STIFF PERSON SYNDROME
UNDERSTANDING TREATMENT OPTIONS

There is currently no cure available for Stiff Person Syndrome, an immune-mediated central nervous system disorder characterized by fluctuating muscle stiffness, disabling spasms, and heightened sensitivity to external stimuli. Up to 80% of patients with SPS have anti–glutamic acid decarboxylase (GAD) antibodies in the serum or cerebral spinal fluid (CSF). Whether these antibodies are clinically relevant and correlate with disease severity is unknown.

http://archneur.jamanetwork.com/article.aspx?articleid=786003

According to a study by the National Institutes of Health, "*In patients with anti-GAD antibody titers in serum and CSF do not correlate with disease severity or duration. Anti-GAD antibodies are an excellent marker for SPS, but monitoring their titers during the course of the disease may not be of practical value*." The levels can be low or high, some articles suggest the level fluctuates. While the exact cause of SPS is unknown, the symptoms suggest a disturbance in the GABA system.

Symptoms associated with central nervous systems disorders are classified into positive and negative categories. Positive symptoms include those that increase muscle activity through hyper-excitability of the stretch reflex (i.e., rigidity and spasticity) where negative symptoms include those of insufficient muscle activity (i.e. weakness) and reduced motor function. Often the two classifications are thought to be separate entities of a disorder; however, some authors propose that they may be closely related.

http://en.wikipedia.org/wiki/Hypertonia

GABA is the chief inhibitory neurotransmitter in the central nervous system. It plays a role in regulating neuronal excitability throughout the nervous system. In humans, GABA is directly responsible for the regulation of muscle tone. When GABA absorption becomes impaired, it leads to hypertonia (*a term sometimes used synonymously with spasticity*) of the muscles. In the spinal cord, a reduced level of GABA leads to hyperexcitable motor neurons, rigidity, and spasms of both agonist and antagonist muscles. An "antagonist" is a muscle that acts opposite to the specific movement generated by the agonist and is responsible for controlling the motion, slowing it down and returning a limb to its initial position.
GAD (glutamic acid decarboxylase) is an enzyme that facilitates the creation of GABA. When autoantibodies target GAD65 and 67 enzymes, they reduce the available amount of GAD65/67 which in turn interferes with the production of GABA. GAD65 also produces GABA in pancreatic beta cells and dysfunction in this area may contribute to the pathogenesis of insulin-dependent diabetes mellitus.
There are several autoimmune diseases that sometimes accompany Stiff Person Syndrome such as Graves (hyperthyroidism) or Hashiomoto's thyroiditis (hypothyroidism), Type 1 Diabetes, vitiligo, and pernicious anemia. If you have been diagnosed with one or more of these, the suspicion for autoimmune muscle disease is heightened.

DO YOU HAVE STIFF PERSON SYNDROME: THE TRIAL AND ERROR PHASE

When a patient presents at a family physician's office with a complaint of muscle stiffness, pain, weakness, cramps, or spasms, SPS is not the first cause they think of. They are not neuromuscular specialists. They will at first attempt to treat the pain and spasms with muscle relaxers, pain medications, or a combination of the two. They run blood tests looking for the usual suspects, just as a police detective looks for the usual suspects in a murder case. It is not until a great deal of detective work has been done that they realize they have a serial killer on the loose, aka a rare autoimmune disease.

Once the detective work has been done, and enough time has passed that they realize it is not a passing phase, the patient is usually sent to a neurologist or neuromuscular specialist. Even neuromuscular specialists may not be familiar with SPS.

The specialist will assemble a list of differential diagnoses based on the core symptoms: weakness, numbness, proximal (close up) or axial (further out) muscle involvement and distribution, level and location of pain, restrictions in range of motion, gait disturbance, muscle cramps versus muscle spasms, or muscle fatigue. They will run tests to determine the potential cause. Stiff Person Syndrome is largely a diagnosis of elimination of other suspects. The occurrence of the GAD-65 autoantibodies is a strong clue, but it is not present in every case.

Spastic hypertonia involves uncontrollable muscle spasms, stiffening or straightening out of muscles, shock-like contractions of all or part of a group of muscles, and abnormal muscle tone. It is seen in disorders such as cerebral palsy, stroke, and spinal cord injury. Rigidity is a severe state of hypertonia where muscle resistance occurs throughout the entire range of motion of the affected joint independent of velocity. It is frequently associated with lesions of the basal ganglia. Individuals with rigidity present with stiffness, decreased range of motion and loss of motor control. Dystonic hypertonia refers to muscle resistance to passive stretching (in which a therapist gently stretches the inactive contracted muscle to a comfortable length at very low speeds of movement) and a tendency of a limb to return to a fixed involuntary (and sometimes abnormal) posture following movement.

Once the specialist has gone through the process of elimination, and he arrives at a diagnosis of Stiff Person Syndrome, he will develop a treatment plan.

Since there is no cure, the therapeutic goal is to treat the spasms and rigidity and improve the patient's quality of life. They will take into consideration the severity of the symptoms. There are several approaches to treatment. The first line of defense is to treat the symptoms through various pharmaceutical approaches. The second line of defense consists of reducing the circulating autoantibodies through plasmapheresis or immunomodulating drugs, or augmenting with "good" antibodies through intravenous immunoglobulin infusions.

Each method of attack has pros and cons. The age of the patient, the overall physical condition, and the patient's additional medical problems play a part in determining the most effect plan of attack.

I. PLASMAPHERESIS

Plasmapheresis is the removal, treatment, and return of (components of) blood plasma from blood circulation. It is thus an extracorporeal therapy (a medical procedure performed outside the body). The procedure is used to treat a variety of disorders, including those of the immune system. There are no studies supporting that removing the circulating antibodies through plasmapheresis is truly effective. The data is inconclusive. Evidence supporting plasma exchange is less well established than for IVIG and there have been several conflicting results. Some patients enjoyed improvements in symptoms and serological and electrophysiological markers. An equal number had no benefit. Patients showing improvement were on concomitant medications. There has been no reported randomized placebo-controlled study to date.

No real prescribed dosage exists for plasmapheresis. The time of plasmapheresis, amount of supplementary albumin, and other parameters are controlled on a patient-by-patient basis by the pathologist running the blood bank involved in the procedure. A 5-treatment series administered every other day is considered a standard regimen for autoimmune diseases, but longer and shorter regimens have been used.
The efficacy is then evaluated and further treatment is decided on a patient-by-patient basis, usually as a collaborative effort with the insurance company physicians because it is such an expensive procedure. Possible adverse effects include hypotension, bleeding, arrhythmias, and infection.

http://emedicine.medscape.com/article/1172135-treatment

II. REDUCE CIRCULATING AUTO-ANTIBODIES WITH DRUGS

They can attempt to reduce autoantibodies with immunomodulating drugs. Ideally, it would be best to selectively kill off the GAD65/67 autoantibodies. Targeted technology does not as yet exist. Research has suggested a connection to the GABARAP genes. Immunotherapies either amplify an immune response or reduce or suppress the immune system. There are several immunomodulating drugs that have been prescribed for SPS.

A) Azathioprine/Azasan/Imuran/Azamun/Imurel

Azathioprine belongs to the chemical class of purine analogues. It has been widely used as an immunosuppressant for more than 50 years. Azathioprine acts as a prodrug for mercaptopurine, inhibiting an enzyme that is required for the synthesis of DNA. Thus it most strongly affects proliferating cells, such as the T cells and B cells of the immune system. The main adverse effect of azathioprine is bone marrow suppression, which can be life-threatening, especially in people with a genetic deficiency of the enzyme thiopurine S-methyltransferase. It is also listed by the International Agency for Research on Cancer as a Group 1 carcinogen (carcinogenic to humans). Azathioprine is sometimes used in systemic lupus erythematosus patients who require a maintenance dose of 15 mg or higher of prednisone and those who experience recurrent flares. It is used as an adjuvant in the oral steroid therapy of pemphigus and myasthenia gravis, as a "steroid-sparing" agent for reducing the dose of corticosteroids. It was widely used for the treatment of multiple sclerosis until the first half of the 1990s. Concerns about increased risk of malignancy has led to a decreased use, yet it is still used in maintenance treatment for patients who frequently relapse.

http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682167.html

B) Cyclophosphemide/Endoxan/Cytoxan/Neosar/Procytox/Revimmune/ Cytophosphane

Cyclophosphemide is is a nitrogen mustard alkylating agent, from the oxazophorines group. It is used to treat cancers and autoimmune disorders. As a prodrug, it is converted in the liver to active forms that have chemotherapeutic activity. Cyclophosphamide has severe and life-threatening adverse effects, includingacute myeloid leukemia, bladder cancer, hemorrhagic cystitis, and permanent infertility, especially at higher doses. For autoimmune diseases, doctors often substitute less-toxic methotrexate or azathioprine after an acute crisis.

http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682080.html

C) Cyclosporine/Ciclosporine/Cyclosporin/CsA/Neurostat.

Cyclosporine is an immunosuppressant drug widely used in organ transplantation to prevent rejection. It reduces the activity of the immune system by interfering with the activity and growth of T cells. The drug exhibits very poor solubility in water, and, as a consequence, suspension and emulsion forms of the drug have been developed for oral administration and for injection. Cyclosporine was originally brought to market by Sandoz, now Novartis, under the brand name Sandimmune, which is available as soft gelatin capsules, as an oral solution, and as a formulation for intravenous administration.

http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601207.html

D) Mycophenolate mofetil/CellCept

CellCept is an immunosuppressant and prodrug of mycophenolic acid, used extensively in transplant medicine. It is a reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH) in purine (guanine) biosynthesis which is necessary for the growth of T cells and B cells. Other cells are able to recover purines via a separate scavenger pathway and are thus able to escape the effect.
MMF is also used in the treatment of autoimmune diseases, such as Behçet's disease, pemphigus vulgaris, systemic lupus erythematosus and refractory incomplete lupus erythematosus.[2] Suppressing T cells and B cells stops them from attacking healthy cells, but also weakens their ability to defend against infections. Among the most common side-effects of this drug are high blood sugars and increased blood cholesterol levels. Other changes in blood chemistry such as hypomagnesemia, hypocalcemia, hyperkalemia, and an increase in BUN are regularly noted. Coughing and issues with breathing are not uncommon - pleural effusions being noted in approximately 1:3. There is a similar occurrence ratio of Infections; with leukopenia and anemia reflecting the immunosuppressive and myelosuppressive nature of the drug. Back and abdominal pain – in addition to headache, nausea, diarrhea, and fever – are also experienced with this drug. More rarely, various neoplasia occur: melanoma, lymphoma, other malignancies having an occurrences of 1 in 20 to 1 in 200, depending on the type, with Neoplasia in the skin being the most common site.

http://en.wikipedia.org/wiki/Mycophenolate_mofetil

E) Rituximab/Rituxin/MabThera

Rituximab is a chimeric monoclonal antibody against the protein CD20, which is primarily found on the surface of immune system B cells (this should not be confused with pancreatic β- or beta cells). Rituximab destroys B cells and is therefore used to treat diseases which are characterized by excessive numbers of B cells, overactive B cells, or dysfunctional B cells. This includes many lymphomas, leukemias, transplant rejection, and autoimmune disorders. Rituximab was recently shown to give symptomatic and serological remission in patients with otherwise refractory SPS.

There is some evidence for efficacy, but not necessarily safety, in a range of other autoimmune diseases, and rituximab is widely used off-label to treat difficult cases of multiple sclerosis, systemic lupus erythematosus, and autoimmune anemias. The most dangerous, although among the most rare, side effect is progressive multifocal leukoencephalopathy (PML) infection, which is usually fatal however only a very small number of cases have been recorded occurring in autoimmune diseases.

Serious adverse events, which can cause death and disability, include: Severe infusion reaction, cardiac arrest, cytokine release syndrome, tumor lysis syndrome, causing acute renal failure, infections, hepatitis B reactivation, other viral infections, Progressive multifocal leukoencephalopathy (PML), Immune toxicity, with depletion of B cells in 70% to 80% of lymphoma patients, Pulmonary toxicity. Two patients with systemic lupus erythematosus died of progressive multifocal leukoencephalopathy (PML) after being treated with rituximab. PML is caused by activation of JC virus, a common virus in the brain which is usually latent. Reactivation of the JC virus usually results in death or severe brain damage. At least one patient with rheumatoid arthritis developed PML after treatment with rituximab. Rituximab has been reported as a possible cofactor in a chronic Hepatitis E infection in a person with lymphoma. Hepatitis E infection is normally an acute infection, suggesting the drug in combination with lymphoma may have weakened the body's immune response to the virus.

http://www.nlm.nih.gov/medlineplus/druginfo/meds/a607038.html

F) Sirolimus/Rapamycin

Sirolimus is an immunosuppressant drug used to prevent rejection in organ transplantation; it is especially useful in kidney transplants. It prevents activation of T cells and B cells by inhibiting their response to interleukin-2 (IL-2). Sirolimus works, in part, by eliminating old and abnormal white blood cells. Sirolimus is effective in mice with autoimmunity and in children with a rare condition called autoimmune lymphoproliferative syndrome (ALPS). Sirolimus may increase the risk that you will develop an infection or cancer, especially lymphoma (cancer of a part of the immune system) or skin cancer. Sirolimus inhibits a protein kinase complex known as mTORC1, and this appears to provide most of the beneficial effects of the drug (including life-lengthening in animal studies). Sirolimus also acts on a related complex known as mTORC2. Disruption of mTORC2 produces the diabetes-like symptoms of decreased glucose tolerance and insensitivity to insulin also associated with sirolimus.

http://www.nlm.nih.gov/medlineplus/druginfo/meds/a602026.html

G) Tacrolimus/fujimycin/Prograf, Advagraf, Protopic

Tacrolimus is an immunosuppressive drug that is mainly used after allogeneic organ transplant to reduce the activity of the patient's immune system and so lower the risk of organ rejection. It is also used in a topical preparation in the treatment of atopic dermatitis (eczema), severe refractory uveitis after bone marrow transplants, exacerbations of minimal change disease, and the skin condition vitiligo. It reduces interleukin-2 (IL-2) production by T-cells.

Side effects can be severe and include infection, cardiac damage, hypertension, blurred vision, liver and kidney problems (tacrolimus nephrotoxicity), hyperkalemia, hypomagnesemia, hyperglycemia, diabetes mellitus, itching, lung damage (sirolimus also causes lung damage), and various neuropsychiatric problems such as loss of appetite, insomnia, Posterior reversible encephalopathy syndrome, confusion, weakness, depression, cramps, neuropathy, seizures, tremors, and catatonia. In addition it may potentially increase the severity of existing fungal or infectious conditions such as herpes zoster or polyoma viral infections. In people receiving immunosuppressants to reduce transplant graft rejection, an increase risk of malignancy is a recognised complication. The most common cancers are non-Hodgkin's lymphoma and skin cancers. The risk appears to be related to the intensity and duration of treatment.

For more information: http://www.nlm.nih.gov/medlineplus/druginfo/meds/a608037.html

III. AUGMENTING THE IMMUNE SYSTEM WITH "GOOD" ANTIBODIES WITH IVIG

A) Intravenous Immunoglobulin

IVIG is a blood product administered intravenously. It contains the pooled, polyvalent, IgG (immunoglobulin (antibody) G) extracted from the plasma of over one thousand blood donors. Antibodies are major components of the immune system. IgG is the main antibody isotype found in blood and extracellular fluid allowing it to control infection of body tissues. By binding many kinds of pathogens—representing viruses, bacteria, and fungi—IgG protects the body from infection. It does this via several immune mechanisms: IgG-mediated binding of pathogens causes their immobilization and binding together via agglutination; IgG coating of pathogen surfaces allows their recognition and ingestion by phagocytic immune cells; IgG activates the classical pathway of the complement system, a cascade of immune protein production that results in pathogen elimination; IgG also binds and neutralizes toxins.

http://en.wikipedia.org/wiki/Immunoglobulin_G

IVIG's effects last between 2 weeks and 3 months. The precise mechanism by which IVIG suppresses harmful inflammation has not been definitively established. The massive quantity of antibody may stimulate the host's complement system, leading to enhanced removal of all antibodies, including the harmful ones. IVIG also blocks the antibody receptors on immune cells (macrophages), leading to decreased damage by these cells, or regulation of macrophage phagocytosis.

http://en.wikipedia.org/wiki/Intravenous_immunoglobulin

IVIG is a second-line treatment for patients with severe or refractory SPS. IVIG treated patients reported improvement of symptoms and the ability to undertake activities of daily living, lasting between six weeks and one year. The GAD autoantibody titers fell.

While it is considered generally safe, neurologists should be aware of common and important adverse effects. These include immediate infusion reactions (mild to severe) with a small but potential risk of fatal anaphylaxis. This occurs typically in IgA-deficient patients, which is therefor a relative contraindication for IVIG. There may be skin reactions, headaches, aseptic meningitis, and renal tubular acidosis. Venous thromboembolic disease is a significant risk, particularly in those with limited mobility. Arterial thrombus formation may lead to stroke, myocardial infarction, pulmonary embolism, or ischemia affecting other tissue beds. Cost remains a major factor.

Intravenous immunoglobulin (IVIG) has also been used in the inpatient setting for the treatment of stiff person syndrome. The usual dose is 2 g/kg, administered over 2-5 days.

The length of the series is variable and dependent upon patient response. Treatment may extend past the inpatient period. (Documentation of patient response is usually necessary for ongoing reimbursement by third party payers.)

http://www.phscorporation.com/IVIGComparison.pdf

There are different brands of IVIG. Some patients have tried different types with different effects. Some patients have reported relief. Some patients have reported a period of relief with a return, even an increase, of symptoms.

Currently, a four dose course of IVIG for a 70 kg person at 2 g/kg would cost $25,000-$26 000.

http://www.medscape.com/viewarticle/523523_5

1) Privigen®, human polyvalent immunoglobulin, liquid 10% solution for intravenous injection. http://www.drugs.com/privigen.html

2) Carimune® NF, Sandoglobulin®, Sanglopor® human normal immunoglobulin, freeze-dried formulations for intravenous administration. http://www.drugs.com/mtm/carimune-igiv.html

3) Sandoglobulin ® NF Liquid, Redimune®, Redimune® NF Liquid, human normal immunoglobulin, liquid 12% solution for intravenous administration http://www.drugs.com/mtm/sandoglobulin-igiv.html

4) Rhophylac® human anti-D immunoglobulin. Prefilled syringes of highly purified anti-Rhesus factor D IgG for intravenous administration and intramuscular injection. http://www.drugs.com/rhophylac.html Flebogamma® 5% is a highly purified (≥ 99% IgG), unmodified, human IgG that contains the antibody specificities found in the donor population. http://www.drugs.com/pro/flebogamma.html

5) Gamunex® 10% http://www.drugs.com/gamunex.html

6) Gammagard D/D® http://www.drugs.com/mtm/gammagard-igiv.html

7) Gammagard Liquid® http://www.drugs.com/mtm/gammagard-igiv.html

8) Octagam Liquid 10%® http://www.drugs.com/octagam.html

9) Bigivam http://www.rxlist.com/bivigam-drug.htm

B) Hizentra

Hizentra is an immunoglobulin (Ig) replacement therapy that you infuse yourself, using a small needle and infusion pump. It is approved by the US Food and Drug Administration (FDA) for people with primary immunodeficiency disease (PI, also known as PIDD). Because Hizentra is ready to use at room temperature, you can infuse whether you're at home or on the go. Hizentra provides proven protection against infection. In the US clinical trial, the rate of serious bacterial infections4 (SBIs) was 0 per subject-year, while the annual rate of infections was 2.76 per subject-year. This means that patients did not experience any serious infections (meaning pneumonia, bronchitis, etc). On average, all patients had fewer than 3 infections of any type per year.

In the US clinical trial for Hizentra, the most common adverse reactions to Hizentra were redness, swelling, itching, heat, or pain at the infusion site (ie, local site reactions). 93% were mild, while 6% were moderate. The most common drug-related adverse reactions in the clinical trial for Hizentra were swelling, pain, redness, heat or itching at the site of injection; headache; back pain; diarrhea; tiredness; cough; rash; itching; nausea and vomiting.
Hizentra is made from components of human blood. The risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated.

Dosing varies, but prices for 1 vial (20ml) of Hizentra 4g (brand)runs $550-570 per vial at common US pharmacies.

http://www.hizentra.com/patients/

IV. TREATMENT OF SYMPTOMS WITH GABA MODERATING DRUGS

A GABA agonist is a drug which acts to stimulate the GABA receptor, producing typically sedative effects, and may also cause other effects such as anxiolytic and muscle relaxant effects. There are three receptors of the gamma-aminobutyric acid. The two receptors GABA-α and GABA-ρ are ion channels that signal chloride and diminish further action potentials. The GABA-β receptor belongs to the class of G-Protein coupled receptors that inhibit adenylyl cyclase, therefore leading to decreased cyclic adenosine monophosphate (cAMP). GABA-α and GABA-ρ receptors produces sedative and hypnotic effects as well as producing anti-convulsion properties. GABA-β receptors also produce sedative effects and also lead to changes in gene transcription.

http://en.wikipedia.org/wiki/GABA_agonist

A) GABA A AGONISTS

1) Acamprosate/N-acetyl homotaurine/Campral

Acamprosate works by possibly by antagonizing glutamatergic N-methyl-D-aspartate receptors and agonizing gamma-aminobutyric acid (GABA) type A receptors. Certain serious side effects include diarrhea, allergic reactions, irregular heartbeats, and low or high blood pressure, while less serious side effects include headaches, insomnia, and impotence

http://www.drugs.com/mtm/acamprosate.html

2) Carisoprodol/SOMA/Carisoma/Sanoma

Carisoprodol is a centrally acting skeletal muscle relaxant that works by blocking pain sensations between the nerves and the brain. Effects include analgesia, anxiolysis, muscle relaxation (and relief from hypertonia), sedation, somnolence. The usual dose of 350 mg is unlikely to engender prominent side effects other than somnolence, and mild to significant euphoria or dysphoria, but the euphoria is generally short lived. The intensity of the side effects of carisoprodol tends to lessen as therapy continues. Carisoprodol was a modification of meprobamate, intended to have better muscle relaxing properties, less potential for abuse, and less risk of overdose

http://www.drugs.com/carisoprodol.html

3) Etaqualone/Aolan/Athinazone/ Ethinazone

Etaqualone is an analogue of methaqualone. It has sedative, hypnotic, muscle relaxant, and central nervous system depressant properties, and was used for the treatment of insomnia.

4) Kava/Kava Kava

Kava is a plant whose roots are used to produce a drink with sedative and anesthetic properties. Kava is consumed throughout the Pacific Ocean cultures of Polynesia, including Hawaii, Vanuatu, Melanesia and some parts of Micronesia. Kava is sedating and is primarily consumed to relax without disrupting mental clarity. Its active ingredients are called kavalactones. Kava's active principal ingredients are the kavalactones, of which at least 15 have been identified and are all considered psychoactive. Only six of them produce noticeable effects, and their concentrations in kava plants vary. Research has suggested that kavalactones potentiate GABAA activity, but do not alter levels of dopamine and serotonin in the CNS. It is thought to do this via modulating GABA activity via altering the lipid membrane structure and sodium channel function. However, it has also been shown that administration of the GABA antagonist Flumazenil does not have an antagonistic effect on kavalactones, suggesting that an alternative pathway may be involved.

There are some big safety concerns about kava. Many cases of liver damage and even some deaths have been traced to kava use. Heavy, long-term kava use does not cause any reduction of ability in saccade and cognitive tests, but is associated with elevated liver enzymes

http://www.nlm.nih.gov/medlineplus/druginfo/natural/872.html

5) Methaqualone/Quaalude

Methaqualone is a sedative-hypnotic drug that is similar in effect to barbiturates, a general central nervous system depressant that increases the activity of the GABA receptors in the brain and nervous

system. When GABA activity is increased, blood pressure drops and the breathing and pulse rates slow, leading to a state of deep relaxation. Methaqualone peaks in the bloodstream within several hours, its effects generally lasting four to eight hours. Regular users build up a physical tolerance, requiring larger doses for the same effect. Overdose can lead to nervous system shut down, coma and death. Effects can include euphoria, drowsiness, reduced heart rate, reduced respiration, increased sexual arousal (aphrodisia), and paresthesias (numbness of the fingers and toes). Larger doses can bring about respiratory depression, slurred speech, headache, and photophobia (a symptom of excessive sensitivity to light).

http://en.wikipedia.org/wiki/Methaqualone

6) Muscimol

Muscimol (agarin, pantherine) is the major psychoactive alkaloid present in many mushrooms of the Amanita genus. Muscimol is a potent, selective agonist for the GABAA receptors and displays sedative-hypnotic effects. Muscimol actually binds to the same site on the GABAA receptor complex as GABA itself, as opposed to other GABAergic drugs such as barbiturates and benzodiazepines which bind to separate regulatory sites. GABAA receptors are widely distributed in the brain, and so when muscimol is administered, it alters neuronal activity in multiple regions including the cerebral cortex, hippocampus, and cerebellum. While muscimol is conventionally thought of as a selective GABAA agonist, it is also a partial agonist at the GABAA-rho receptor, and so its range of effects results from a combined action at both targets. In patients with Huntington's disease and chronic schizophrenia, oral doses of muscimol have been found to cause a rise of both prolactin and growth hormone. Many of muscimol's effects are consistent with its pharmacology as a GABAA receptor agonist, presenting many depressant or sedative-hypnotic effects. Atypical of the effect profile of sedative drugs generally however, muscimol, like Z-drugs, can cause dissociative hallucinations.

http://en.wikipedia.org/wiki/Muscimol

7) Picamilon

Picamilon (also known as nicotinoyl-GABA, pycamilon, and pikamilon) is a dietary supplement formed by combining niacin with GABA. Picamilon is sold in the United States as a dietary supplement, while in Russia it is sold as a prescription drug. Picamilon is able to cross the blood–brain barrier and then is hydrolyzed into GABA and niacin. The released GABA in theory would activate GABA receptors potentially producing an anxiolytic response. The second released component, niacin acts as a strong vasodilator, which might be useful for the treatment of migraine headaches.

http://en.wikipedia.org/wiki/Picamilon

8) Progabide/Gabrene

Progabide is an analog and prodrug of gamma-aminobutyric acid used in the treatment of epilepsy. It has agonistic activity at the GABAA, GABAB, and GABAρ receptors. Progabide has been investigated for many diseases besides epilepsy, including Parkinson's disease, schizophrenia, clinical depression, anxiety disorder and spasticity with various levels of success.

http://en.wikipedia.org/wiki/Progabide

9) Propofol/Diprivan

Propofol is a short-acting, intravenously administered hypnotic/amnestic agent. Propofol has been proposed to have several mechanisms of action both through potentiation of GABAA receptor activity, thereby slowing the channel-closing time, and also acting as a sodium channel blocker. Recent research has also suggested that the endocannabinoid system may contribute significantly to propofol's anesthetic action and to its unique properties. EEG research upon those undergoing general anesthesia with propofol finds that it causes a prominent reduction in the brain's information integration capacity at gamma wave band frequencies. Researchers at Washington University School of Medicine in St. Louis and Imperial College London have identified the site where propofol binds to GABAA receptors in the brain. Patients show great variability in their response to propofol, at times showing profound sedation with small doses. A more serious but rare side effect is dystonia. Mild myoclonic movements are common, as with other intravenous hypnotic agents. This is for professional use only.

http://www.drugs.com/propofol.html

10) Scullcap

Scutellaria barbata is a species of flowering plant in the mint family, Lamiaceae. It has been tested in clinical trials for the treatment of metastatic breast cancer. Extracts induced apoptosis in prostate cancer cells in laboratory studies. The plant is used as an herbal remedy for inflammation and traumatic injury. May inhibit pituitary and chorionic gonadotropins, as well as prolactin.

http://en.wikipedia.org/wiki/Scullcap

11) Tiagabine/Gabitril

Tiagabine is in a class of medications called anticonvulsants. It is not known exactly how tiagabine works, but it increases the amount of natural chemicals in the brain that prevent seizure activity. It is believed that the pharmacology is related to its ability, documented in in vitro experiments, to enhance the activity of gamma aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system. These experiments have shown that tiagabine binds to recognition sites associated with the GABA uptake carrier. It is thought that, by this action, tiagabine blocks GABA uptake into presynaptic neurons, permitting more GABA to be available for receptor binding on the surfaces of post-synaptic cells. Evidence is available that it operates as a selective GABA reuptake inhibitor. Tiagabine's most common side effects include confusion, difficulty speaking clearly/stuttering, mild sedation, and in doses over 8 mg, a tingling sensation (paresthesia) in the body's extremities, particularly the hands and fingers. Tiagabine may induce seizures in those without epilepsy, especially if they are taking another drug which lowers the seizure threshold.

http://www.nlm.nih.gov/medlineplus/druginfo/meds/a698014.html

12) Valerian

Valerian, in pharmacology and herbal medicine, is the name of a herb or dietary supplement prepared from roots of the plant. Crude extract of the root is often sold in the form of capsules. Valerian root has sedative and anxiolytic effects. It can also be classified as a drug, since its consumption produces a

sedative or medicinal effect, while it is not exclusively a type of food. These effects are suspected to be mediated through the GABA receptor. The amino acid valine is named after this plant. The mechanism of action of valerian in general, and as a mild sedative in particular has not been fully elucidated, but it is generally believed that some of the GABA-analogs particularly valerenic acids as components of the essential oil along with other semi-volatile sesquiterpenoids appear to have some affinity for the GABAA receptor, a class of receptors on which benzodiazepines are known to act. Valeric acid, which is responsible for the typical odor of mostly older valerian roots, does not have any sedative properties. Valerian also contains isovaltrate, which has been shown to be an inverse agonist for adenosine A1 receptor sites. This action likely does not contribute to the herb's sedative effects, which would be expected from an agonist, rather than an inverse agonist, at this particular binding site. Hydrophilic extractions of the herb commonly sold over-the-counter, however, probably do not contain significant amounts of isovaltrate (according to the paper cited previously).

http://ods.od.nih.gov/factsheets/Valerian-HealthProfessional/

13) Valproate/Depakote/Depakote ER/ Depakene/ Depakene Crono/Depacon/Depakine/ Valparin/Stavzor.

Valproate's mechanism of action includes enhanced neurotransmission of GABA (by inhibiting GABA transaminase, which breaks down GABA). Valproic acid was first synthesized in 1882 by B.S. Burton as an analogue of valeric acid, found naturally in valerian. As an anticonvulsant, valproic acid is used to control absence seizures, tonic-clonic seizures (grand mal), complex partial seizures, juvenile myoclonic epilepsy, and the seizures associated with Lennox-Gastaut syndrome. It is also used in treatment of myoclonus. In some countries, parenteral preparations of valproate are used also as second-line treatment of status epilepticus as an alternative to phenytoin. Valproate is one of the most common drugs used to treat post-traumatic epilepsy. It is more recently being used to treat neuropathic pain, as a second-line agent, particularly lancinating pain from A delta fibers.

http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682412.html

B) GABA positive allosteric modulators

Contrary to popular misconception, many commonly used sedative and anxiolytic drugs that affect the GABA receptor complex aren't actually agonists. These drugs are known as positive allosteric modulators, and while they do bind to the GABA receptors, they cannot induce a response from the neuron without an actual agonist being present. Drugs that fall into this class exert their pharmacodynamic action by increasing the effects that an agonist has when potentiation is achieved. Positive allosteric modulators work by increasing the frequency with which the chlorine channel opens when an agonist binds to its own site on the GABA receptor. The resulting increase in the concentration of Cl- ions in the postsynaptic neuron immediately hyperpolarizes this neuron, making it less excitable and thus inhibiting the possibility of an action-potential.

1) Barbituates/Allobarbital/Amobarbital/Aprobarbital/Alphenal/Barbital/Brallobarbital /Phenobarbital

Barbiturates are drugs that act as central nervous system depressants, and can therefore produce a wide spectrum of effects, from mild sedation to total anesthesia. They are also effective as anxiolytics, hypnotics, and anticonvulsants. Barbiturates also have analgesic effects; however, these effects are

somewhat weak, preventing barbiturates from being used in surgery in the absence of other analgesics. They have addiction potential, both physical and psychological. Barbiturates have now largely been replaced by benzodiazepines in routine medical practice – for example, in the treatment of anxiety and insomnia – mainly because benzodiazepines are significantly less dangerous in overdose. However, barbiturates are still used in general anesthesia, for epilepsy, and assisted suicide. Barbiturates are derivatives of barbituric acid. . Barbiturates bind to the GABAA receptor at the beta subunit, which are binding sites distinct from GABA itself and also distinct from the benzodiazepine binding site. Like benzodiazepines, barbiturates potentiate the effect of GABA at this receptor. In addition to this GABA-ergic effect, barbiturates also block the AMPA receptor, a subtype of glutamate receptor. Glutamate is the principal excitatory neurotransmitter in the mammalian CNS. Taken together, the findings that barbiturates potentiate inhibitory GABAA receptors and inhibit excitatory AMPA receptors can explain the CNS-depressant effects of these agents. At higher concentration, they inhibit the Ca2+-dependent release of neurotransmitters. Barbiturates produce their pharmacological effects by increasing the duration of chloride ion channel opening at the GABAA receptor (pharmacodynamics: This increases the efficacy of GABA), whereas benzodiazepines increase the frequency of the chloride ion channel opening at the GABAA receptor (pharmacodynamics: This increases the potency of GABA). The direct gating or opening of the chloride ion channel is the reason for the increased toxicity of barbiturates compared to benzodiazepines in overdose

http://en.wikipedia.org/wiki/Barbituates

2) Benzodiazepine/Valium/Midazolam/Diazepam/Lorazepam/Clonazepam

Benzodiazepines enhance the effect of the neurotransmitter gamma-aminobutyric acid (GABA) at the GABAA receptor, resulting in sedative, hypnotic (sleep-inducing), anxiolytic (anti-anxiety), anticonvulsant, and muscle relaxant properties; also seen in the applied pharmacology of high doses of many shorter-acting benzodiazepines are amnesic-dissociative actions. These properties make benzodiazepines useful in treating anxiety, insomnia, agitation, seizures, muscle spasms, alcohol withdrawal and as a premedication for medical or dental procedures. Benzodiazepines are categorized as either short-, intermediate- or long-acting. Short- and intermediate-acting benzodiazepines are preferred for the treatment of insomnia; longer-acting benzodiazepines are recommended for the treatment of anxiety. In general, benzodiazepines are safe and effective in the short term, although cognitive impairments and paradoxical effects such as aggression or behavioral disinhibition occasionally occur. Long-term use is controversial due to concerns about adverse psychological and physical effects, increased questioning of effectiveness and because benzodiazepines are prone to cause tolerance, physical dependence, and, upon cessation of use after long term use, a withdrawal syndrome

http://en.wikipedia.org/wiki/Benzodiazepines

C) GABA B Agonists

1) Baclofen/Kemstro/Lioresal/Liofen/Gablofen/Beklo/Baclosan

Baclofen is a derivative of gamma-aminobutyric acid (GABA). It is primarily used to treat spasticity and is in the early research stages for use for the treatment of alcoholism. It is also used by compounding pharmacies in topical pain creams as a muscle relaxant. It is an agonist for the GABAB receptors. Its beneficial effects in spasticity result from actions at spinal and supraspinal sites. Baclofen can also be

used to treat hiccups, and has been shown to prevent rises in body temperature induced by the drug MDMA in rats.

A beneficial property of baclofen is that tolerance does not seem to occur to a significant degree — baclofen retains its therapeutic anti-spasmodic effects even after many years of continued use. Newer studies, however, indicate that tolerance may develop in some patients receiving intrathecal baclofen treatment. Oral dosage must be carefully regulated; significantly high doses of the drug, particularly 80 mg per day or higher, can cause excessive ataxia and/or drowsiness that can interfere with daily function.

http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682530.html

2) GHB (γ-Hydroxybutyric acid)

γ-Hydroxybutyric acid (GHB), also known as 4-hydroxybutanoic acid, is a naturally occurring substance found in the human central nervous system, as well as in wine, beef, small citrus fruits, and almost all animals in small amounts. It is also categorized as an illegal drug in many countries. GHB has been used in a medical setting as a general anesthetic, to treat conditions such as insomnia, clinical depression, narcolepsy, and alcoholism, and to improve athletic performance. It is also used as an intoxicant (illegally in many jurisdictions) or as a date rape drug. GHB is naturally produced in the human body's cells and is structurally related to the ketone body beta-hydroxybutyrate. As a supplement or drug, it is used most commonly in the form of a salt, such as sodium gamma-hydroxybutyrate (Na.GHB, sodium oxybate, or Xyrem) or potassium gamma-hydroxybutyrate (K.GHB, potassium oxybate). GHB is also produced as a result of fermentation, and so is found in small quantities in some beers and wines. Succinic semialdehyde dehydrogenase deficiency is a disease that causes GHB to accumulate in the blood.

GHB has at least two distinct binding sites in the central nervous system. GHB is an agonist at the newly characterized GHB receptor, which is excitatory, and it is a weak agonist at the GABAB receptor, which is inhibitory. GHB is a naturally occurring substance that acts in a similar fashion to some neurotransmitters in the mammalian brain. GHB is probably synthesized from GABA in GABAergic neurons, and released when the neurons fire. If taken orally, GABA itself does not effectively cross the blood-brain-barrier. However, at therapeutic doses, GHB reaches much higher concentrations in the brain and activates GABAB receptors, which are primarily responsible for its sedative effects. GHB's sedative effects are blocked by GABAB antagonists. Activation of both the GHB receptor and GABA(B) is responsible for the addictive profile of GHB. GHB's effect on dopamine release is biphasic. Low concentrations stimulate dopamine release via the GHB receptor. Higher concentrations inhibit dopamine release via GABA(B) receptors as do other GABA(B) agonists such as baclofen and phenibut. After an initial phase of inhibition, dopamine release is then increased via the GHB receptor. Both the inhibition and increase of dopamine release by GHB are inhibited by opioid antagonists such as naloxone and naltrexone. Dynorphin may play a role in the inhibition of dopamine release via kappa opioid receptors

http://www.nlm.nih.gov/medlineplus/druginfo/meds/a605032.html

3) Phenibut/Noofen

β-Phenyl-γ-aminobutyric acid, better known as phenibut or less commonly fenibut or phenybut, is a derivative of the naturally occurring inhibitory neurotransmitter γ-aminobutyric acid (GABA). The addition of a phenyl ring allows phenibut to cross the blood brain barrier. Phenibut is sold as a nutritional supplement, and is not approved as a pharmaceutical in the United States or Europe, but in Russia it is sold as a psychotropic drug. It has been reported by some to possess nootropic actions for its ability to improve neurological functions, but other researchers have not observed these effects. It is generally accepted that phenibut has anxiolytic effects in both animal models and in humans. Phenibut was discovered in the Soviet Union in the 1960s, and has since been used there to treat a wide range of ailments including post-traumatic stress disorder, anxiety, and insomnia.

The pharmacological effects of phenibut are similar to baclofen, but less potent per milligram of dosage. Phenibut exerts its effects by being an agonist at the metabotropic GABAB receptor, and at higher doses also at the ionotropic GABAA receptor. Some studies found that phenibut antagonizes the effects of phenylethylamine (PEA), while others found no effect on PEA induced anxiety. Furthermore, phenibut has been shown to enhance levels of dopamine. The literature reports that phenibut has almost no negative side effects, with only an increase in sleepiness observed, however this effect is not nearly as pronounced as with benzodiazepine usage. Tolerance has been reported with extended use of high doses (e.g. 5–10 grams) of phenibut. There are numerous reports of withdrawal symptoms on Internet forums and blogs. They seem mainly due to misuse or excess. There is one reported case of withdrawal involving "nervousness and shakiness, psychomotor agitation, feeling easily annoyed and irritated, fatigue, poor appetite, heart pounding and racing, nausea, insomnia, and feeling tense and keyed up", consistent with its GABAB agonist properties. There has been no systematic study of this problem.

http://en.wikipedia.org/wiki/Phenibut

D) GABA-ρ agonists

1) (Z)-4-Amino-2-butenoic acid

Z)-4-Amino-2-butenoic acid (CACA, cis-4-aminocrotonic acid) is a GABA receptor partial agonist selective for the GABAA-ρ (previously known as GABAC) subtype.

2) (+)-cis-2-Aminomethylcyclopropane carboxylic acid

+)-*cis*-2-Aminomethylcyclopropane carboxylic acid ((+)-CAMP) is a GABA agonist selective for the $GABA_A$-ρ (previously known as $GABA_C$) subtype.

3) N4-Chloroacetylcytosine arabinoside/Gamibetal/Buxamin

4) GABOB (γ-Amino-beta-hydroxybutyric acid)

gamma-Amino-beta-hydroxybutyric acid (GABOB) is a derivative of the neurotransmitter GABA. It is found naturally in the human body but it is not known whether it has an important physiological role at normal concentrations. GABOB has anticonvulsant properties, but is of relatively low potency when used by itself, and is more useful as an adjuvant treatment used alongside another anticonvulsant drug. It has

two stereoisomers, with the (3S) isomer d-GABOB being around twice as potent an anticonvulsant as the (3R) isomer l-GABOB.

Other studies have suggested it may produce improved learning and memory function, probably through a cholinergic mechanism, as well as boosting growth hormone release. However its effectiveness for these purposes has not been well established and it is not widely used in medicine, although it is sold as a dietary supplement.

http://www.ncbi.nlm.nih.gov/pubmed/23019493

5) Progabide/Gabrene

Progabide is an analog and prodrug of gamma-aminobutyric acid used in the treatment of epilepsy. It has agonistic activity at the GABAA, GABAB, and GABAρ receptors.

Progabide has been investigated for many diseases besides epilepsy, including Parkinson's disease, schizophrenia, clinical depression, anxiety disorder and spasticity with various levels of success.

http://www.drugbank.ca/drugs/DB00837

E) GABA reuptake inhibitors

Reuptake inhibitors block receptors so there are increased extracellular concentrations of GABA. It's like blocking the sink drain so the water level rises.

1) Deramciclane

Deramciclane (EGIS-3886) is a drug which acts as an antagonist at the 5-HT2A receptor, as an inverse agonist at the 5-HT2C receptor, and as a GABA reuptake inhibitor. In 2003 Orion Pharma of Finland and partner Pharmacia discontinued the development of deramciclane for generalized anxiety disorder, owing to a lack of efficacy in the combined results of the Phase III trials of the agent.

2) Hyperforin

Hyperforin is a phytochemical produced by some of the members of the plant genus Hypericum, notably Hypericum perforatum (St John's wort). It is believed to be one of the chief active constituents of St. John's wort (along with hypericin, pseudohypericin, adhyperforin and several flavonoid constituents). In healthy male volunteers, 612 mg dry extract of St. John's wort produced hyperforin pharmacokinetics characterised by a half life of 19.64 hours. It appears to be metabolised, at least in part, by CYP3A and CYP2B into hydroxyl metabolites.

Hyperforin is believed to be the primary active constituent responsible for the antidepressant and anxiolytic properties of the extracts of St. John's wort. It acts as a reuptake inhibitor of monoamines, including serotonin, norepinephrine, dopamine, and of GABA and glutamate, with IC50 values of 0.05-0.10 μg/mL for all compounds, with the exception of glutamate, which is in the 0.5 μg/mL range. Hyperforin also inhibits the reuptake of glycine[14] and choline (IC50=8.5μM). It also modulates acetylcholine release in rat hippocampus and facilitates acetylcholine release in the striatum. It appears to exert these effects by activating the transient receptor potential ion channel TRPC6. Activation of

TRPC6 induces the entry of sodium and calcium into the cell which causes inhibition of monoamine reuptake. It also antagonises the NMDA receptor, AMPA receptor and GABA receptors.

http://en.wikipedia.org/wiki/Hyperforin

3) Tiagabine/Gabatril

Tiagabine is an anti-convulsive medication. It is believed that the pharmacology is related to its ability, documented in in vitro experiments, to enhance the activity of gamma aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system. These experiments have shown that tiagabine binds to recognition sites associated with the GABA uptake carrier. It is thought that by this action, tigabine blocks GABA uptake into presynaptic neurons, permitting more GABA to be available for receptor binding on the surfaces of post-synaptic cells. Evidence is available that it operates as a selective GABA uptake inhibitor. Common side effects include confusion, difficulty speaking clearly/stuttering, mild sedation, and in doses over 8 mg, a tingling sensation (paresthesia) in the body's extremities, particularly the hands and fingers. Tigabine may induce seizures in those without epilepsy, especially if they are taking another drug which lowers the seizure threshold.

http://www.nlm.nih.gov/medlineplus/druginfo/meds/a698014.html

F) GABA-transaminase inhibitors

GABA-transaminase inhibitors are drugs which bind to enzymes and decreases their activity. Since blocking an enzyme's activity can kill a pathogen or correct a metabolic imbalance, many drugs are enzyme inhibitors, (as are some pesticides and herbicides).

1) Gabaculine

Gabaculine is a naturally occurring neurotoxin first isolated from the bacteria Streptomyces toyacaensis, which acts as a potent and irreversible GABA transaminase inhibitor, and also a GABA reuptake inhibitor.

http://en.wikipedia.org/wiki/Gabaculine

2) Phenelzine/Nardil/Nardelzine

Phenelzine is a non-selective and irreversible monoamine oxidase inhibitor (MAOI) of the hydrazine class which is used as an antidepressant and anxiolytic. Along with tranylcypromine and isocarboxazid, phenelzine is one of the few non-selective MAOIs still in widespread clinical use. It is typically available in 15 mg tablets and doses usually range from 30-90 mg per day, with 15 mg every day or every other day suggested as a maintenance dose following a successful course of treatment.

Phenelzine is a non-selective and irreversible inhibitor of the enzyme monoamine oxidase (MAO). It inhibits both of the respective isoforms of MAO, MAO-A and MAO-B, and does so almost equally, with slight preference for the former. By inhibiting MAO, phenelzine prevents the breakdown of the monoamine neurotransmitters serotonin, melatonin, norepinephrine, epinephrine, and dopamine, as well as the trace amine neuromodulators such as phenethylamine, tyramine, octopamine, and tryptamine. This leads to an increase in the extracellular concentrations of these neurochemicals and therefore an

alteration in neurochemistry and neurotransmission. This action is thought to be the primary mediator in phenelzine's therapeutic benefits.

Phenelzine and its metabolites also inhibit at least two other enzymes to a lesser extent, of which are alanine transaminase (ALA-T), and γ-Aminobutyric acid transaminase (GABA-T), the latter of which is not caused by phenelzine itself, but by a phenelzine metabolite phenylethylidenehydrazine (PEH). By inhibiting ALA-T and GABA-T, phenelzine causes an increase in the alanine and GABA levels in the brain and body. GABA is the major inhibitory neurotransmitter in the mammalian central nervous system, and is very important for the normal suppression of anxiety, stress, and depression. Phenelzine's action in increasing GABA concentrations may significantly contribute to its antidepressant, and especially, anxiolytic/antipanic properties, the latter of which have been considered superior to those of other antidepressants. As for ALA-T inhibition, though the consequences of disabling this enzyme are currently not well understood, there is some evidence to suggest that it is this action of the hydrazines (including phenelzine) which may be responsible for the occasional incidence of hepatitis and liver failure.

http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682089.html

3) Vigabatrin/Sabril
Vigabatrin is an antiepileptic drug that inhibits the catabolism of gamma-aminobutyric acid (GABA) by irreversibly inhibiting GABA transaminase. It is an analog of GABA, but it is not a receptor agonist. Vigabatrin can cause permanent vision damage, including loss of peripheral vision and having blurry vision. Although vision loss is possible with any amount of vigabatrin, your risk may be greater with the more vigabatrin that you take daily and the longer you take it. Vision loss can happen at any time during treatment with vigabatrin. Vigabatrin is only available through a special program called SHARE. You and your doctor will need to be enrolled in this program before you can receive vigabatrin. You will need to get vigabatrin from a specialty pharmacy that is enrolled in the program.

http://www.nlm.nih.gov/medlineplus/druginfo/meds/a610016.html

4) Lemon balm (Melissa officinalis).

Lemon balm (Melissa officinalis), also known as balm[2] or balm mint and not to be confused with bee balm (which is genus Monarda), is a perennial herb in the mint family Lamiaceae, native to center-southern Europe and the Mediterranean region.

High doses of purified lemon balm extracts were found to be effective in the amelioration of laboratory-induced stress in human subjects, producing "significantly increased self-ratings of calmness and reduced self-ratings of alertness." The authors further report a "significant increase in the speed of mathematical processing, with no reduction in accuracy" following the administration of a 300 mg dose of extract.

Lemon balm extract was identified as a potent in vitro inhibitor of GABA transaminase, which explains anxiolytic effects. The major compound responsible for GABA transaminase inhibition activity in lemon balm was then found to be rosmarinic acid.

Caution: Lemon balm is believed to inhibit the absorption of the thyroid medication thyroxine.

http://en.wikipedia.org/wiki/Lemon_Balm

G) GABA analogues

GABA analogues are drugs that perform inhibitory actions similar to GABA .

1) Atagabalin

Atagabalin (PD-0200,390) is a drug developed by Pfizer and related to gabapentin, which similarly binds to the α2δ calcium channels. It is under development as a treatment for insomnia.

http://en.wikipedia.org/wiki/Atagabalin

2) Gabapentin/Neurontin

Gabapentin (Neurontin) is a pharmaceutical drug, specifically a GABA analog. It was originally developed to treat epilepsy, and currently is also used to relieve neuropathic pain. There are, however, concerns regarding the quality of the trials conducted for a number of conditions. It may be effective in reducing pain and spasticity in multiple sclerosis.

Gabapentin's most common side effects in adult patients include dizziness, fatigue, weight gain, drowsiness, and peripheral edema (swelling of extremities); these mainly occur at higher doses in the elderly. Also, in children 3 to 12 years of age, researchers observed susceptibility to mild-to-moderate mood swings, hostility, concentration problems, and hyperactivity. Though rare, the literature reports several cases of hepatotoxicity. Gabapentin should be used carefully in patients with renal impairment due to possible accumulation and toxicity. An increase in formation of adenocarcinomas was observed in rats during preclinical trials; however, the clinical significance of these results remains undetermined. Gabapentin is also known to induce pancreatic acinar cell carcinomas in rats through an unknown mechanism, perhaps by stimulation of DNA synthesis; these tumors did not affect the lifespan of the rats and did not metastasize.

Gabapentin has been associated with an increased risk of suicidal acts or violent deaths. In 2009 the U.S. Food and Drug Administration issued a warning of an increased risk of depression and suicidal thoughts and behaviors in patients taking gabapentin, along with other anticonvulsant drugs modifying the packaging insert to reflect this. In July 2009 the manufacturer of gabapentin (Pfizer) went to trial regarding the association between gabapentin and the increased risk of suicide.

http://www.nlm.nih.gov/medlineplus/druginfo/meds/a694007.html

3) Gabapentin enacarbil /Regnit/Horizant

Gabapentin is a prodrug for the anticonvulsant and analgesic drug gabapentin. It was designed for increased oral bioavailability over gabapentin, and human trials showed it to produce extended release of gabapentin with almost twice the overall bioavailability, especially when taken with a fatty meal. Gabapentin enacarbil has passed human clinical trials for the treatment of restless legs syndrome, and initial results have shown it to be well tolerated and reasonably effective. Gabapentin enacarbil was denied approval by the U.S. Food and Drug Administration (FDA) in February 2010, citing concerns about possible increased cancer risk shown by some animal studies. Similar concerns had been raised about gabapentin itself in the past, but were felt to be outweighed by its clinical utility as an anticonvulsant, whereas the treatment of restless legs syndrome was not seen to justify the same kind of risk.

http://en.wikipedia.org/wiki/Gabapentin_enacarbil

4) Hopantenic acid/homopantothenic acid/Pantogam

Hopantenic acid is a central nervous system drug. Formulated as the calcium salt, it is used in the Russian Federation for a variety of neurological, psychological and psychiatric conditions. Pantogam range of actions is related to the presence in its structure of gamma-aminobutyric acid. The mechanism of action is due to a direct effect on GABA-B-receptor-channel complex. The drug has neuroprotective and anticonvulsant effects. Pantogam increases brain resistance to hypoxia and the effects of toxic substances, stimulates anabolic processes in neurons that combines moderate sedation with a mild stimulating effect, reduces the excitability of the motor activates the mental and physical performance.

http://en.wikipedia.org/wiki/Hopantenic_acid

5) Imagabalin

Imagabalin is a drug which acts as a ligand for the α2δ subunit of the voltage-dependent calcium channel] with some selectivity for the α2δ1 subunit over α2δ2. Under development by Pfizer as a pharmaceutical medication, it has demonstrated preclinical efficacy of anxiolytic, analgesic, hypnotic, and anticonvulsant-like activity and is currently in phase III clinical trials for the treatment of generalized anxiety disorder.

http://en.wikipedia.org/wiki/Imagabalin

6)4-Methylpregabalin

4-Methylpregabalin is a drug developed by Pfizer and related to pregabalin, which similarly acts as an analgesic with effectiveness against difficult to treat "atypical" pain syndromes such as neuropathic pain. The effectiveness of pregabalin and its older relative gabapentin against these kind of pain syndromes (which tend to respond poorly to other analgesic drugs) has led to their widespread use, and these drugs have subsequently been found to be useful for many other medical applications, including as anticonvulsants, muscle relaxants, anxiolytics and mood stabilizers. However these drugs are still of relatively low potency, and scientists have struggled for years to come up with an improvement on pregabalin, with increasing pressure to find a suitably improved replacement before the patent on pregabalin expires in 2018. While it was determined that the mechanism of action involves modulation of the α2δ calcium channel subunits (1 and 2), derivatives that appeared to be more potent and effective than pregabalin at this target when tested in vitro, repeatedly turned out to be weak or inactive when tested in animals. Eventually it was discovered that pregabalin is actively transported across the blood–brain barrier by the system L neutral amino acid transporter protein, which usually functions to transport certain amino acids, including leucine, valine and isoleucine, into the brain.

http://en.wikipedia.org/wiki/4-Methylpregabalin

7) Pregabalin/Lyrica

Pregabalin is an anticonvulsant drug used for neuropathic pain and as an adjunct therapy for partial seizures with or without secondary generalization in adults. It has also been found effective for generalized anxiety disorder and is (as of 2007) approved for this use in the European Union and Russia. It was designed as a more potent successor to gabapentin. It was previously thought that pregabalin increased neuronal GABA levels by producing a dose-dependent increase in glutamic acid decarboxylase activity. However it is currently believed that pregabalin exerts its acitivity by modulation of alpha-2-delta-subtype of neuronal calcium channels.

Like gabapentin, pregabalin binds to the α2δ (alpha-2-delta) subunit of the voltage-dependent calcium channel in the central nervous system. Pregabalin decreases the release of neurotransmitters including glutamate, norepinephrine, substance P and calcitonin gene-related peptide. However, unlike anxiolytic compounds (e.g., benzodiazepines) which exert their therapeutic effects through binding to GABAA, pregabalin neither binds directly to these receptors nor augments GABAA currents or affects GABA metabolism (Pfizer Inc., 2006). The half-life for pregabalin is 6.3 hours.

http://www.nlm.nih.gov/medlineplus/druginfo/meds/a605045.html

V. OTHER TREATMENT OPTIONS

A) Dantrolene/Dantrium/Dantrium/Dantamacrin/Dantrolen

Dantrolene sodium is a muscle relaxant that acts by abolishing excitation-contraction coupling in muscle cells, probably by action on the ryanodine receptor and decreasing free intracellular calcium concentration. It is the only specific and effective treatment for malignant hyperthermia, a rare, life-threatening disorder triggered by general anesthesia. It is also used in the management of neuroleptic malignant syndrome, muscle spasticity (e.g. after strokes, in paraplegia, cerebral palsy, or patients with multiple sclerosis), 3,4-methylenedioxymethamphetamine ("ecstasy") intoxication, serotonin syndrome, and 2,4-dinitrophenol poisoning. Chemically it is a hydantoin derivative, but does not exhibit antiepileptic activity like other hydantoin derivates such as phenytoin.

Oral dantrolene cannot be used in people with: pre-existing liver disease, compromised lung function, severe cardiovascular impairment, known hypersensitivity to dantrolene, pediatric patients under five years of age, whenever good muscular balance/strength is needed to maintain an upright position, motoric function, or proper neuromuscular balance.

Central nervous system side effects are quite frequently noted and encompass speech and visual disturbances, mental depression and confusion, hallucinations, headache, insomnia and exacerbation or precipitation of seizures, and increased nervousness. Infrequent cases of respiratory depression or a feeling of suffocation have been observed. Dantrolene often causes sedation severe enough to incapacitate the patient to drive or operate machinery.

Gastrointestinal effects include bad taste, anorexia, nausea, vomiting, abdominal cramps, and diarrhea. Hepatic side effects may be seen either as asymptomatic elevation of liver enzymes and/or bilirubin or, most severe, as fatal and nonfatal hepatitis. The risk of hepatitis is associated with the duration of

treatment and the daily dose. In patients treated for hyperthermia, no liver toxicity has been observed so far.

Pleural effusion with pericarditis (oral treatment only), rare cases of bone marrow damage, diffuse myalgias, backache, dermatologic reactions, transient cardiovascular reactions, and crystalluria have additionally been seen. Muscle weakness may persist for several days following treatment.

http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682576.html

B) Carbamazepine/Tegretol/Equetro

Carbamazepine is an anticonvulsant and mood-stabilizing drug used primarily in the treatment of epilepsy and bipolar disorder, as well as trigeminal neuralgia. It is also used off-label for a variety of indications, including attention-deficit hyperactivity disorder (ADHD), schizophrenia, phantom limb syndrome, complex regional pain syndrome, paroxysmal extreme pain disorder, neuromyotonia, intermittent explosive disorder, borderline personality disorder, Myotonia congenita and post-traumatic stress disorder.

The mechanism of action of carbamazepine and its derivatives is relatively well-understood. Carbamazepine stabilizes the inactivated state of Voltage-gated sodium channels, making fewer of these channels available to subsequently open. This leaves the affected cells less excitable until the drug dissociates. Carbamazepine has also been shown to potentiate GABA receptors made up of alpha1, beta2, gamma2 subunits. This may be relevant to its efficacy in neuropathic pain and manic-depressive illness.

http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682237.html

C) Corticosteroids

Corticosteroids are used as monotherapy or combined with other therapeutic agents with improvement of spasms and autoantibody titre. There has never been a good quality clinical trial to determine the overall role in SPS. Corticosteroids are a class of chemicals that includes steroid hormones naturally produced in the adrenal cortex of vertebrates and analogues of these hormones that are synthesized in laboratories. Corticosteroids are involved in a wide range of physiological processes, including stress response, immune response, and regulation of inflammation, carbohydrate metabolism, protein catabolism, blood electrolyte levels, and behavior.

Glucocorticoids such as cortisol control carbohydrate, fat and protein metabolism are anti-inflammatory by preventing phospholipid release, decreasing eosinophil action and a number of other mechanisms.

Mineralocorticoids such as aldosterone control electrolyte and water levels, mainly by promoting sodium retention in the kidney.

Group A — Hydrocortisone type
Hydrocortisone, hydrocortisone acetate, cortisone acetate, tixocortol pivalate, prednisolone, methylprednisolone, and prednisone (Short- to medium-acting glucocorticoids).

Group B — Acetonides (and related substances)
Triamcinolone acetonide, triamcinolone alcohol, mometasone, amcinonide, budesonide, desonide, fluocinonide, fluocinolone acetonide, and halcinonide.

Group C — Betamethasone type
Betamethasone, betamethasone sodium phosphate, dexamethasone, dexamethasone sodium phosphate, and fluocortolone.

http://www.nationaljewish.org/healthinfo/medications/lung-diseases/longterm/about-steroids/

D) Levetiracetam/Keppra

Levetiracetam has been approved in the European Union as a monotherapy treatment for epilepsy in the case of partial seizures, or as an adjunctive therapy for partial, myoclonic and tonic-clonic seizures. Levetiracetam has potential benefits for other psychiatric and neurologic conditions such as Tourette syndrome, autism, bipolar disorder and anxiety disorder, as well as Alzheimer's disease. However, its most serious adverse effects are behavioral, and its benefit-risk ratio in these conditions is not well understood.
Along with other anticonvulsants like gabapentin, it is also sometimes used to treat neuropathic pain. It has not been found to be useful for essential tremors.

Levetiracetam was the subject of a single-blind placebo controlled trial in three patients and benefitted both symptoms and electrophysioligical findings. The exact mechanism by which levetiracetam acts to treat epilepsy is unknown. However, the drug binds to a synaptic vesicle glycoprotein, SV2A,and inhibits presynaptic calcium channels. This is believed to impede impulse conduction across synapses.

Levetiracetam is generally well tolerated, but may cause drowsiness, weakness, unsteady gait, fatigue, coordination problems, headache, pain, forgetfulness, anxiety, irritability or agitation, dizziness, mood changes, nervousness, loss of appetite, vomiting, diarrhea, throat pain, constipation, and changes in skin pigmentation. Serious side effects may include depression, hallucinations, suicidal thoughts, seizures that are worse or different, fever, sore throat, signs of infection, double vision, itching, rash, swelling of the face. A study published in 2005 suggests that the addition of pyridoxine (vitamin B6) may curtail some of the psychiatric symptoms. A rare side effect of Levetiracitam is a pins and needles sensation in the patient's legs, similar to neuropathy.

http://www.nlm.nih.gov/medlineplus/druginfo/meds/a699059.html

E) Opiate analgesics

While reducing the pain of rigidity and spasms may, opiate analgesics, on rare occasions, worsen them. Opioids work by binding to opioid receptors, which are found principally in the central and peripheral nervous system and the gastrointestinal tract. The receptors in these organ systems mediate both the beneficial effects and the side effects of opioids. The analgesic (painkiller) effects of opioids are due to decreased perception of pain, decreased reaction to pain as well as increased pain tolerance. The side effects of opioids include sedation, respiratory depression, constipation, and a strong sense of euphoria. Opioids can cause cough suppression, which can be both an indication for opioid administration or an

unintended side effect. Opioid dependence can develop with ongoing administration, leading to a withdrawal syndrome with abrupt discontinuation. Opioids are not only well known for their addictive properties, but also for their ability to produce a feeling of euphoria, motivating some to use opioids recreationally.

Drugs in this category include, but are not restricted to: Codeine, Morphine, Hydrocodone, Oxycodone Propoxyphene. They include trade names such as Tramadol, Vicodin, Demerol, Fentanyl, Oxycontin, Nucynta, etc.

For a more complete list go to: http://en.wikipedia.org/wiki/Opioid_analgesic

For more information go to: http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm095673.htm

F) Physical Therapy

Physical therapy may worsen symptoms of SPS during certain phases of the disease; therefore careful use of physical therapy, including passive range-of-motion is advised.

G) GAD-65/Diamyd Replacement

Diamyd Medical is developing a vaccine consisting of GAD65, for Type 1 diabetes. GAD (glutamic acid decarboxylase) is a protein present in the beta cells of the pancreas and is one of the most important targets when the immune system attacks these cells in autoimmune diabetes. Treatment with Diamyd® is thought to induce tolerance to GAD, thereby intervening in the autoimmune attack and preserving the capacity to produce insulin in patients with autoimmune diabetes, i.e. type 1 diabetes and LADA.

It may be beneficial to replace the GAD65 for SPS, but the makers of Diamyd said it would be cost prohibitive and has never made it to trials for SPS.

http://www.diamyd.com/

H) GABA Replacement

GABA itself cannot just be taken orally. The medical literature is pretty clear that there is little chance that GABA taken orally will penetrate the blood-brain barrier. However, there is evidence that GABA administered through an IV or intramuscular injection will penetrate the blood-brain barrier.

There are some over-the-counter supplements that are derivatives of GABA such as phenibut and picamilon. Picamilon combines niacin and GABA and crosses the blood–brain barrier as a prodrug that later hydrolyzes into GABA and niacin.

GABA injections are being tested as a cure for Type 1 Diabetes, which suggests injectable GABA exists, but has not been tried for SPS.http://healthesolutions.com/gaba-injections-prevented-and-reversed-type-1-diabetes-in-mice/

GABA injections are also being used by a company to help rehabilitate addicts.
http://novusdetox.com/intramuscular-injectables.php)

I) STEM CELL TRANSPLANT

The body's main line of defense against invasion by infectious organisms is the immune system. To succeed, an immune system must distinguish the many cellular components of its own body (self) from the cells or components of invading organisms (nonself). "Nonself" should be attacked while "self" should not. Therefore, two general types of errors can be made by the immune system. If the immune system fails to quickly detect and destroy an invading organism, an infection will result. However, if the immune system fails to recognize self cells or components and mistakenly attacks them, the result is known as an autoimmune disease. Common autoimmune diseases include rheumatoid arthritis, systemic lupus erythematosis (lupus), type 1 diabetes, multiple sclerosis, Sjogren's syndrome and inflammatory bowel disease. Although each of these diseases has different symptoms, they share the unfortunate reality that, for some reason, the body's immune system has turned against itself.

In recent years, researchers have contemplated the use of stem cells to treat autoimmune disorders. The immune-mediated injury in autoimmune diseases can be organ-specific, such as type 1 diabetes which is the consequence of the destruction of the pancreatic beta islet cells or multiple sclerosis which results from the breakdown of the myelin covering of nerves. These autoimmune diseases are amenable to treatments involving the repair or replacement of damaged or destroyed cells or tissue. In contrast, non-organ-specific autoimmune diseases, such as lupus, are characterized by widespread injury due to immune reactions against many different organs and tissues.

The objective of hematopoietic stem cell therapy for lupus is to destroy the mature, long-lived, and auto-reactive immune cells and to generate a new, properly functioning immune system. In most of these trials, the patient's own stem cells have been used in a procedure known as autologous (from "one's self") hematopoietic stem cell transplantation. First, patients receive injections of a growth factor, which coaxes large numbers of hematopoietic stem cells to be released from the bone marrow into the blood stream. These cells are harvested from the blood, purified away from mature immune cells, and stored. After sufficient quantities of these cells are obtained, the patient undergoes a regimen of cytotoxic (cell-killing) drug and/or radiation therapy, which eliminates the mature immune cells. Then, the hematopoietic stem cells are returned to the patient via a blood transfusion into the circulation where they migrate to the bone marrow and begin to differentiate to become mature immune cells. The body's immune system is then restored. Nonetheless, the recovery phase, until the immune system is reconstituted represents a period of dramatically increased susceptibility to bacterial, fungal, and viral infection, making this a high-risk therapy.

There are many articles regarding stem cell treatment of autoimmune diseases. A few are referenced here. There is no specific trial for SPS. The cost is extremely high – around a half a million dollars or more. The patient's immune system is sometimes wiped out and reset. If the stem cells are not autologous (donated by the patient) they may have to be on anti-rejection medications permanently. Currently stem cell transplants are in the research stage, but do offer hope for one day finding cures for many autoimmune diseases.

http://www.ncbi.nlm.nih.gov/pubmed/22160046

http://stemcells.nih.gov/info/scireport/pages/chapter6.aspx

http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=1721

http://www.haematologica.org/content/95/2/185.full

http://clinicaltrials.gov/show/NCT00716066

http://www.chch.com/stiff-person-syndrome/