caregivers rated QOL changes at a single time point after initiating N-acetyl-DL-leucine treatment (Fig. 24). No change in seizures, sleep, communication, or problem behaviors were reported; no negative effects were reported. After 12 weeks, the caregivers were highly satisfied with their child's improvements and continued to include N-acetyl-DL-leucine in their medication regimen.

Case Report # 15

[0331] A 4-year-old male (20 kg) with SynGAP1-RD (c.3718 C>T was treated orally with 0.5-1.5 grams of Tanganil® daily. The patient's baseline medications included ML41 anti-epileptic eyeglass filter and Butyrate. No adjustments were made to his existing medications before initiation of treatment. A caregiver monitored the effects of drug treatment using the approach outlined above. At the time this case report was prepared, the patient had just completed 13 weeks of N-acetyl-DL-leucine treatment and the study is ongoing.

[0332] Caregivers used an escalating dose up to 1.5 grams per day (Fig.25A). Starting in week 2, N-acetyl-DL-leucine was provided three times per day. At week 8, N-acetyl-DL-leucine dose was reduced to 1 gram per day. Frequent eyelid myoclonus were reported prior to and throughout treatment (Fig.25B).

[0333] Nighttime sleep duration was unaffected by treatment, while time awake at night decreased over time (Fig.25C). Quality of life was scored from +5 (great day) to -5 (terrible day), with 0 being the same as baseline. Quality of life ratings for the patient and family increased with initiation of treatment (Fig.25D). At several points QOL measures declined to baseline or below but continued to be positive over the 13 weeks of treatment.

[0334] Caregivers daily diary reports indicate improvements in communication, behaviors and coordination. No additional information was provided. After 13 weeks, the parents were satisfied with their child's improvements and continued to include N-acetyl-DL-leucine in their medication regimen.

Case Report # 16

[0335] A 5-year-old female (19 kg) with SynGAP1-RD was treated orally with 0.5-1.5 grams of Tanganil® daily. The patient's baseline medications included Keppra, Butyrate Magnesim Supplement, Vitamin D Multivitamin, Carnitine, and Levocertirizine. No adjustments were made to her existing medications before initiation of treatment. A caregiver monitored the effects of drug treatment using the approach outlined above. At the time this case report was prepared, the patient had just completed 4 weeks of N-acetyl-DL-leucine treatment and the study is ongoing.

[0336] Caregivers used an escalating dose up to 1.5 grams per day (Fig.26A). Starting after 2 weeks, N-acetyl-DL-leucine was provided three times per day. No seizures were reported prior to or during treatment (Fig.26B). Nighttime sleep duration varied throughout the 4 week period (Fig.26C). Quality of life was scored from +5 (great day) to -5 (terrible day), with 0 being the same as baseline. Quality of life ratings for the patient and family increased over time with higher ratings reported for the patient than the family (Fig.26D).

[0337] Caregiver daily diary reports indicate improvements in communication and coordination. No additional information was provided. After 4 weeks, the caregivers were satisfied with their child's improvements and continued to include N-acetyl-DL-leucine in their medication regimen.

Case Report # 17

[0338] A 3-year-old female (14 kg) with SynGAP1-RD (PT, c.2776_27 77del) was treated orally with 0.5 grams of Tanganil® daily. The patient's baseline medications included Keppra, Melotonin, and Multivitamin. No adjustments were made to her existing

medications before initiation of treatment. A caregiver monitored the effects of drug treatment using the approach outlined above. At the time this case report was prepared, the patient had just completed 4 weeks of N-acetyl-DL-leucine treatment and the study is ongoing.

[0339] Caregivers used a dose of 0.5 gram per day given in split doses twice a day (Fig.27A). No visible seizures were reported prior to or during treatment (Fig.27B). Duration of nighttime sleep did not change in any noteworthy measure over time (Fig.27C). Quality of life was scored from +5 (great day) to -5 (terrible day), with 0 being the same as baseline. Quality of life was variable over the 4 week treatment period (Fig.27D). No adverse events were reported.

[0340] Caregivers rated weekly changes in seizures, sleep, communication, behaviors and physical abilities. Ratings were also reported on a scale from +5 (really improved) to -5 (much worse). A modest improvement in expressive communication was noted at week 3 (Fig.27E and Fig.27F). Cumulative ratings generated for each category are shown in Fig.27E.) Longitudinal ratings for specific features for each category demonstrating change over time are shown in Fig. 27F. No other changes were reported.

[0341] In case report # 17, N-acetyl-DL-leucine appeared to be safe, but the outcomes appear to be minimal. The parents continue to use N-acetyl-DL-leucine after 4 weeks of treatment.

Case Report # 18

[0342] A 3-year-old female (16 kg) with SynGAP1-RD was treated orally with 0.25-0.5 grams of Tanganil® daily. The patient didn't receive any baseline medications. A caregiver monitored the effects of drug treatment using the approach outlined above. At the time this case report was prepared, the patient had just completed 6 weeks of N-acetyl-DL-leucine treatment and the study is ongoing.

[0343] Caregivers initially used 0.5 gram per day split between two doses, then reduced the dose to 0.25 grams per day after two days (Fig.28A). No visible seizures were reported prior to or during treatment (Fig.28B). Daily sleep duration was largely unaffected, while night-time waking time decreased over time (Fig. 28C). Quality of life was scored from +5 (great day) to -5 (terrible day), with 0 being the same as baseline. Quality of life was variable over time but trended to be positive for both the patient and family (Fig.28D). No other adverse events were reported.

[0344] Caregivers rated weekly changes in seizures, sleep, communication, behaviors and physical abilities. Ratings were also reported on a scale from +5 (really improved) to -5 (much worse). Cumulative ratings were generated for each category. Initially improvements in communication, behavior and physical functioning were reported, improvements in communication and physical abilities continued through 6 weeks (Fig. 28E). Improvements in sleep were observed at weeks 5 and 6. Overall the greatest and most consistent gains were observed in expressive communication and understanding (Fig. 28F).

[0345] Caregivers provided statements to describe improvements in communication:

[0346] "She has shown improvements in her comprehension, increased word capacity, and awareness of her surroundings. She continues to add several words per week!! Although she does not incorporate the words regularly, and doesn't always say them again when asked. But she's saying them at least a couple times initially."

[0347] In case report # 18, N-acetyl-DL-leucine was observed to be safe, well-tolerated, and effective at improving communication, physical abilities, behaviors and sleep. After 6 weeks, the caregivers were highly satisfied with their child's improvements and continued to include N-acetyl-DL-leucine in their medication regimen.

Case Report # 19

[0348] A 7-year-old female (19 kg) with SynGAP1-RD (chr6:33409 151 G>A) was treated orally with 0.125-0.25 gram of Tanganil® daily. The patient's baseline medications included only Lamortagine. No adjustments were made to her existing medications before initiation of treatment. A caregiver monitored the effects of drug treatment using the approach outlined above. At the time this case report was prepared, the patient had just completed 2 weeks of N-acetyl-DL-leucine treatment and the study is ongoing.

[0349] Caregivers used an escalating dose up to 0.5 grams per day given in split doses twice a day (Fig.29A). Seizures were reported for the first 8 days, including eyelid myoclonia, dropping, and arm flailing (Fig.29B). The number of seizures were not reported. Daily sleep duration was largely unaffected (Fig.29C). Quality of life was scored from +5 (great day) to -5 (terrible day), with 0 being the same as baseline. Quality of life increased and remained high for the first 2 weeks of treatment for the patient and family (Fig.29D). No other adverse events were reported.

[0350] Caregiver's daily diary indicated improved mood and response to denied access. No other information was provided. After 2 weeks the parents continue to use N-acetyl-DL-leucine in their treatment regimen.

Case Report # 20

[0351] A 8-year-old male (23 kg) with SynGAP1-RD (PT; c.490 C>T) was treated orally with 2 grams of Tanganil® daily. The patient's baseline medications included Epidilex and Onfi. No adjustments were made to his existing medications before initiation of treatment. Caregivers monitored the effects of drug treatment using the approach outlined above. At the time this case report was prepared, the patient had just completed 26 weeks of N-acetyl-DL-leucine treatment and the study is ongoing.

[0352] Caregiver notes on the impact of N-acetyl-DL-leucine during the first five weeks of treatment were reported and are summarized in the table below. The medication was well-tolerated and no safety concerns were noted. Significant improvements in seizure frequency, sleep, and problematic behaviors were observed within the first month of treatment. Within 2 weeks of treatment, the patient had no identifiable seizures during the day. Within 3 weeks of treatment, the patient began sleeping through the night. Within 4 weeks, marked improvements in behaviors were observed by multiple caregivers at home, at school, and during group activities. Improvements in communication and sensory issues were also observed. Minimal improvements were observed for GI issues; an upset stomach was reported at week 5, but this may have been unrelated.

[0353] Caregivers recorded quality of life impact of N-acetyl-DL-leucine treatment on SynGAP1-RD symptoms 5 weeks (Table 1). Changing symptoms are indicated with upward arrows if the desired outcomes were observed or downward arrows if undesired were observed. Changes were scored as mild, moderate, or significant, relative to how the change impacted the patient and family life overall.

Table 1. Quality of Life Impact of N-acetyl-DL-leucine Treatment on SynGAP1-RD Symptoms at 5 Weeks

	Weeks after initiation of N-acetyl-DL-leucine					
Symptoms	Pre-initiation	Week 1	Week 2	Week 3	Week 4	Week 5
Seizures	Average of 5 absence seizures per day.	Average of 5 absence seizures per day.	No seizures during the day. (↑↑↑)	No seizures during the day. (↑↑↑)	No seizures during the day. (↑↑↑)	No seizures during the day. (↑↑↑)
Sleep	Difficulty falling asleep. Restless at night. Up at 4am.	Difficulty falling asleep. Restless at night. Up at 4am.	Difficulty falling asleep. More restful during night. Up at 4am.(↑)	Fell asleep quickly. Slept all night. (↑↑↑)	Fell asleep quickly. Slept all night. (↑↑↑)	Fell asleep quickly. Slept all night. (↑↑↑)
Behaviors	no change	More centered. Easier transitions. Followed directions. (↑)	Improvements following instructions, staying on task, and initiating activities. Increased patience and independence. Reduced obsessions. Noted improvements by teachers, therapists and coach. (↑↑)	Improvements completing school work. More focused non-electronic toys. No issues with lunchtime or transitions. Increased independence. Reduced elopement. (↑↑)	Improvements using the toilet independently, following directions and completing school work. Did not have tantrum during challenging event. (↑↑↑)	Improvements following directions and completing school work. Increased engagement with siblings. Report of significantly improved behaviors at school. (↑↑↑)

Communication	no change	no change	Increased focus on communication. (↑)	Improved labeling, both verbally and with AAC device. Increased focus and participation during speech therapy. (↑↑)	Increased focus and participation during speech therapy. (↑↑)	Improvements communicating emotions and needs. Attempting to use new words. (↑↑)
Sensory	no change	no change	no change	Showed appropriate satiation response; stopped eating when normally wouldn't. (↑)	no change	Remained clothed when normally would prefer to be naked. (↑)
GI	no change	no change	no change	no change	no change	Upset stomach. (↓)

Desired changes: significant (↑↑↑), moderate (↑↑), mild (↑); undesired changes: significant (↓↓↓), moderate (↓↓), mild (↓). Symptoms not labeled indicate no change.

[0354] At 7 weeks after initiating drug treatment, the patient completed an EEG. The patient's neurologist compared results of the post-treatment EEG to the pre-treatment EEG to identify potential differences and provided the following statement. "The patient had an EEG then a repeat study approximately 6 months later. Both studies were routine in nature and between 35-45 minutes in order to capture sleep. While both studies were abnormal with some slowing and generalized discharges, the second study had a significant decrease in spike burden noted during stage 2 sleep. I would estimate an improvement of about 60-70 percent."

[0355] Function and behavior changes were rated by parents before and 3 months after drug treatment using the Nisonger Child Behavior Rating Form and NICHQ Vanderbilt Assessment Scale, Figure below. The assessment forms were used to rate positive and problem behaviors, then relative changes in overall behaviors were evaluated. An overall increase in positive behaviors were observed, most notably an increase in compliant and calm demeanor. A decrease in problem behaviors were observed, most notably a reduction in hyperactivity and inattention. The reduction in problem behaviors neared statistical significance ($p<0.0625$ by Wilcoxon matched-pairs signed rank test).

[0356] Results of standardized assessments taken before (green) and 3 months after (purple) initiation of N-acetyl-DL-leucine treatment are shown in Figs. 30A-C. Assessment in Fig. 30A is Nisonger Child Behavior Rating form; Fig. 30B shows NICHQ Vanderbilt Assessment Scale; Fig. 30C demonstrates relative changes in overall positive and problem behaviors between these two assessments; an increase in positive behaviors and decrease in problem behaviors indicate improved function.

[0357] In Case Report # 20, N-acetyl-DL-leucine was observed to be safe, well-tolerated, and effective at controlling seizures, as well as SynGAP1-RD symptoms. Improvements in seizures were visible by EEG within 2 months of treatment. At three months, the patient showed an increase in calm, compliant behaviors and a reduction in hyperactivity and inattention. After 6 months, the caregivers were highly satisfied with their child's improvements and continued to include N-acetyl-DL-leucine in their medication regimen.

Conclusions

[0358] Results from the case reports reflect the potentially beneficial and variable effects of N-acetyl-DL-leucine treatment. Across these case reports, drug dose was arrived at independently and dosing was not consistent based on weight or age.

[0359] Across these case reports, communication was most consistently and significantly improved. Physical function was also improved in some patients. Some patients reported no change.

[0360] Sleep and behaviors had the most variable change, with some patients reporting improvements while others reporting no change or a worsening condition. Of the patients evaluated here, some had limited improvements or had increased aggressions. In some cases, patients were also being treated with valproic acid for seizures, while the other patients with observed beneficial impact of treatment were not using valproic acid. The potential impact of N-acetyl-DL-leucine and valproic acid co-treatment will be evaluated further in both this observational study as well as in pre-clinical studies.

[0361] It is to be understood that the foregoing embodiments and exemplifications are not intended to be limiting in any respect to the scope of the disclosure, and that the claims presented herein are intended to encompass all embodiments and exemplifications whether or not explicitly presented herein.

[0362] All patents and publications cited herein are fully incorporated by reference in their entirety.

WHAT IS CLAIMED IS:

1. A method of treating a SYNGAP1-related disorder, or a symptom thereof, in a subject in need thereof, the method comprising administering a therapeutically effective amount of N-acetyl-DL-leucine or N-acetyl-L-leucine to the subject.

2. The method of claim 1 wherein the subject has been diagnosed with a pathogenic variant in the SYNGAP1 gene by genetic testing.

3. The method of claims 1 or 2, wherein the N-acetyl-DL-leucine or N-acetyl-L-leucine is administered to the subject to treat the SYNGAP1-related disorder.

4. The method of claims 1 or 2, wherein the N-acetyl-DL-leucine or N-acetyl-L-leucine is administered to the subject to treat a symptom of the SYNGAP1-related disorder.

5. The method of claim 4, wherein the symptom of the SYNGAP1-related disorder is mild to severe intellectual disability, hypotonia, global development delay, epilepsy, sensory processing disorder, gross and fine motor skill delays, dyspraxia, mild to severe speech delay/apraxia, autism spectrum disorder, sleep disorder, behavior disorder, or visual abnormality, or a combination thereof.

6. The method of any one of claims 1-5, wherein a total dose of about 1 g to about 30 g of N-acetyl-DL-leucine is administered to the subject per day.

7. The method of claim 6, wherein a total dose of about 2 g to about 15 g of N-acetyl-DL-leucine is administered to the subject per day.

8. The method of claim 7, wherein a total dose of about 3 g to about 10 g of N-acetyl-DL-leucine is administered to the subject per day.

9. The method of claim 8, wherein a total dose of about 4 g to about 8 g of N-acetyl-DL-leucine is administered to the subject per day.

10. The method of any one of claims 6-9, wherein the N-acetyl-DL-leucine is administered once a day, twice a day, or three times a day to the subject to achieve the total daily dose.

11. The method of any one of claims 6-10, wherein the N-acetyl-DL-leucine is administered to the subject as a tablet or as an oral suspension.

12. The method of any one of claims 1-5, wherein a total dose of about 1 g to about 30 g of N-acetyl-L-leucine is administered to the subject per day.

13. The method of claim 12, wherein a total dose of about 2 g to about 15 g of N-acetyl-L-leucine is administered to the subject per day.

14. The method of claim 13, wherein a total dose of about 3 g to about 10 g of N-acetyl-L-leucine is administered to the subject per day.

15. The method of claim 14, wherein a total dose of about 4 g to about 8 g of N-acetyl-L-leucine is administered to the subject per day.

16. The method of any one of claims 12-15, wherein the N-acetyl-L-leucine is administered once a day, twice a day, or three times a day to the subject to achieve the total daily dose.

17. The method of any one of claims 12-16, wherein the N-acetyl-L-leucine is administered to the subject as a tablet or as an oral suspension.

18. A kit comprising N-acetyl-DL-leucine and instructions for administering N-acetyl-DL-leucine, or a pharmaceutically acceptable to a subject having SYNGAP1-related disorder, or a symptom thereof.

19. A kit comprising N-acetyl-L-leucine and instructions for administering N-acetyl-L-leucine, or a pharmaceutically acceptable to a subject having SYNGAP1-related disorder, or a symptom thereof.

20. The kit of claims 18 or 19, wherein the symptom of the SYNGAP1-related disorder is mild to severe intellectual disability, hypotonia, global development delay, epilepsy, sensory processing disorder, gross and fine motor skill delays, dyspraxia, mild to severe speech delay/apraxia, autism spectrum disorder, sleep disorder, behavior disorder, or visual abnormality, or a combination thereof.

21. A method of treating a subject having mild to severe intellectual disability, hypotonia, global development delay, epilepsy, sensory processing disorder, gross and fine motor skill delays, dyspraxia, mild to severe speech delay/apraxia, autism spectrum disorder, sleep disorder, behavior disorder, or visual abnormality, or a combination thereof, the method comprising:

(a) determining whether a pathogenic variant in the *SYNGAP1* gene is present or absent in a biological sample taken from the subject; and

(b) administering a therapeutically effective amount of N-acetyl leucine to the subject if a pathogenic variant in the *SYNGAP1* gene is present in the biological sample.

22. A method, comprising administering a therapeutically effective amount of N-acetyl leucine to a subject in need thereof, wherein:

(a) the subject has mild to severe intellectual disability, hypotonia, global development delay, epilepsy, sensory processing disorder, gross and fine motor skill delays, dyspraxia, mild to severe speech delay/apraxia, autism spectrum disorder, sleep disorder, behavior disorder, or visual abnormality, or a combination thereof; and

(b) a pathogenic variant in the *SYNGAP1* gene is present in a biological sample taken from the subject.