Pharmacotherapy for CFS

Relatively few research studies or clinical trials have been done on prescription drugs, supplements or herbal remedies for treating chronic fatigue syndrome. In fact, no prescription drugs have been developed specifically to treat CFS. Here, we review the research done thus far and the best options for patients.

By Loretta Spotila, PhD, Guest Contributor

There is no known cause and no known cure for chronic fatigue syndrome (CFS). Despite the complexity and mystery of this disease, there are a number of therapies available that target one or more of the endocrinological, neurological, immunological or psychological effects of CFS.

According to research conducted by the Centers for Disease Control and Prevention (CDC), CFS patients are more likely to use drugs of any category than are nonfatigued subjects.[1] However, both groups use pain relievers and supplements/vitamins as the two most frequent drugs. The percentage of CFS patients reporting use of pain relievers in this survey was 87.8%, and 52% were medicated with hormones. Antidepressants, gastrointestinal and central nervous system drugs were used by 41%, 32% and 24% of the CFS patient population, respectively.

In general, the choice of therapy should reflect a careful consideration of the individual's general health status and severity of particular symptoms. The CDC recommends that an individually tailored program should be developed in consultation with a health care provider. The CDC also cautions that some treatments are unproven and may actually be harmful. Thus, CFS patients should understand that self-medication poses risks.

Drug treatment regimens address the symptoms experienced by CFS patients. For instance, a study conducted in 2001 showed that treatment of patients with CFS and fibromyalgia (FM) according to their symptoms resulted in significant improvement in all outcomes.[2] However, the efficacy of regimens varies not only from drug to drug but from patient to patient, and some experimentation may be required before the doctor-patient team finds the best drug or nondrug treatment to alleviate a patient's symptoms.

This article will address both the state of research into drug therapies for CFS and the most common drugs physicians are using to treat patients. Research studies summarized in this article (see chart on page 6) were selected from medical literature.

Prescription drugs, over the counter (OTC) drugs, nutritional supplements and herbal remedies are included in this article. Since the symptomology of CFS is the basis for treatment, the various lists of treatments are organized by symptom.

Difficulty of CFS research

In order to evaluate the current state of research in this area, it's helpful to have some guidelines and to be aware of the limitations in studying CFS. In general, studies with more participants

produce more reliable results. The most objective type of study is a randomized clinical trial (RCT) in which the study cohort has been selected according to predetermined criteria and has been randomly assigned to receive the study drug or placebo. Other factors that increase the reliability of a study's findings are the use of a crossover double-blinded design and the length of the study. In a controlled clinical trial (CCT), patients aren't necessarily assigned to treatment or placebo on a random basis. A clinical trial (CT) isn't placebo-controlled, and a case study (CS) reports on treatment of only a single patient or several patients.

Drugs that treat mood and/or cognition

Antidepressants. There are three classes of antidepressants used to treat mood or cognitive difficulties in CFS patients: selective serotonin reuptake inhibitors (SSRI), serotonin norepinephrine reuptake inhibitors (SNRI) and monomamine oxidase (MAO) inhibitors. Drugs in each class act in different ways and may affect individual patients differently. The only SSRI to be studied in clinical trials in CFS patients is fluoxetine. In one RCT fluoxetine didn't improve any measure of CFS status in depressed or nondepressed patients.[3] In another RCT, a comparison of graded exercise with fluoxetine indicated that the latter improved only depression.[4] Bupropion is the only SNRI to undergo testing in CFS patients.[5] Although it offered some improvement to the nine patients in the study, the trial was open-label and not controlled for a placebo effect. The remaining SSRIs and SNRIs listed in the chart on page 6 haven't been formally studied in patients with CFS.

The MAO inhibitors that have been tested in CFS patients are moclobimide, nefazodone, selegiline and phenelzine. Two studies of moclobimide had different outcomes: the first conducted in 1997 was a clinical trial with 49 patients of whom 14 were depressed. There was no overall benefit, although 50% of the depressed participants reported dramatic improvement.[6] In a randomized placebo-controlled study conducted in 2000, 51% of those receiving the drug reported improvement characterized as an increase in subjective sense of vigor independent of psychological distress.[7] Nefazodone,[8,9] selegiline[10] and phenelzine[11] have resulted in modest improvement independent of depressive illness. Clinicians don't use these drugs regularly; moclobimide isn't available in the United States, and nefazadone can cause liver damage.

Mood stabilizers. Anticonvulsant and antipsychotic drugs are sometimes prescribed as mood stabilizers. While these drugs have been extensively tested in clinical trials, none has been tested in a clinical trial of CFS.

Stimulants. Several stimulants have been the subject of clinical trials in CFS patients. Dexamphetamine,[12] modafinil,[13,14] and pyridostigmine[15] improved fatigue in one small RCT[12] and three case studies.[13-15] Of note is a large multicenter RCT of the stimulant galantamine hydrobromide that showed no benefit (see sidebar on this page).[16] Of these stimulants, only modafinil is sometimes prescribed by physicians to treat their CFS patients, although success has been limited. Lastly, the stimulant atomoxetine, used in the

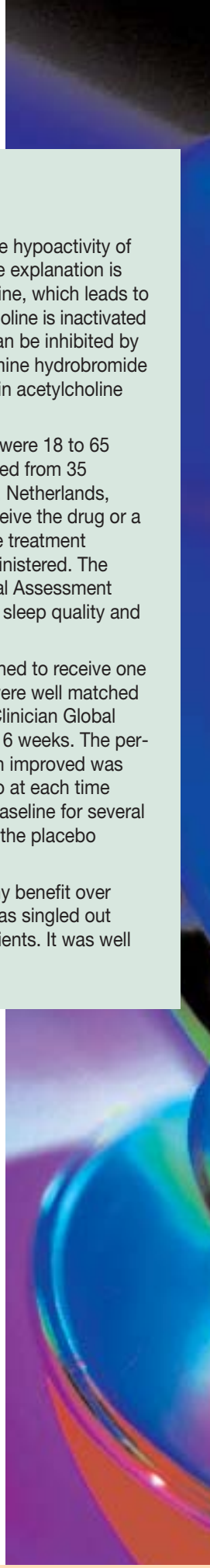
Galantamine Hydrobromide Tested for Sleep and Cognition

BACKGROUND. Some patients with CFS are noted to have hypoactivity of the hypothalamic-pituitary-adrenal (HPA) axis. One possible explanation is that there is a deficiency of the neurotransmitter acetylcholine, which leads to sleep disturbance and impaired response to stress. Acetylcholine is inactivated by the enzyme acetylcholinesterase, but this inactivation can be inhibited by drugs of the class aceytlcholinesterase inhibitors. Galantamine hydrobromide is one such drug that, in theory, could correct a deficiency in acetylcholine and perhaps increase the activity of the HPA axis.

METHODS. Patients who met the Fukuda criteria for CFS, were 18 to 65 years old and had been ill for less than 7 years were recruited from 35 primary care centers in the United Kingdom, United States, Netherlands, Sweden and Belgium. They were randomly assigned to receive the drug or a placebo, and neither the patient nor the physician knew the treatment assignment. Four different doses of galantamine were administered. The main outcome measured was change in the Clinician Global Assessment Scale, and secondary outcomes included several scales of sleep quality and cognitive function.

RESULTS. A total of 434 patients were recruited and assigned to receive one or four doses of galantamine or placebo. The five groups were well matched for age, gender, country, ethnic origin, weight and height. Clinician Global Impression Scores were measured at 4-week intervals for 16 weeks. The percentage of patients who were very much improved or much improved was not significantly different for each dosage level and placebo at each time point of the trial. Although there were improvements over baseline for several secondary outcomes, none was significantly different from the placebo group.

Although galantamine hydrobromide didn't demonstrate any benefit over placebo in the treatment of patients with CFS, this study was singled out because it's the largest randomized clinical trial of CFS patients. It was well designed and properly carried out.



Medications for Treating CFS

This chart lists drugs commonly prescribed by physicians for treating CFS patients. It's not intended to be comprehensive, and patients should keep in mind that what works for one patient may not work for them. Physicians and patients may need to systematically try various drug interventions to determine which works best. People with CFS are highly sensitive to medications, so dosages are generally started out at a fraction of the normal dose and then adjusted to levels that are both well-tolerated and therapeutic.

Some drugs act on multiple systems and symptoms. For instance, tricyclic antidepressants may not only improve mood, but may help with sleep and pain. Prescribing such drugs allows the use of fewer medications to address multiple symptoms with minimal side effects.

CLASS OF DRUG	DRUG NAME (Brand/Generic)
Sleep Improvement	
Sleep initiators	Xanax (alprazolam) Restoril (temazepam) Klonopin (clonazepam)
Sleep sustainers	Elavil, Endep (amitriptyline) Sinequan (doxepin) Desyrel (trazodone) Remeron (mirtazapine) Zanaflex (tizanidine) Flexeril (cyclobenzaprine) Neurontin (gabapentin)
Sleep initiators & sustainers	Ambien (zolpidem) Sonata (zaleplon) Lunesta (eszopiclone) ProSom (estazolam)
Anticonvulsants	
Used in CFS as mood stabilizers or for pain relief and sleep	Lamictal (lamotrigine) Depakote (divalproex sodium) Neurontin (gabapentin) Topamax (topiramate) Lyrica (pregabalin)
Stimulants	
Used in CFS for wakefulness and mental acuity	Provigil (modafinil) Adderall (amphetamine salts) Ritalin (methylphenidate) Strattera (atomoxetine) Xyrem (sodium oxybate)
Muscle Relaxants	
Used in CFS for pain, sleep	Zanaflex (tizanidine) Flexeril (cyclobenzaprine) Skelaxin (metaxalone) Robaxin (methocarbamol) Norflex (orphenadrine)
Antidepressants	
SSRI class of antidepressants	Prozac (fluoxetine) Zoloft (sertraline) Paxil (paroxetine) Celexa (citalopram) Lexapro (escitalopram)
SNRI class of antidepressants	Effexor (venlafaxine) Cymbalta (duloxetine) Wellbutrin (buproprion)
Tricyclic class of antidepressants *Treats multiple symptoms; may help with mood, sleep and pain*	Elavil, Endep (amitriptyline) Sinequan (doxepin) Norpramin (desipramine)
Receptor antagonist class of antidepressants	Desyrel (trazodone) Remeron (mirtazapine)
Restless Legs Syndrome	
	Requip (ropinirole) Mirapex (pramipexole) Sinemet (carbidopa-levodopa)
Orthostatic Intolerance	
	Florinef (fludrocortisone) ProAmatine (midodrine) Tenormin (atenolol)
Analgesics (Pain Relief)	
Nonsteroidal anti-inflammatory	Advil/Motrin (ibuprofen) Aleve (naproxen) Mobic (meloxicam)
Cox II inhibitors	Celebrex (celecoxib)
Analgesic	Tylenol (acetaminophen)
Short-acting narcotics/opiates	Darvocet-N (propoxyphene) Various brands containing oxycodone, codeine or hydrocodone
Long-acting narcotics/opiates	MS Contin (morphine sulfate) Kadian (morphine sulfate) Avinza (morphine sulfate) Duragesic (fentanyl transdermal patch)
Narcotic-like analgesics	Ultram (tramadol) Ultracet (tramadol with acetaminophen)
Topical	Lidoderm (lidocaine transdermal patch)

treatment of attention deficit disorder, is sometimes used.

Antiemetics. Granisetron, tropisetron and ondansetron are usually prescribed for their anti-nausea and antivomiting effect. They act by inhibiting a specific serotonin receptor called 5-HT3. Although the trials in CFS patients have been limited, early positive results suggest that larger controlled studies may be justified.[17,18] These drugs aren't generally used by most clinicians who treat CFS patients.

Drugs that improve sleep

There have been no clinical trials of sleep-inducing or sleep-sustaining drugs in CFS patients. However, many different drugs of this type have been efficacious in clinical trials of other conditions, and thus offer potential benefit to CFS patients.

Drugs used to treat pain

Similar to the therapies for improving sleep, the drugs for alleviating pain haven't been specifically tested in CFS patients. The list is long, and physicians generally start with the mildest pain reliever and progress to more potent ones only if necessary.

Drugs used to treat endocrine and neuroendocrine abnormalities

Several pharmacological trials have been based on data that suggest the hypothalamic-pituitary-adrenal (HPA) axis functioning is reduced in CFS patients. This physiological system is involved in response to stress, and thus corticosteroids and factors that regulate them are targets for investigation. Orthostatic intolerance (OI) or neurally mediated hypotension (NMH) is one aspect of a disrupted HPA axis. Since the initial demonstration of abnormal tilt table tests in CFS patients, many studies have investigated drugs that mediate blood pressure or adrenal function. In an early study, 9 of 22 patients who were treated for OI responded with nearly complete or complete recovery. Results of more recent studies have been more diverse. Three studies of hydrocortisone treatment have demonstrated favorable results,[19-21] but two studies of fludrocortisone showed no improvement or no difference between drug and placebo.[22,23] In a single study comparing hydrocortisone and fludrocortisone with placebo there were no between-group differences.[24] A study that combined corticotrophin-releasing hormone (CRH) with hydrocortisone therapy showed that levels of DHEA (a precursor of sex steroids that has functions in memory, sleep and depression) correlated with self-reported disability.[25] Hydrocortisone treatment led to a reduction in these levels and increased response to CRH that was most dramatic in those who also showed a clinical response.

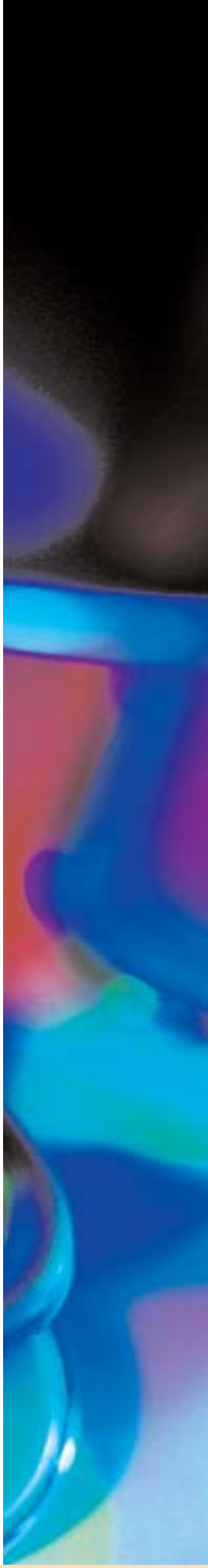
Two other drugs that increase blood pressure have been evaluated. Desmopressin in combination with CRH normalizes the HPA response.[26] A case report of midodrine, a stimulant that causes small blood vessels to contract, thus increasing blood pressure, suggested improvement of fatigue.[27]

Physicians usually start treating OI with increased dietary salt intake and increased fluids. If these aren't successful, then either fludrocortisone or hydrocortisone will be tried.

Melatonin is a hormone secreted by the pineal gland in the brain. It's necessary for regulating sleep/wake cycles, and thus was hypothesized to be helpful for CFS. One clinical study demonstrated improvement of quality of life and physical functioning in patients after treatment.[28] However, a randomized controlled trial failed to show any benefit.[29] Levels of growth hormone, secreted by the pituitary gland, were below normal in some patients with CFS. In a small, randomized, placebo-controlled clinical trial of growth hormone therapy, there was no improvement on quality of life questionnaires for the 12-week study duration.[30] Nevertheless, four patients were able to return to work.

Immunological and antiviral therapies

On the theory that CFS is a disease of impaired immunity, several trials have been conducted of gammaglobulin and immunoglobulin, both of which stimulate the immune system. Results have been mixed[31-34], but the largest trial using monthly injections of three different doses of immunoglobulin



ON THE FRONTIER

Two Studies Suggest Oral NADH May Be Helpful in Treating CFS

NADH is important for production of energy by all cells of the body. On the theory that increasing body stores of NADH will increase cellular stores of ATP, two small randomized clinical trials (RCTs) have been conducted.

The first trial[47] followed 26 CFS patients who met the Fukuda criteria and ranged in age from 20 to 70 years. They were selected from referrals or recruited from the Division of Allergy-Immunology at the Georgetown University Medical Center in Washington, D.C. Patients were assigned to receive NADH or a placebo in a randomized, double-blind, crossover protocol that lasted for 12 weeks. For the first 4 weeks patients were given placebo or NADH; the second 4 weeks no study treatment was given; and the last 4 weeks the patients were switched to receive the alternate treatment. Laboratory tests were performed and an in-house clinical well-being questionnaire was administered. A patient was considered improved if she/he demonstrated at least 10% improvement on the questionnaire. Of the CFS patients treated with NADH, 31% improved by at least 10%, whereas only 8% of those treated with placebo reached this level of improvement.

It should be noted that this group of patients had a high incidence of allergies. Nevertheless, the authors concluded that this pilot study should be followed with larger clinical trials.

The second study[48] followed 31 patients in Puerto Rico who were selected on the basis of the Fukuda criteria. They were randomly assigned to receive either NADH or nutritional supplements along with psychological therapy for 24 months. Patients were assessed at 8-month intervals. Twelve patients who received NADH improved dramatically with a statistically significant reduction on their mean symptom score during the first interval. After that, the scores were similar in the placebo and NADH groups.

The authors concluded that a larger study should be conducted.

showed no benefit to any of the self-reported measures or the Karnofsky performance scale.[32]

Ampligen, a double-stranded RNA with both antiviral and immunomodulatory activities, is still experimental and not generally available. Early reports were positive, and some patients have benefited,[35] but the results of large Phase III trials haven't yet been published by the manufacturer, Hemispherx Biopharma. There are reports that the exercise treadmill duration and maximum oxygen utililization improved with Ampligen compared to placebo in the trials.

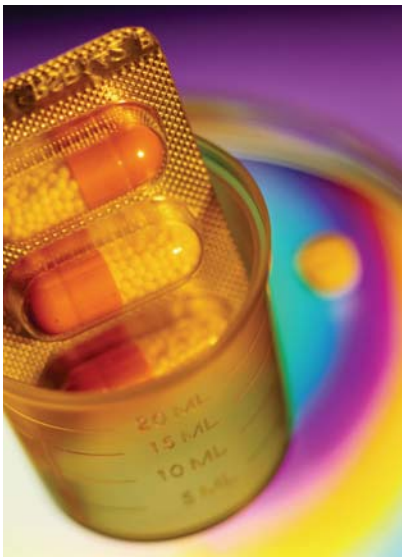
Terfenadine, a nonsedating antihistamine wasn't effective in one randomized clinical trial.[36] It has been taken off the market because of possibly dangerous side effects when taken with certain cardiac drugs. Alpha-interferon is produced by the immune system during viral infection. Treatment with 2*a*-interferon offered benefit only to the CFS patients who had NK cell dysfunction in a single randomized clinical trial.[37]

Two studies have evaluated response to injections of Staphylococcus toxoid, an immune system stimulant.[38,39] The larger trial[38] showed that 65% of the intent-to-treat group responded with improved global ratings and symptom reduction, whereas only 18% of the placebo group did. However, fibromyalgia and CFS patients weren't analyzed separately in this study.

Based on the observation that CFS is often associated with a viral infection at its outset, several antiviral agents have been studied.[40-44] Results have been mixed with regard to subjective improvement scores and virus titers. In general, physicians only treat with antivirals or antibiotics if there's clinical evidence of a viral or bacterial infection.

Dietary supplements

Physicians wish to promote good general health in their CFS patients, so a multivitamin is always recommended. Some physicians also recommend other nutritional supplements such as NADH, high-dose vitamin B12 and essential fatty acids. Other physicians may not recommend such supplements, but are agreeable if the patient wants to use them as long as there is no danger of interfering with other drugs the patient may be taking.



Essential fatty acids (EFA). Fish oil, primrose oil and flaxseed oil are rich in EFAs. In 1990 a randomized placebo-controlled clinical trial of high-dose EFAs (as fish oil) suggested that patients with postviral fatigue improved in self-assessment questionnaires.[45] However, when the same treatment was tested nine years later in patients who adhered to the Oxford Criteria for CFS, there was no

DRUG (Brand/Generic)	YEAR	TYPE OF STUDY	NUMBER OF SUBJECTS	MAJOR OUTCOME
Mood/Cognition				
Prozac (fluoxetine)	1996	RCT	96	No improvement in any dimension of CFS[3]
	1998	RCT	96	Improved only depression[4]
Wellbutrin (bupropion)	1992	Open label	9	Improved Hamilton Depression Rating Scale[5]
Manerix (moclobimide)	2000	RCT	90	Subjective improvement in energy[7]
	1997	CT	49	Modest overall improvement[6]
Serzone (nefazodone)	1999	CT	10	Some improvement in fatigue, sleep, mood[8]
	1999	Case study	3	Improved sleep, pain, NK cell function[9]
Carbex (selegiline)	1998	CT	25	Improved mood and reduced fatigue[10]
Dexamphetamine	2003	RCT	20	Improved fatigue severity scale scores[12]
Razadyne (galantamine hydrobromide)	2004	RCT	434	No difference between placebo and drug in the Clinical Global Impression Scale[16]
Novoban (tropisetron) and Zofran (ondansetron)	2000	CT	20	Improved visual analog scales for fatigue[18]
Neuroendocrine/Endocrine				
Florinef (fludrocortisone)	2001	RCT	100	No difference between groups in Global Wellness[22]
	1998	RCT	25	No improvement in severity, functional measures[23]
Cortef (hydrocortisone)	2001	RCT	64	Increased leptin levels correlated with positive therapeutic response[19]
	1999	RCT	32	Reduced fatigue and disability[20]
	1999	RCT	70	Higher average Global Wellness score, but adverse side effects[21]
Hydrocortisone/fludrocortisone	2003	RCT	100	No difference in fatigue or well-being[24]
Fludrocortisone and other agents directed at NMH	1995	Open	23	Complete recovery in 9 patients[64]
CRH/hydrocortisone	2004	CT	32	Improvement in fatigue correlated with increased response of DHEA to CRH[25]
ProAmatine (midodrine)	2004	Case study	1	Reduced fatigue; corrected dysautonomia[27]
Melatonin	2002	RCT	30	No improvement of symptoms or health measures[29]
	2002	CT	38	Improved several Quality of Life scores[28]
Growth hormone	1998	RCT	20	No Quality of Life improvement[30]
Immunological & Antiviral				
Gammagobulin	1997	RCT	71	Functional improvement[31]
Immunoglobulin	1997	RCT	99	No improvement[32]
	1990	CT	30	No improvement in symptoms or function[33]
	1990	RCT	49	Improvement in physical, immune measures[34]
Ampligen (Poly(I)-Poly(C))	1994	RCT	92	Increased global performance and cognition scores[35]
	??			
Staphylococcus toxoid	2002	RCT	100	Increased responders for symptom reduction[38]
	1998	CT	28	Improvement in CPRS[39]
Alpha-interferon	1996	RCT	30	Improved QOL in those with NK cell dysfunction[37]
Isoprinosine	2003	CT	16	Clinical improvement; increased NK cell activity[44]
Zorivax (acyclovir)	1988	CT	27	Subjective improvement; EBV titers unchanged[41]
Valtrex (valacyclovir)	2002	Pilot study	25	Improvement in EBV virus titers[42]

What's Been Studied?

This chart lists some prescription and non-prescription therapies that have undergone clinical testing in CFS patients. It's not intended to be comprehensive.

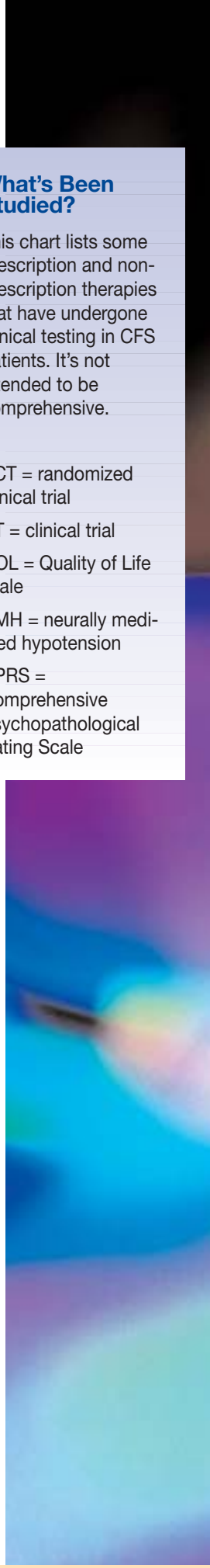
RCT = randomized clinical trial

CT = clinical trial

QOL = Quality of Life scale

NMH = neurally mediated hypotension

CPRS = Comprehensive Psychopathological Rating Scale



significant improvement.[46]

Energy supplements. Nicotinamide adenine dinucleotide (NADH) is a coenzyme made from vitamin B2 (niacin). It's necessary for energy metabolism and normal enzyme function. Two randomized, placebo-controlled clinical studies have suggested that this therapy may be helpful in some patients to increase energy or decrease fatigue.[47,48] Carnitine is essential for energy production in mitochondria, which are the powerhouses of cells. Several forms of carnitine tested in randomized clinical trials have suggested improvement of symptoms.[40,49]

Other nutritional supplements. Glyconutrients (simple sugars) have been tested *in vitro* on cells from CFS patients.[50] Although there was improved cell functioning, the effects on the patients weren't measured. In a Japanese case study, magnesium treatment reduced fatigability and improved daily functioning.[51] Two clinical trials reported that magnesium supplementation increased red blood cell magnesium stores,[52,53] and patients in a RCT reported improved energy levels and less pain.[53]

Two supplements, one of magnesium, calcium, B vitamins and vitamin C ("Myers' cocktail")[54] and the other of mixed phosphate salts[55] had a positive outcome in two case reports. A single case report of vitamin C infusion suggested increased function,[56] but a randomized clinical trial of liver extract offered no improvement over placebo.[57]

Coenzyme Q10 is a cofactor in many enzymatic reactions and is reported to have antioxidant properties. A single open-label study in 115 fatigued patients, 28 of whom had CFS, reported some improvement in all subjects.[58]

Herbal remedies

Five studies have evaluated five different compounds: bojungikki-tang, Echinacea, ginseng, Kuibitang and aloe vera extract. There are many chemicals in each of these supplements, and it's not known which one may be responsible for the observed effect. Use of these compounds isn't regulated by any drug safety organization, so potential risks are unknown. In effect, each is a mixture of untested pharmacological agents. Although some may be harmless, CFS patients should always consult a health care professional before using them to find out if their physician has any experience with the chosen agent or knows of any potentially harmful interactions with other drugs the patient is taking.

Three studies were performed *in vitro*, that is using cells from CFS patients.[59-61] Consequently, the effects of these agents on the patient aren't known. However, the results were positive and may foster clinical trials.

When Siberian ginseng was tested in a randomized placebo-controlled clinical trial of 96 subjects, patients with moderate fatigue and patients with fatigue of five years or less duration experienced some improvement.[62] The selection of study subjects was based on the requirement of having fatigue that had lasted more than six months, and 70% of subjects were classified as having a CFS-like illness, not CFS. In another study, 50 subjects were evaluated after they had self-selected various aloe vera and vegetable/fruit containing extracts.[63] The subjects noted reduction of symptom severity.

Summary

It's apparent that the number of clinical studies of prescription and nonprescription drugs in patients with CFS is small. Nevertheless, because the symptomatology of CFS shares aspects with other diseases, the number of drugs in the physicians' armamentarium is large. Clinical trials of these drugs have shown their efficacy in treating particular symptoms, and this is the basis upon which the physician builds an individualized treatment regimen.

As one study aptly states: "The pursuit of symptom relief in the absence of supportive clinical trials is a strong indication of the desire of CFS patients to improve or to alleviate their symptoms and should serve as impetus for further research into the origins, consequences and treatment of fatiguing illnesses."[1] ■

This is an online bonus to the 2005/2006 special issue of the CFIDS Chronicle, the Science & Research of CFS. Copies of this 65-page special issue can be ordered (while supplies last). 704-365-2343 or www.cfids.org

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