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(54) METHODS AND COMPOSITIONS FOR TREATING ARG

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(57) **ABSTRACT**

The invention provides dilute and concentrated, aqueous, pharmaceutical compositions comprising gamma-hydroxybutyric acid or pharmaceutically acceptable salts thereof; gamma-butyryl lactone; 1,4-butanediol; 4-hydroxyl pentanoic acid or pharmaceutically acceptable salts thereof; 4-hydroxyl pentanoic acid lactone, or combinations thereof, and a coloring agent and/or flavoring agent that is useful in preventing sexual assault or date rape. Methods of treating conditions responsive to the administration of gamma-hydroxyl butyric acid and/or its pharmaceutically acceptable salts; gamma-butyryl lactone; 1,4-butanediol; 4-hydroxyl pentanoic acid and/or its pharmaceutically acceptable salts; and 4-hydroxyl pentanoic acid lactone are also described. The invention provides methods for treating patients with acquired resistance to GABAnergic agents.

METHODS AND COMPOSITIONS FOR TREATING ARG

BACKGROUND

[0001] Gamma-hydroxyl butyric acid (GHB) is an endogenous compound with hypnotic properties that is found in many human body tissues. GHB is present, for example, in the mammalian brain and other tissues. In brain the highest GHB concentration is found in the hypothalamus and basal ganglia and GHB is postulated to function as a neurotransmitter. The neuropharmacologic effects of GHB include increases in brain acetylcholine, increases in brain dopamine, inhibition of GABA-ketoglutarate transaminase and depression of glucose utilization but not oxygen consumption in the brain. GHB is converted to succinate and then metabolized via the Krebs cycle. Clinical trials have shown that GHB increases delta sleep and improves the continuity of sleep.

[0002] GHB has several clinical applications other than narcolepsy and sleep disorders. GHB has been reported to reduce alcohol craving, the number of daily drinks consumed, and the symptoms of alcohol withdrawal in patients. GHB has been used to decrease the symptoms of opiate withdrawal, including both heroin and methadone withdrawal. It has analgesic effects that make it suitable as a pain reliever. Intravenous administration of GHB has been reported to reduce intracranial pressure in patients. Also, administration of GHB was reported to increase growth hormone levels in patients.

[0003] GHB is also colorless and odorless. It has typically been administered in clinical trials as an oral solution. GHB treatment substantially reduces the signs and symptoms of narcolepsy, i.e. daytime sleepiness, cataplexy, sleep paralysis and hypnagogic hallucinations. In addition, GHB increases total sleep time and REM sleep, and it decreases REM latency and improves general anesthesia.

[0004] GHB has risks beyond unintended disinhibition, however. The drug can cause unconsciousness, respiratory depression, bradycardia, nausea, vomiting, seizures and coma. The severity of symptoms and the duration of action are dose dependent and can be affected by the presence of other CNS depressants.

[0005] 1,4-butanediol and gamma-butyryl lactone (GBL) have similar physiologic effects as gamma-hydroxyl butyrate (GHB). 1,4-butanediol and GBL are clear, colorless liquids. GHB; gamma-butyryl lactone; and 1,4-butanediol may be aggravators of central and obstructive sleep apnea in some patients. 4-hydroxyl pentanoic acid, pharmaceutically acceptable salts thereof (4-HPA), and 4-hydroxyl pentanoic acid lactone (4-HPA lactone) have similar relaxant effects as GHB but are less toxic.

[0006] In the brain, 1,4-butanediol is converted to gamma-hydroxylbutyryl aldehyde by alcohol dehydrogenase. Gamma-hydroxylbutyryl aldehyde is converted into gamma-hydroxyl butyrate (GHB). GHB is convertible to gamma-aminobutyric acid (GABA) through enzymatic changes. Gamma-butyryl lactone, when ingested orally, is transformed to GHB via peripheral lactonases. In the body, GHB is transformed to Krebs cycle intermediates and succinate, which enters the Krebs cycle. When ingested orally, gamma-aminobutyric acid has little biological effect. It is poorly absorbed and it does not cross the blood-brain barrier. In contrast, GHB is readily absorbed when ingested orally and crosses the blood brain barrier.

[0007] GHB; GBL; and 1,4-butanediol are central nervous system (CNS) depressants at low doses, and have the curious effects of reducing anxiety and producing euphoria and relaxation, sedating the recipient.

[0008] Because of these properties, the drugs have been abused through surreptitious administration to unsuspecting users in a variety of settings, including college parties and bars in the United States. The drugs have thus become known as agents of sexual assault, used to disable persons who have unknowingly ingested the drug in a product they otherwise intended to consume.

[0009] GHB; GBL, and 1,4-butanediol have risks beyond unintended disinhibition, however. The drugs can cause unconsciousness, respiratory depression, bradycardia, nausea, vomiting, seizures and coma. The severity of symptoms and the duration of action are dose dependent and can be affected by the presence of other central nervous system depressants.

[0010] GHB; GBL; and 1,4-butanediol have steep dose-response curves. A 1-gram dose of GHB for a 150-pound person provides a low degree of effect, causing a sense of euphoria and loss of inhibitions. However, a 2.5-gram dose to the same individual can lead to coma. A typical dose of sodium gamma-hydroxybutyrate for the treatment of narcolepsy is 3 to 4.5 grams.

[0011] Since GHB; 1,4-butanediol; GBL; 4-HPA solutions; and 4-HPA lactone are clear, colorless, and not strong tasting when diluted, they can be surreptitiously administered to an un-suspecting person. The relationship between 4-hydroxyl pentanoic acid, salts thereof, and 4-hydroxyl pentanoic acid lactone has been documented and these agents are expected to be therapeutic for similar conditions treatable with GHB, although the substances have different properties as GHB and individual metabolism varies between patients. 4-hydroxyl pentanoic acid, salts thereof, and 4-hydroxyl pentanoic acid lactone are less toxic than GHB. 4-hydroxyl pentanoic acid lactone has been reported to bind the GHB receptor (United States patent application 20020132846). Previous solid or semi-solid formulations of salts of gamma-hydroxyl butyric acid have not been intended to warn un-suspecting persons that unintended substances have been added to food or beverage, and therefore have not included colors which are more distinctive than typical pills or capsules, and have not included unusual or distinctive tastes for a pharmaceutical agent. Solid state formulations of GHB are known but have not been intended to prevent sexual assault. For example, Gessa in U.S. Pat. No. 4,983,632 discloses an effervescent tablet of the sodium salt of GHB (NaGHB) in example 3 but only for the purposes of palatability and does not include in any particularly distinctive taste or color. Gessa(ibid.) discloses an effervescent sachet in example 4. However, examination of the ingredients, which are NaGHB, lyophilized orange juice, orange flavoring, sodium saccharin, and saccharose, reveals that the composition is not effervescent, as it contains only small amounts of appropriate acidifying agents such as citric acid in the dried orange juice and no gas-emitting substance. Gessa was referring in example 4 to a sparkling taste and not effervescence.

[0012] Orphan Medical in U.S. Pat. No. 6,472,431 makes vague references to GHB in tablets, pills, and capsules including excipients. Orphan Medical(ibid.) in U.S. Pat. No. 6,472,431 envisioned easy and undetectable or hardly detectable addition of GHB to food or beverage and stated(ibid.) " . . . oral compositions . . . may be compressed into tablets . . . to be

admixed with an aqueous medium for oral or injectable formulations, or they may be incorporated directly with food (i.e. beverage) of the diet." As illustrated by this quote, Orphan Medical was not concerned with date rape. Consequently, there is a need to formulate the substances in such a way that cannot be administered to an unsuspecting person.

[0013] Acquired resistance to GABAnergic agents (ARG) has been a plague amongst humanity for centuries. ARG is associated with unrestful sleep and alpha-wave intrusion into sleep. Because ARG may be associated with other sleep disorders, although it usually occurs in isolation, a discussion of other sleep disorders is warranted. Obstructive sleep apnea (OSA) is a disease in which the pharynx, usually at the level of the tongue base or soft palate, intermittently collapses during sleep, resulting in attempted inspiration against a closed airway. Increased negative pressure is generated in the chest cavity during these inspiratory efforts. The episodes of increased negative pressure are brief and do not span the length of the apnea. Negative intrathoracic pressures as high as negative about 80-90 cm water have been documented. Normally, negative intrathoracic pressure does not dip below negative 8 cm water. Apneas typically last from 10 to 45 seconds but can last over two minutes. A low number of apneas is 5 to 20 per minute of sleep. 21 to 40 apneas may be considered moderate. Over forty apneas is considered severe. However, as few as 6 or 7 apneas per hour can cause significant symptomotology. The degree to which OSA causes fatigue is largely based on the degree to which stages 3 and 4 sleep (slow wave sleep) are reduced. Typically, a young adult has 20% stages 3 and 4 sleep. The amount of stages 3 and 4 sleep decreases with age. Patients below the age of 60 years who are chronically getting 0% stages 3 and 4 sleep due to sleep disorders are typically tired. Prolongation of sleep time with medications may be used to compensate for decreased stages 3 and 4 sleep. Treatments which increase stages 3 and 4 sleep sometimes decrease fatigue, although their are many polysomnographic criteria, and reliance on polysomnographic criteria is less important than questioning the patient about subjective improvements in symptoms such as fatigue. In fact, little to no increase in stages 3/4 sleep does not mean that a treatment is ineffective; on the contrary, the treatment may nonetheless be very effective. OSA has been associated with altered cerebral hemodynamics (Sleep apnea and autonomic cerebrovascular dysfunction; Loeppky J A, Voyles W F, Eldridge M W, Sikes C W; Sleep 1987 February; 10(1):25-34; Intracranial hemodynamics in sleep apnea; Fischer, Chauduri B A, Taorima M, Aktar B; Chest 1992 November; 102(5):1402-1406, 1992; Cerebral hemodynamics in obstructive sleep apnea; Siebler M, Nachtmann A; Chest 1993 April 103(4):1118-1119; Impairment of cerebral perfusion during obstructive sleep apnea; Balfors E M, Franklin K A; American Journal of Respiratory and Critical Care Medicine 1994(150):1587-1591; Changes in cerebral oxygenation and hemodynamics during obstructive sleep apneas; Hayakawa T, Terashima M, Kayukawa Y, Ohta T, Okada T; Chest 1996 April; 109(4):916-21; Sleep apnea syndrome and cerebral hemodynamics; Hajak G, Klingenhoefer J, Schulz-Varzegi M, sander D, Ruether E; Chest September 1996 110 (3): 1670-679). Whether this is due to oxygen desaturations during sleep or related to episodes of increased negative intrathoracic pressure is unclear. The most common symptom of OSA is fatigue. Other symptoms include poor attention span, attention deficit, symptoms vaguely reminiscent of bipolar disease, increased desire to sleep during the day, tendency to nap frequently or doze unintentionally, and insomnia. Often a patient has increased desire to sleep during the day yet has insomnia at night.

[0014] Chronic untreated OSA has been associated with congestive heart failure and cardiomyopathy, such as dilated cardiomyopathy. The negative intrathoracic pressures generated by some patients are sufficient to suck blood from the abdomen into the low pressure side of the heart, the right ventricle, thus dilating it and compressing the left ventricle briefly. Abnormalities in atrial natriuretic factor, a cardiac hormone, may occur. Also, such patients typically have oxygen desaurations during sleep. Cardiomyopathy associated with OSA may be referred to as negative pressure cardiomyopathy.

[0015] Narcolepsy is a disease that is also characterized by fatigue. Most narcolepsy patients have an increased desire to sleep during the day. Other symptoms of narcolepsy include hallucinations just after awakening or just prior to sleep (hypnagogic and hypnapompic hallucinations). Such hallucinations are typically people standing around the bed, geometric patterns, brightly colored objects and lights, or auditory hallucinations. Pleasant or vindictive voices may be heard. Often the patient is aware that the hallucinations are not real and can think lucidly while viewing or hearing them. Sleep paralysis is associated with narcolepsy and occasionally with OSA. During sleep paralysis, the patient wakes up and is briefly paralyzed although may occasionally be able to open the eyes or attempt to mumble words. The episodes are brief but are at times perceived by the patient to last for hours. Hypnogogic hallucinations may co-occur with sleep paralysis. Vivid or surreal dreams are common in narcolepsy. Patients who fall asleep during the day and have vivid dreams during short naps (less than 30 minutes) often have OSA or narcolepsy. Some narcolepsy patients experience strobe dreaming, in which on certain nights they have numerous vivid dreams interrupted by frequent awakenings. After awakening for just a few seconds, the patients then rapidly falls back asleep into the dream world. A minority of narcolepsy patients experience cataplexy, which are episodes of difficulty initiating movement in the body while awake, or difficulty maintaining muscle tone. Occasionally the patient goes to sleep after an episode of cataplexy. Cataplexy can occur without inciting factors or may be triggered by laughter or excitement.

[0016] The pathophysiology of narcolepsy is unknown. Hypothalamic dysfunction has been implicated. A subset of patients have very low levels of hypocretin-1 in the cerebral spinal fluid.

[0017] Postulation of the following would go far in explaining the pathophysiology of narcolepsy: there may be one or more central sleep debt monitors in or near the hypothalamus. As sleep debt increases during the day, the central sleep debt monitors eventually sensitize neurons to the sleep-inducing effects of a variety of compounds. If the sleep debt monitor or sensitization to sleep debt become dysfunctional, the patient develops some degree of narcolepsy. The patient has chronic sleep debt because the sleep debt monitor/sleep sensitization system cannot ensure proper triggering and maintenance of sleep. Thus, the peripheral brain regulates sleep. Hypothalamically-driven sleep is preferable to peripherally-driven sleep.

[0018] Classic cases of narcolepsy occur in roughly 1 in 2000 patients. These cases of narcolepsy may be referred to as narcolepsy major. However, mild to moderate cases of dysfunction of sleep debt monitoring or sensitization to sleep

debt (narcolepsy minor) probably occur in roughly 1 in 300 patients. Narcolepsy major and narcolepsy minor are treated similarly involving one or more GABAnergic agents prior to sleep.

[0019] Idiopathic hypersomnia (IHS) is a condition characterized by severe fatigue and sleepiness and unrestful sleep. Idiopathic hypersomnia is less common than narcolepsy major. However, recent studies have shown that a subset of patients with IHS have low levels of hypocretin-1, indicating that some patients in fact have narcolepsy. Whether a subset of IHS patients have hypersensitivity to endogenous GABAnergic agents is unknown.

[0020] The multiple sleep latency test (MSLT) is roughly 60 percent sensitive in detecting narcolepsy major. Patients who test positive exhibit rapid entry into REM sleep when given nap opportunities. However, some patients with narcolepsy major have normal sleep latencies. Patients with IHS tend to enter non-REM sleep quickly on MSLT. However, some narcolepsy patients show the same pattern, and in practice it can be difficult to distinguish narcolepsy major or narcolepsy minor from IHS.

[0021] Neither narcolepsy major, narcolepsy minor, nor idiopathic hypersomnia segregate independently from obstructive sleep apnea. A higher proportion than expected of narcolepsy/IHS patients have osA. This is likely due the altered cerebral hemodynamics associated with OSA. Abnormal blood flow to the postulated central sleep debt monitors may trigger some degree of narcolepsy. Patients who have underlying narcolepsy minor may develop narcolepsy major upon developing OSA.

[0022] The most common treatment for OSA is continuous positive airway pressure (CPAP). This is accomplished by delivering positive air pressure, usually by a nasal mask, to the patient during sleep. In response the pressure, the tongue either is passively made to abut against the palate or reflexively contracts upward, and the pharynx is pneumatically splinted to prevent collapse of the airway. The lowest pressure to eliminate apneas is used, typically 5 cm to 18 cm water pressure. Although chronic use of CPAP is highly beneficial to most patients with coexisting OSA and narcolepsy, the pressures of CPAP are significant and on occasion chronic use of CPAP can aggravate narcolepsy or cause sleep pattern similar to IHS in which sleep becomes unrestful and the patient has chronic desire or tendency to sleep. This condition may be referred to as CPAP-induced hypersomnia. Again, however, it is noted that CPAP is beneficial for the majority of patients.

[0023] Restless legs syndrome (RLS) is characterized by the desire to move the legs while lying flat and which is relieved by standing or walking. Often motor restlessness occurs and is increased prior to sleep. A minority of patients with RLS report odd sensations in the legs while lying flat such as crawling, quivering, painful, cramping, or electrical sensations when lying flat. RLS is associated with periodic limb movement disorder, a condition in which the legs move in a stereotypic manner at intervals during sleep. Periodic limb movement disorder (PLMD) often occurs on some nights and not others for a given patient. However, such patients often have insomnia on a nightly basis. It is expected that some patients with insomnia, anxiety, attention deficit, hyperactivity, or motor hyperactivity have subclinical restless legs syndrome or subclinical periodic limb movement disorder. Subclinical restless legs syndrome is manifested by subtle restlessness or symptoms which do not meet current criteria for restless legs syndrome. Subclinical periodic limb movement disorder is manifested by non-specific polysomnographic abnormalities such as frequent brief awakenings or arousals not associated with stereotypic leg movements. The treatment of RLS and subclinical RLS is expected to be the same, as is the treatment of PLMD and subclinical PLMD.

[0024] REM sleep behavior disorder is a condition in which the patient hits, fights, or screams during REM sleep. The condition typically occurs in men in the sixth or seventh decade of life, many of whom have Parkinson's disease. However, REM sleep behavior disorder can occasionally occur in younger patients who do not have Parkinson's disease. The most common treatment of REM sleep behavior disorder is clonazepam 0.5-2 mg prior to sleep, although younger patients may be tried on higher doses.

[0025] ARG typically falls into one of two categories although some cases of ARG do not fall into either category. ARG type I is typified by chronic fatigue and has hitherto been referred to as chronic fatigue syndrome. ARG type II is typified by fatigue and myalgias or arthralgias and has hitherto been referred to as fibromyalgia, fibrositis, or neuromyasthenia. Some patients with ARG have psychiatric symptoms such as depression, attention deficit, hyperactivity, symptoms reminiscent of bipolar disorder, anxiety disorders, and obsessive compulsiveness but minimal fatigue and cannot be classified as ARG type I or ARG type II.

[0026] The present invention relates generally to treating ARG. Some patients with ARG cannot be categorized as ARG type I or ARG type II but may be treated with the methods described herein. ARG type I and ARG type II are distinct disease entities sometimes occurring in isolation.

FIELD OF THE INVENTION REGARDING TREATMENT OF ARG, ARG TYPE I AND ARG TYPE II

[0027] Although it is clear to the inventor that ARG type I and ARG type II are diseases, there is no general agreement that ARG type I or ARG type II are diseases in the medical community. Some physicians continue to refer to ARG type II as "psychogenic rheumatism," a totally inappropriate term which suggests the patient is not ill. Many physicians refuse to acknowledge ARG type I or ARG type II at all.

[0028] Acquired resistance to GABAminergic agents (ARG) is a disease the symptoms of which may be varied including chronic, severe fatigue (the feeling of tiredness), myalgias (muscle aching), arthralgias (joint aching), difficulty concentrating (brain fog), and unrestful sleep. ARG has hitherto been thought to be a mysterious syndrome. Others have postulated dysfunction of the hypothalamus as the etiology. The association between ARG and intrusion of waking brain wave patterns into sleep has been documented and is referred to as alpha-wave intrusion. ARG has heretofore been referred to as fibromyalgia, fibrositis, neuromyasthenia, chronic fatigue syndrome, and chronic fatigue and immune dysfunction syndrome. Patients with myalgias and arthralgias are typically diagnosed with fibromyalgia, whereas patients with unexplained fatigue are diagnosed with chronic fatigue syndrome. A minority of patients have intermittent or chronic infections such as candida or cold sores or intermittently swollen lymph nodes. ARG effects roughly six million patients in the United States.

[0029] The typical age of onset of ARG is in the third through sixth decade of life. After the sixth and seventh decades the disease frequently wanes. The majority of sufferers are women.

[0030] Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter of the brain. Cumulative evidence suggests that resistance to GABA and its cogeners are the etiology of chronic fatigue syndrome and fibromyalgia. The GABA receptor is a large protein with multiple subunits. In effect the GABA receptor functions as many different receptors. Numerous subunits of the GABA-A, GABA-B, and GABA-C receptors have been identified.

[0031] GABAnergic agents, which are also referred to as GABAminergic agents, are substances which bind the GABA receptor or augment the actions of GABA and its cogeners.

[0032] The function of sleep in adult humans may be to decrease the amount of energy at the neuronal cell surface membrane, to decrease the number of synapses in use, or to decrease the amount of electrical bleed between neighboring synapses. The most common symptom of most sleep disorders is fatigue. Fascinatingly, many sleep specialists refuse to use either the words "fatigued" or "tired" and refuse to design a scale for fatigue. Such an attitude makes the study of sleep disorders and disorders of sleep/wake impossible. Fatigue as the feeling of tiredness should be distinguished from muscle fatigue, which is weakness due to exertion or weakness due to repetitive muscle contraction. Although some patients with sleep disorders and ARG complain of lack of energy, they may in fact have an excess of energy on the neuronal cell surface membrane, leading to the symptom of fatigue, which may be disabling, interfering with concentration and activities of daily living. Much of intracellular energy is generated in the mitochondria. Whether patients with ARG have a deficiency in neuronal mitochondrial energy is unknown.

[0033] Improvement in subjective symptoms such as decrease in fatigue or increased feeling of well being are more important than improvement in polysomnographic parameters in treating patients with ARG.

[0034] Patients with demyelinating diseases such as multiple sclerosis have decreased flow of electricity along the central nervous system neuronal cell surface membranes and also complain of severe fatigue. Thus, having either increased or decreased energy at the neuronal surface membrane leads to fatigue.

[0035] GHB has typically been administered in clinical trials as an oral solution. GHB treatment substantially reduces the signs and symptoms of narcolepsy, i.e. daytime sleepiness, cataplexy, sleep paralysis and hypnagogic hallucinations. GHB may be an aggravator of central and obstructive sleep apnea in some patients.

[0036] Three documents are particularly relevant when discussing ARG and GHB. They are: 1) Document A, which is U.S. Pat. No. 5,990,162; inventor Martin B. Scharf; 2) Document B, which is Martin B. Scharf et al.: {Effect of gamma-hydroxybutyrate on pain, fatigue, and the alpha sleep anomaly in patients with fibromyalgia. Preliminary report.; Scharf M B, Hauck M, Stover R, McDannold M, Berkowitz D; Journal of Rheumatology. 1998 October; 25(10): 1986-1990.}; 3) Document C, which is Martin B. Scharf et al.: {The effects of sodium oxybate on clinical symptoms and sleep patterns in patients with fibromyalgia; Scharf M B, Baumann M, Berkowitz D V, Journal of Rheumatology. 2003 May; 30(5):1070-4}.

[0037] The sodium salt of GHB has been used at times in inappropriately low doses in the treatment of ARG type I and ARG type II and has led to false conclusions regarding the treatment of ARG type I and ARG type II. In document B Scharf et al. described what they called the baffling symptoms of fibromyalgia (ARG type II) and administered 2.25 grams of the sodium salt of GHB prior to sleep and again four hours later. In some patients the dosage of GHB was "adjusted slightly upwards." GABAnergic agents including zolpidem, clonazepam, and alprazolam were withdrawn from the medication regimens of some patients prior to institution of treatment with GHB. An additional sedating compound which was unspecified was used in some patients.

[0038] In document C Scharf et al. administered 3 grams of the sodium salt of GHB prior to sleep and then a second 3 gram dose 4 hours later. No further GABAminergic agents were instituted other than GHB. Again, the failure to treat with adequate dosages and sufficient varieties of GABAminergic agents was based on the failure to comprehend the pathophysiology of the disease.

[0039] In documents A, B, and C Scharf or Scharf et al. were unaware that they were treating ARG and therefore use incorrect terminology. The low doses of GHB used and discontinuation of useful GABAnergic agents rather than an increase of dosage of GABAnergic agents indicate an incorrect understanding of ARG and led to treatment recommendations which do not adequately treat many patients with ARG.

[0040] The statements of Scharf or Scharf et al. in documents A, B, and C are contradictory. After patenting a method of treating both chronic fatigue syndrome (ARG type I) and fibromyalgia (ARG type II) in document A, Scharf then reversed his position and stated that his treatment is ineffective for chronic fatigue syndrome (ARG type I) in document C. Scharf et al. in document C state in regards to Scharf et al. in document B "In our pilot open label trial, sodium oxybate had no effect in patients diagnosed with chronic fatigue syndrome—a condition with symptoms overlapping with FM." Scharf at times refers to GHB as sodium oxybate. FM refers to fibromyalgia. Scharf et al. did not comprehend that their treatment failure was due to insufficient dosages of GHB and the failure to use any other GABAnergic agent.

[0041] Scharf et al. in document C state the following regarding fibromyalgia and chronic fatigue syndrome "In the sleep laboratory, the 2 conditions can be distinguished on the basis of alpha intrusion, which was only present in the patients with FM, suggesting the potential utility of PSG [polysomnography] along with ACR [American College of Rheumatology] guidelines in making a definitive diagnosis of FM." On the contrary, alpha wave intrusion is in fact nonspecific as Scharf had previously stated in document B. Scharf in document A and Scharf et al. in document B indicate that both fibromyalgia (ARG type II) and chronic fatigue syndrome (ARG type I) are associated with alpha wave intrusion but Scharf et al. in document C indicate that alpha wave intrusion is associated with fibromyalgia and not with chronic fatigue syndrome.

[0042] ARG is a clinical diagnosis not dependent on polysomnography. The ACR (American College of Rheumatology) criteria for fibromyalgia are misleading and only address a subset of patients with ARG type II, namely those with extensive trigger point tenderness, which is discussed below. Neither polysomnography nor abnormally tender trigger points are necessary for the diagnosis of ARG. The primary

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