

This is a free abridged eBook version of my book *Reviving the Broken Marionette: Treatments for CFS/ME and Fibromyalgia*, published in 2008. The original book has 346 pages and is available both in print and as an eBook. It contains descriptions of all the drugs featured here, as well as all the different drug groups and types.

Besides most descriptions, this free version also omits a lot of other content, such as the Preface, Introduction, a short section where I discuss the terminology I use (CFS/ME/fibromyalgia), three appendices (Drug interactions, Surgery and Vaccinations), Glossary and Index, as well as all the references—more than 1,000 in total.

For this eBook the contents of the book have not been otherwise altered, except that I have added asterisks to mark drugs that are commonly available over-the-counter. (In the original book there is more detailed availability information for all the drugs.)

The book's website is at <http://www.brokenmarionettebook.com>. The printed book can be purchased from Amazon and most other online bookstores, but for the full eBook version you have to go to the book's website.

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CHAPTER 1.

Sleep aids, tranquilizers and muscle relaxants

CFS/ME and fibromyalgia are frequently associated with major sleep disturbances. This is even a part of the Canadian diagnostic criteria for CFS/ME.¹ Most likely the disordered sleep is not the cause of the fatigue or other symptoms, but it can often worsen them and lower quality of life. Even modest sleep deprivation increases the secretion of inflammatory cytokines such as IL-6, which can contribute to pain, fatigue, malaise and flu-like symptoms.² IL-6 in particular causes muscular hyperalgesia (heightened sensitivity to pain).

The sleep problems can include low quality of sleep, sleep apnea, insomnia, hypersomnia and hypnagogic states. Other related problems such as nocturia and involuntary movements are also common. According to Dr. Robert Bennett restless legs syndrome is the most common sleep disorder in fibromyalgia and up to one fifth of the patients suffer from sleep apnea.³

Patients often experience frequent awakenings during the night and cannot easily fall asleep again. Thus quick-acting medications may not always be of much help. The quality of sleep may suffer because of frequent need to urinate. In such cases medication for nocturia should be considered.

The “Z drugs”

zolpidem (Ambien, Stilnoct, Stilnox, Zoldem, Ivadal)

As the half-life of zolpidem is only 2–3 hours, some patients may wake up at night and cannot fall asleep again. Compared to the other Z drugs zolpidem appears to be slightly more effective, better tolerated and less likely to lead to rebound insomnia on discontinuation.⁵ Jay Goldstein notes that zolpidem works as an effective analgesic for some patients and is sometimes activating.⁶

A small double-blind study concluded that zolpidem improved sleep and daytime energy levels in patients with fibromyalgia, but other symptoms such as pain, tender points and morning fatigue did not get better.⁷ Patients in the placebo group actually reported more adverse effects than those getting zolpidem. In a large survey of fibromyalgia patients zolpidem was ranked as one of the most effective medications.⁸ Zolpidem may also help nocturia⁹ and restless legs.¹⁰

Paradoxically, in some cases zolpidem is able to arouse people diagnosed as being in a permanent vegetative state (a deep comatose state thought to have almost zero hope of awakening).¹¹ This may seem to bear no relevance to CFS/ME and fibromyalgia, but later the drug has been shown to help many other neurological conditions as well, such as Bell’s palsy and Parkinson’s disease.¹² It can be hypothesized that zolpidem might be worth a try in severe CFS/ME. Other similar sedative drugs do not appear to be effective in this use.

Carbamazepine, phenytoin,azole antifungals, many different antibiotics, nefazodone and verapamil may either decrease or increase the blood levels of zolpidem.

Zolpidem is available in the United States, the United Kingdom, Australia and many other countries, but not in Canada. It is very inexpensive. A quick acting oral spray formulation is waiting for FDA approval.

zaleplon (Sonata, Starnoc, Zalep, Zaplon, Zerene)

zopiclone (Imovane, Zimovane, Zileze, Zopiclone)
eszopiclone (Lunesta)

Benzodiazepines

diazepam (Valium, Stesolid, Diazepam, Apaurin, Seduxen)

alprazolam (Xanax, Alprox, Frontin, Helex, Tafil)

temazepam (Restoril, Normison, Euhypnos, Remestan, Levanxol)

clonazepam (Klonopin, Rivotril, Paxam, Clonapam, Antelepsin)

Clonazepam is a stronger anticonvulsant and muscle relaxant than most other benzodiazepines. It is probably the most commonly used benzodiazepine in CFS/ME and fibromyalgia. Usually a small dose of 0.5 mg is prescribed. Paul Cheney, one of the most prominent CFS/ME specialists, swears by clonazepam. According to him very small doses during the daytime can improve energy levels.²⁵ He believes this to be because of the inhibitory effect GABA has on the NMDA receptors, reducing excessive nitric oxide production.

Clonazepam is also recommended by Charles Lapp, another CFS/ME expert.²⁶ He believes the best sleep aid is a combination of clonazepam to induce sleep and trazodone to maintain sleep. In a fibromyalgia newsletter published in 1999 nine experts listed the treatments they considered the most helpful and clonazepam made it to six lists.²⁷ This opinion is also shared by the fibromyalgia patients, who ranked clonazepam among the most effective medications in a large survey.²⁸

Because of its muscle relaxant properties clonazepam is often used to treat pain similar to diazepam. Some patients with CFS/ME note improvement in both cognitive symptoms and flu-like pains and aches.²⁹ Clonazepam proved helpful for dysautonomia of CFS/ME in a small study.³⁰ It often works for restless legs³¹ and sometimes for skin tenderness and headaches.³² Dr. David Bell believes clonazepam is effective for those who feel “tired and wired,” but not for the sleepy– fatigued type.³³

Carbamazepine, phenytoin and St. John’s wort can decrease andazole antifungals, macrolides, diclofenac, nefazodone and verapamil increase the blood levels of clonazepam.

Clonazepam is available in the United States, the United Kingdom, Canada, Australia and many other countries. It is very inexpensive.

lorazepam (Ativan, Merlit, Lorans, Temesta, Lorapam)

triazolam (Halcion, Trycam)

Other sleep aids

See also:

anticonvulsants (CHAPTER 3), trazodone, mirtazapine, mianserin, olanzapine, risperidone, quetiapine (CHAPTER 5), dextromethorphan, cholinesterase inhibitors, hydroxyzine, diphenhydramine, doxylamine, cannabinoids, parenteral magnesium, ranitidine/cimetidine, granisetron/tropisetron/ ondansetron (CHAPTER 9), acamprosate

(CHAPTER 10)

melatonin (Transzone, Circadin)*

ramelteon (Rozerem)

sodium oxybate (Xyrem, Alcover)

Sodium oxybate (gamma–hydroxybutyrate) is an endogenous substance which has been used as an anesthetic. Unfortunately it has gained a questionable reputation owing to its use as a recreational and “date rape” drug. It is only lately that it has been approved for the treatment of narcolepsy and specifically the cataplexy attacks caused by the condition.

Sodium oxybate is a highly effective sleep aid and helps many people whose insomnia is not relieved by other agents. It is a powerful muscle relaxant and may act as an antidepressant. It increases growth hormone secretion.⁵³ In studies with FM patients sodium oxybate has not only improved quality of sleep but fatigue and pain as well.^{54,55,56,57} Trials of the drug in CFS/ME and several more for fibromyalgia were running at the time of the writing.

Despite its bad reputation sodium oxybate is a safe, well–tolerated and non–addictive drug when used according to the instructions. Most people experience no morning “hangover” of any kind. Side effects can include nausea, confusion, headache, tremor and dizziness. Sodium oxybate has no known metabolic interactions with other substances, but taking it with any other sedatives (including alcohol and muscle relaxants) is dangerous.

Sodium oxybate is available in the United States, Canada, the United Kingdom and some other European countries, but not Australia. It is very expensive and thus most likely inaccessible to patients lacking insurance or those whose insurance does not cover it.

Muscle relaxants

See also:

clonazepam, diazepam, sodium oxybate (CHAPTER 1), flupirtine, thiocolchicoside (CHAPTER 2), gabapentin, pregabalin (CHAPTER 3), cannabinoids, parenteral magnesium (CHAPTER 9)

tizanidine (Zanaflex, Sirdalud)

orphenadrine (Norflex, Disipal, Biorphen, Relaflex)

baclofen (Lioresal, Liotec, Baclofen, Clofen)

Baclofen is an agonist of the GABA_B receptor. It is used to treat spasticity in e.g. multiple sclerosis. Baclofen may also help to relieve aches, cramps and related symptoms of CFS/ME and fibromyalgia, including muscle weakness. Like sodium oxybate/GHB, baclofen increases the secretion of growth hormone⁶⁶ and this response in CFS/ME does not differ from that in the healthy persons.⁶⁷ Baclofen can also help bladder problems⁶⁸, GERD (acid reflux)⁶⁹ and trigeminal neuralgia.⁷⁰

Dr. Jay Goldstein believes that baclofen is one of the most effective treatments for CFS/ME (especially for pain, including headache) and he uses a dose of 10–20 mg three times a day.⁷¹ He has found it helpful

for anxiety and sometimes for fatigue too. If baclofen produces adverse effects, he suggests trying estrogen, oxytocin, mexiletine or reboxetine, which have somewhat opposite effects.⁷² Dr. David Bell has found that baclofen does not work very often, but when it does, the results can be dramatic.⁷³

Baclofen can lower blood pressure, which may be problematic for many patients with CFS/ME. Drowsiness, dizziness and nausea are common side effects. Some people may experience a worsening in muscle weakness, especially if they also use tricyclic antidepressants. The treatment should not be discontinued abruptly, as that may lead to seizures or other withdrawal symptoms.

Baclofen is available in the United States, the United Kingdom, Canada, Australia and many other countries. It is inexpensive.

carisoprodol (Soma, Carisoma, Somadril)

cyclobenzaprine (Flexeril, Flexitec, Flexiban)

chlorzoxazone (Parafon Forte, Paraflex)

metaxalone (Skelaxin)

methocarbamol (Robaxin)

dantrolene (Dantrium, Dantrolen, Dantamacrin)

CHAPTER 2.

Painkillers

Non-specific anti-inflammatory drugs (NSAIDs)

aspirin (Aspirin, Bayer Aspirin, Aspro, Aspirina, Disprin)*

ibuprofen (Advil, Motril, Brufen, Nurofen, Ibutop)*

naproxen (Aleve, Anaprox, Naprosyn, Proxen, Apranax)*

indometacin (Indocin, Indocid, Elmetacin, Indocollyre, Indogestic)

piroxicam (Feldene, Candyl, Piroxicam, Felden, Artrilase)

meloxicam (Mobic, Movalis)

etodolac (Lodine, Elderin)

nabumetone (Relafen, Relifex, Nabugesic, Naburen)

diclofenac (Voltaren, Cataflam, Almiral, Diclac, Diclogestic)*

Diclofenac is well tolerated and because of its selectivity for COX-2 it has a lower risk for gastrointestinal complications than most other NSAIDs. It is usually taken 2–3 times a day. It is believed to have anti-inflammatory modes of action that other NSAIDs do not have.

Diclofenac has been shown to increase plasma levels of beta endorphin.¹⁸ This may be helpful for both pain and other symptoms. One study found diclofenac effective against *E. coli* bacteria and suggested it as a treatment for urinary tract infections.¹⁹ Headache, dizziness and itchiness are fairly common side effects. The risk of liver toxicity may be higher with diclofenac compared to other NSAIDs.

Diclofenac is available virtually everywhere. Many different preparations exist, including immediate release and modified release tablets, gels, creams, suppositories, sprays and patches. Oral forms are inexpensive. Diclofenac is available over-the-counter in Germany, Australia and New Zealand, but is usually prescription-only. Topical creams and gels are often available over the counter. In Arthrotec diclofenac is combined with misoprostol (see CHAPTER 10). In some European countries a combination of diclofenac and codeine is sold as Combaren.

flurbiprofen (Ansaid, Froben, Flugalin)

celecoxib (Celebrex, Celebra)

etoricoxib (Arcoxia, Tauxib)

Narcotic painkillers

codeine (Tricodein, Codicaps)

oxycodone (OxyContin, Roxicodone, Proladone, Oxynorm)

hydrocodone (Vicodin, Lortab)

hydromorphone (Dilaudid, Palladone, Palladon, Opidol)

morphine (Avinza, Kadian, Kapanol, Skenan, Oramorph)

fentanyl (Duragesic, Durogesic, Actiq, Fentanyl, Sublimaze)

methadone (Dolophine, Methadose, Physeptone, Metadon, Metadol)

pethidine/meperidine (Demerol, Dolantina)

buprenorphine (Buprenex, Subutex, Temgesic, Transtec, Butrans)

dextropropoxyphene/propoxyphene (Darvon, Doloxene, Depronal, Abalgin)

tramadol (Ultram, Zydol, Tramal, Zytrim, Tradonal)

pentazocine (Talwin NX, Fortral, Fortal)

Pentazocine is an atypical opioid, which only has weak affinity for the mu opioid receptor, but acts as an agonist of the kappa opioid receptor and the sigma₁ receptor. It is rarely prescribed and its primary use is the treatment of mild to moderate pain. It is less prone to causing sedation, nausea and hypotension compared to typical opioids. Sigma₁ agonists may be useful in the treatment of depression and cognitive problems. ⁴² Pentazocine has also demonstrated anticonvulsive action.⁴³

Jay Goldstein lists many different possibly beneficial mechanisms for pentazocine in the treatment of CFS/ME and fibromyalgia, not as a painkiller but for general symptom relief.⁴⁴ According to him it works for some patients for whom all other treatment has failed. He includes

two case reports of seriously ill patients refractory to other treatments, whose symptoms were greatly relieved after just one pill of pentazocine and naloxone.

Pentazocine is more likely than other opioids to cause hallucinations and other psychiatric side effects. It has been suspected to cause adverse effects when combined with the muscle relaxant orphenadrine. Smoking may reduce blood levels of the drug.

Pentazocine is available in the United States, the United Kingdom, Canada, Australia and some other countries. In the United States pentazocine is only sold in combination with naloxone, an opioid antagonist. Because naloxone is not absorbed from the stomach, this does not affect the efficacy of the drug, but prevents intravenous administration. In spite of this, pentazocine is a Schedule IV drug in the United States.

Migraine and headache treatments

See also:

melatonin, muscle relaxants (CHAPTER 1), NSAIDs, acetaminophen (paracetamol), narcotic painkillers, botulinum toxin, Sarapin (CHAPTER 2), anticonvulsants (CHAPTER 3), tricyclic antidepressants, moclobemide, phenelzine, buspirone, L-tryptophan/5-hydroxytryptophan, lithium (CHAPTER 5), clonidine, beta blockers, calcium channel blockers (CHAPTER 6), nicergoline, ergoloid (CHAPTER 7), DHEA, naltrexone (CHAPTER 8), NMDA antagonists, cholinesterase inhibitors, cinnarizine, cannabinoids, parenteral magnesium, acetazolamide (CHAPTER 9), montelukast, telmisartan, captopril (CHAPTER 10)

pizotifen (Sandomigran, Sanomigran, Mosegor, Pizotifen)

cyproheptadine (Periactin, Peritol, Viternum)

sumatriptan (Imigran, Imitrex, Imigrane)

naratriptan (Amerge, Naramig)

ergotamine (Ergomar, Migril)

dihydroergotamine (Migranal, Dihydergot, Seglor)

intranasal lidocaine (Altaseptic, Xylocaine)*

Intranasal lidocaine spray can be used as an abortive treatment for migraine headaches. Some studies have not found it effective, but most have demonstrated efficacy in about half of the patients.^{59,60} Lidocaine not only relieves the pain, but nausea and photophobia (light sensitivity) as well. In some patients, however, the efficacy is short-lived and the headache comes back. Local stinging and swelling is a common adverse reaction. Nausea, dizziness and sedation are also possible.

Lidocaine sprays are widely available. They are meant for numbing the mouth and the throat, but they can be used intranasally. It is inexpensive.

Other analgesics

See also: zolpidem, muscle relaxants (CHAPTER 1), anticonvulsants (CHAPTER 3), neomycin (CHAPTER 4), tricyclic antidepressants, venlafaxine, milnacipran, duloxetine, SAM-e, olanzapine (CHAPTER 5), clonidine, moxonidine (CHAPTER 7), oxytocin, naltrexone (CHAPTER 8), NMDA antagonists, cholinesterase inhibitors, cannabinoids, granisetron/tropisetron/ ondansetron, sibutramine, misoprostol (CHAPTER 9), calcitonin, ibudilast, neurotrophin, ACE inhibitors (CHAPTER 10)

acetaminophen/paracetamol (Tylenol, Panadol, Calpol, Perfalgan, Tempra)*

nefopam (Acupan)

flupirtine (Katadolon)

Flupirtine is a non-narcotic, non-NSAID analgesic drug with some muscle relaxant activity. It is used especially for chronic lower back pain. It has also shown efficacy in the treatment of headaches and migraines, cancer pain, dysmenorrhea and neuropathic pain.⁶⁴ In Germany flupirtine is sometimes used for fibromyalgia. One case series has been published about this use.⁶⁵

Flupirtine is much more than just a painkiller though; it has several properties that have been used to treat neurodegenerative illnesses such as Alzheimer's, CJD and some congenital diseases. It is thought to be an NMDA antagonist and a KPNQ potassium channel opener with some alpha₂ adrenergic action. It would thus likely work well for CFS/ME, too. A patent has been filed about the use of flupirtine for overactive bladder.⁶⁶

Flupirtine is usually well-tolerated. Dizziness, drowsiness, dry mouth, pruritus (itching) and stomach upset are the most common side effects. There can also be nausea, headache and sleep disturbances. No drug interactions are known. The only real downside is the short half-life—usually flupirtine is administered 3–4 times a day. There are currently no slow-release formulations, but perhaps one will be developed in the future.

Flupirtine is available in some European countries, such as Germany, Portugal and Italy, as well as Brazil. It is being developed as a fibromyalgia drug under the brand name Effirma by a U.S. company, with a phase II study expected soon. Thus in a few years flupirtine could be available in the United States and many other countries, but currently most patients would need to order it from abroad, as many people with neurological conditions already do. In long-term use it gets somewhat costly.

thiocolchicoside (Coltramy, Miorel, Muscoril, Miotens, Coltrax)

Topical and intravenous pain treatments

See also: ketamine, parenteral magnesium (CHAPTER 9)

botulinum toxin A (Botox, Dysport)
botulinum toxin B (NeuroBloc, Myobloc)

Sarapin (Sarracenia purpurea distillate)

lidocaine/procaine/bupivacaine injections

topical lidocaine (Lidoderm)
topical lidocaine and prilocaine (Emla)*

intravenous lidocaine

Lidocaine is also used intravenously for severe, intractable pain. It is often very effective for fibromyalgia. Dr. Jacob Teitelbaum gives 40–50 mg at first, which may be increased up to 300–400 mg per session if no serious side effects occur.⁷⁸ He notes lidocaine to be particularly helpful when given concomitantly with Myers' cocktails.

In a small double-blinded pilot study lidocaine was much more helpful than conventional treatment alone for pain, but global improvement did not reach significance.⁷⁹ A more recent and much larger study found that intravenous lidocaine provided most fibromyalgia patients with good pain relief lasting for several weeks.⁸⁰

According to Jay Goldstein this treatment helps up to 50% of the patients who have not benefited from oral medication.⁸¹ He even considers intravenous lidocaine to be the most effective treatment for CFS/ME and fibromyalgia. Besides pain, other symptoms such as fatigue, cognitive problems and gut spasms often improve, as well.

Possible side effects include dizziness, tinnitus and orthostatic hypotension. Allergic reactions may occasionally occur. Goldstein stresses that the infusion has to be given very slowly, because otherwise there can be adverse reactions and afterwards the patient will never respond to lidocaine again.⁸²

Lidocaine is available everywhere, though the availability and cost of this treatment in practice may vary.

capsaicin (Zostrix, Axsain)*

CHAPTER 3.

Anticonvulsants

Anticonvulsants (also known as antiepileptic drugs) are used in the prevention of epileptic seizures, which can sometimes accompany CFS/ME. They have many possible modes of action, often several different ones in a single drug, and their ability to prevent different types of seizures (partial seizures, complex seizures and absence seizures) varies. Some anticonvulsants can even worsen some types of seizures.

Despite their different modes of action, almost all anticonvulsants can be used to treat chronic pain, bipolar disorder and for migraine prophylaxis. Many of them are effective for depression, anxiety and sleep problems. Anticonvulsants can also relieve fatigue, flu-like symptoms, cognitive problems, neurological symptoms, IBS, bladder problems and muscle tension. They are one of the most important classes of medications in the treatment of CFS/ME and fibromyalgia.

Different anticonvulsants have completely different side effect profiles. Almost all can cause sedation and dizziness and rarely “freaky” side effects (strange cognitive and neurological reactions), but some of them can also cause life-threatening adverse reactions. Many older anticonvulsants adversely affect bone strength. Carbamazepine, oxcarbazepine and valproate can also impair male fertility.¹

See also: diazepam, clonazepam, melatonin (CHAPTER 1), pentazocine (CHAPTER 2), selegiline (CHAPTER 5), vinpocetine (CHAPTER 6), calcium channel blockers (CHAPTER 7), riluzole, cannabinoids (CHAPTER 10)

carbamazepine (Tegretol, Teril, Finlepsin, Neurotop, Timonil)

oxcarbazepine (Trileptal, Oxcarbatol, Apydan)

valproate (Depacon, Deprakine, Epilim, Valpakine) valproic acid (Depakene, Depakine, Convulex) divalproex (Depakote, Epival)

gabapentin (Neurontin, Gabaran, Gabax)

pregabalin (Lyrica)

vigabatrin (Sabril, Sabrilex)

tiagabine (Gabitril)

lamotrigine (Lamictal, Elmendos)

Lamotrigine primarily works by binding to voltage-sensitive sodium channels and blocking excess glutamate release. It also binds to the sigma receptors to some extent and weakly antagonizes the 5-HT₃ serotonin receptors. It is a common treatment for bipolar disorder, especially if depression predominates. It can be used to treat chronic pain, especially neuropathic pain, and may be useful in some refractory cases. Lamotrigine improves the quality of sleep, especially by increasing the amount of REM sleep.³⁶

Perhaps owing to these multiple modes of action lamotrigine is a medication that improves the condition of many CFS/ME patients. At best the patient can reach almost full remission. The dose used to treat CFS/ME varies from the 25–50 mg used by Jay Goldstein up to 300– 400 mg a day. Jacob Teitelbaum feels that doses below 200 mg a day are not effective.³⁷ Lamotrigine may be useful in PTSD³⁸ and migraine, especially migraine with aura.³⁹ It also has some antiviral action against HHV–6.⁴⁰

When using lamotrigine it is important to consider the possibility of life–threatening rash (Stevens–Johnson syndrome) and begin the treatment with a very low dose which is slowly titrated up. One problem is that up to 1/10 of patients get some kind of a rash from lamotrigine, which is usually a harmless one without fever and other symptoms, but often the medication is discontinued anyway. Most patients can continue taking the drug if it stopped until the rash has healed and then reintroduced even more slowly.

Headache, dizziness and vision impairment are common side effects when using larger doses. Nervousness, nausea, stomach upset, drowsiness, insomnia, muscle aches and tremor are also seen fairly often. Many other drugs can markedly either slow down or speed up the metabolism of lamotrigine so one has to be careful when trying new drugs, especially other anticonvulsants, when on lamotrigine. Acetaminophen (paracetamol) should not be used with lamotrigine.

Lamotrigine is widely available and the smallest tablets only contain 5 mg of the drug. Different “starting kits” are also available.

Lamotrigine is fairly inexpensive.

topiramate (Topamax, Topimax)

zonisamide (Zonegran, Excegran)

levetiracetam (Keppra)

felbamate (Felbatol, Taloxa)

phenytoin (Dilantin, Hydantin, Phenytek, Epanutin)

CHAPTER 4.

Antimicrobials

Antibiotics

See also:

cholestyramine, pioglitazone/rosiglitazone, erdosteine, probenecid, fibrinolytic enzymes (CHAPTER 10)

doxycycline (Vibramycin, Vibramicina, Doryx, Dotur, Unidox)

minocycline (Minocin, Minomycin, Arestin, Cyclomin, Minotab)

Minocycline has an even broader spectrum than other tetracyclines. Its long half-life and good penetration through the blood-brain barrier are definite benefits. It is often used to treat mycoplasma, borrelia and other chronic infections. In Marshall protocol minocycline is combined with olmesartan and vitamin D avoidance with the aim of a permanent cure.¹⁹ Minocycline has also shown efficacy in “post Q fever fatigue syndrome.”²⁰

Minocycline exerts stronger anti-inflammatory activity than other tetracyclines or other types of antibiotics and has neuroprotective properties as well. It suppresses the secretion of IL-6, a major inflammatory cytokine.²¹ It has been successfully tried as a treatment for e.g. multiple sclerosis²², Alzheimer’s disease²³, rheumatoid arthritis²⁴ and even schizophrenia.²⁵ In animal studies minocycline also shows analgesic action.²⁶

The side effects and drug interactions are similar to doxycycline, but minocycline is more likely to cause the rare side effect of increased intracranial pressure. Dizziness is a common side effect. Minocycline can sometimes cause skin discoloration. Despite its efficacy in several autoimmune diseases, several cases of minocycline-induced autoimmune hepatitis and systemic lupus erythematosus-like syndrome have been reported.²⁷

Minocycline is available in the United States, the United Kingdom, Canada, Australia and some other countries. It is fairly expensive in most places.

azithromycin (Zithromax, Zitromax, Aziwok, Aruzilina, Sumamed)

clarithromycin (Biaxin, Klacid, Klaribac, Klaricid, Fromilid)

metronidazole (Flagyl, Metronidazol, Metronidazole, Metrogyl, Klion)

rifaximin (Xifaxan, Normix, Zaxine, Spiraxin, Rifacol)

neomycin (Neo-Rx, Mycitracin)*

cycloserine (Seromycin, Cycloserine, Closina)

Antivirals

See also: immunomodulators (CHAPTER 8), amantadine (CHAPTER 9), probenecid (CHAPTER 10)

aciclovir (Zovirax)

valaciclovir (Valtrex, Valavir)

Valaciclovir has better oral absorption compared to aciclovir and does not require as frequent administration. In a six-month trial valaciclovir was given to 16 CFS/ME patients who had evidence of a persistent EBV infection and they got better.⁷¹ Nine other patients in the trial had both EBV and CMV and they failed to improve. Later a double-blinded study with three-year follow-up showed that valaciclovir was more effective than placebo for CFS/ME patients with EBV.⁷²

Another small study tried both valaciclovir and ganciclovir on 11 patients who suffered from concomitant EBV and CMV infection. All the participants improved and none suffered major adverse effects.⁷³ In general valaciclovir is fairly well tolerated. Valaciclovir has also been tried in fibromyalgia in a double-blind study, but it did not result in any benefit.⁷⁴

Valaciclovir is available in most countries. It is more expensive than aciclovir, but because of the better absorption and less frequent administration the real cost is quite similar.

ganciclovir (Cytovene, Cymevene)

valganciclovir (Valcyte, Valixa)

famciclovir (Famvir)

foscarnet (Foscavir)

cidofovir (Vistide)

ribavirin (Copegus, Rebetol)

Antifungals

nystatin (Mycostatin)

Nystatin is an antifungal which is only used topically for fungal infections of the gastrointestinal tract (including the mouth), as it is not absorbed into the body. It is a popular medication in the treatment of CFS/ME and a large number of patients report having been helped by it.⁹³ Andrew J. Wright prescribes his patients 1–2 tablets four times a day to be used for 2–6 weeks.⁹⁴

In a double-blinded study nystatin was found helpful for “polysymptomatic patients” (people with many different symptoms in different organ systems).⁹⁵ The most striking effect was found for mental, abdominal and urogenital symptoms. Those who also followed a sugar and yeast free diet in addition to nystatin got the most benefit.

Nystatin is low on side effects because of the lack of systemic absorption, but in rare cases it can cause stomach upset and allergic reactions. According to Dr. Jacob Teitelbaum the yeast die-off may provoke unpleasant symptoms, which is why he prescribes pioglitazone as needed.⁹⁶ There are no known drug interactions or contraindications (except for allergy to the product).

Nystatin is available in virtually all countries, though the availability of different forms (e.g. suspension, pastilles, tablets, ointments) varies widely. Usually pure powder form is recommended.

ketoconazole (Nizoral, Fungoral, Oronazol, Ketazol)

fluconazole (Diflucan, Fungata, Mycosyst, Flucomicon, Baten)

itraconazole (Sporanox, Orungal, Isox)

CHAPTER 5.

Psychiatric drugs

Antidepressants are among the medications most frequently used to treat both CFS/ME and fibromyalgia and also the ones most frowned upon by the patients—often for a reason. It is commonly assumed that antidepressants are used to treat these conditions because they are believed to be psychosomatic or psychiatric in origin. This may be true in many cases, but these medications do have valid uses.

Serotonin is much more than just a neurotransmitter that regulates mood. It could be called one of the “master commanders” of the body, as it plays a role in a wide variety of biological functions. Dopamine and norepinephrine (noradrenaline) are important for vigilance and alertness. Antidepressants can be used as immunomodulators, to ameliorate fatigue, to improve sleep and to alleviate chronic pain. Especially the newer antidepressants can also relieve cognitive problems.

Antidepressants have many pharmacological properties that are not widely known. One study found that antidepressants of three different classes downregulated the nitric oxide pathway by inhibiting the NMDA receptor.¹ Some opioidergic action has also been demonstrated.² These effects may explain some of the antidepressant and analgesic properties of the drugs.

There are several practical benefits to antidepressants and some other psychiatric drugs. Excluding some of the newest ones, most of them are very inexpensive. The majority of doctors are familiar with psychiatric drugs and almost any physician agrees to prescribe them—something that cannot be said about all CFS/ME and FM treatments. They are not the most effective therapy and probably not the first-line choice in most cases, but sometimes they prove invaluable.

Of course, many people with CFS/ME and FM do suffer from depression or anxiety. Sometimes antidepressants can help these symptoms, even if the more physical ones are untouched. Nonetheless the depression in most cases is secondary to the burden of the illness and thus it is more useful to treat the person as a whole. Pain and disordered sleep can be the root causes for depression and anxiety. Treating them effectively may provide full relief from psychiatric comorbidities.

One must be careful when prescribing psychiatric medications, as they frequently cause problems for people with these illnesses, especially CFS/ME. Some patients get severe adverse reactions from every single kind of antidepressant. If a few different medications have provoked serious side effects, it often means that the rest would also do more harm than good. Usage should always begin with tiny doses, often doses that would be completely ineffective for the majority of healthy people.

Most psychiatric medications also have the potential to cause significant drug-to-drug interactions, particularly some of the tricyclic antidepressants and SSRIs. Generally the serotonergic drugs (drugs that affect serotonin levels, which includes almost all antidepressants) should not be combined with sibutramine, dextromethorphan, tramadol, many migraine drugs and St. John’s wort without physician’s approval.

This chapter also details the use of some other psychotropic medications, such as neuroleptics and lithium. These drugs carry even more of a stigma than antidepressants, but they may have similar beneficial effects and should not be ignored because of prejudice.

See also: benzodiazepines, orphenadrine (CHAPTER 1), anticonvulsants (CHAPTER 3), cycloserine (CHAPTER 4), piracetam/aniracetam (CHAPTER 6), ketamine, cannabinoids (CHAPTER 9), scopolamine, aprepitant, losartan, ACE inhibitors, naphazoline (CHAPTER 10)

Tricyclic antidepressants (TCAs)

amitriptyline (Elavil, Endep, Tryptanol, Tryptizol, Saroten)

nortriptyline (Pamelor, Allegron, Noritren, Nortrilen, Aventyl)

Nortriptyline is a metabolite of amitriptyline. Compared to amitriptyline it has more effect on norepinephrine than serotonin. Because of its overall higher selectivity it is better tolerated. CFS/ME expert Dr. David Bell considers nortriptyline to have a stronger analgesic effect than amitriptyline.¹⁵ There is one published case study about the use of nortriptyline in the treatment of CFS/ME.¹⁶ A study on fibromyalgia, however, did not find the drug more helpful than placebo.¹⁷

Nortriptyline is less prone to causing orthostatic hypotension or weight gain than other TCAs. Although not as sedative as amitriptyline it can still be used as a sleep aid, but some patients find it energizing and have to take it in the morning. It appears to be less likely to cause cardiac problems compared to most other TCAs, but the noradrenergic action can cause urinary hesitancy.

Nortriptyline is available in the United States, the United Kingdom, Canada, Australia and many other countries. The generic formulations are very inexpensive.

protriptyline (Vivactil, Triptil, Concordin)

clomipramine (Anafranil, Clomipramine, Clofranil, Placil, Hydiphen)

imipramine (Tofranil, Melipramin, Iramil, Imiprex)

desipramine (Norpramin, Pertofran)

trimipramine (Surmontil, Rhotrimine, Tripres, Sapilent)

dosulepin/dothiepin (Prothiaden, Dothapax, Dothep, Thaden)

doxepin (Sinequan, Siquan, Zonalon, Deptran, Xepin)

Selective serotonin reuptake inhibitors (SSRI)

See also: methadone, buprenorphine (CHAPTER 2), dextromethorphan, diphenhydramine, chlorphenamine (CHAPTER 9)

fluoxetine (Prozac, Sarafem, Portal, Fontex, Lovan)

fluvoxamine (Luvox, Fevarin, Faverin, Dumirox, Floxyfral)

sertraline (Zoloft, Lustral, Gladem, Serlain, Altruline)

paroxetine (Paxil, Seroxat, Aropax, Paroxat, Deroxat)

Paroxetine has the strongest effect of the SSRIs on norepinephrine reuptake. Besides depression it is used to treat e.g. anxiety, OCD and PTSD. Paroxetine is not commonly used in CFS/ME or fibromyalgia, but e.g. Jay Goldstein sometimes prescribes it to his patients in doses of 10–20 mg a day.⁵³ According to him it can take between one hour and eight weeks to start working.

Paroxetine inhibits nitric oxide synthesis, which may be important in CFS/ME and fibromyalgia.⁵⁴ Martin Pall, the researcher behind the “NO/ONOO” theory which postulates excessive nitric oxide as the cause of the symptoms in these illnesses, recommends paroxetine for this reason.⁵⁵ A study about controlled release paroxetine for fibromyalgia found it useful for other symptoms, but not so much for pain.⁵⁶ Paroxetine can also be quite helpful for vasovagal syncope, a form of orthostatic intolerance that causes fainting.⁵⁷

Paroxetine often brings out insomnia, but it is also quite prone to causing drowsiness and fatigue compared to other SSRIs. It can elevate the blood levels of e.g. some TCAs, neuroleptics, beta blockers and amphetamines and potentiate the effect of anticoagulants. Some drugs such as ropinirole can elevate the blood levels of paroxetine.

Paroxetine is available virtually everywhere and is very inexpensive.

citalopram (Celexa, Cipramil, Seropram, Cipram, Citalon) escitalopram (Lexapro, Cipralext, Seroplex)

Serotonin and norepinephrine reuptake inhibitors (SNRI)

See also: pethidine/meperidine, tramadol, nefopam (CHAPTER 2), sibutramine (CHAPTER 10)

venlafaxine (Effexor, Efexor, Efectin, Vandal) desvenlafaxine (Pristiq)

Venlafaxine has a much stronger inhibitory effect on serotonin than norepinephrine. Large doses may also affect dopamine reuptake. Smaller dosages are often considered to only have serotonergic action. In any case for many patients venlafaxine is more helpful than the SSRIs and it sometimes helps depression refractory to all the other treatments. It can also be used to treat many different kinds of chronic pain.⁶⁷ Desvenlafaxine is a metabolite of venlafaxine, which is only taken once a day.

Venlafaxine is fairly commonly used in both fibromyalgia and CFS/ME. Jay Goldstein uses a small dose of 37.5–75 mg twice a day, starting out with only 18.5 mg.⁶⁸ He recommends trying SSRIs and bupropion first and venlafaxine only if these agents fail. According to him venlafaxine often works well in combination with risperidone, though this may carry the risk of serotonin syndrome.

One open and one double-blinded study have tried venlafaxine for fibromyalgia with promising results, but both were small and the results cannot be considered conclusive. Nonetheless both studies found significant improvement with venlafaxine.^{69,70} In the first one the improvement was found to be correlated with depression and anxiety; in the latter no such connection was found.

Venlafaxine can cause tachycardia and raise blood pressure, the latter of which could be beneficial for some. Nausea is more common than with the SSRIs. Other common side effects include e.g. psychiatric symptoms, sweating, hot flashes and visual disturbances. According to psychiatrist Eleanor Stein many

CFS/ME patients tolerate the drug better if taken in small, frequent doses instead of slow release formulations.⁷¹

The treatment should never be discontinued abruptly, as venlafaxine is highly prone to causing withdrawal symptoms. Sometimes weaning off long-term use of the drug has to be done extremely slowly, over the course of several months. Venlafaxine has potential interactions with the same drugs as paroxetine. Azoles, macrolides and verapamil may elevate the blood levels of venlafaxine. Desvenlafaxine only potentially interacts with azoles.

Venlafaxine is available in the United States, the United Kingdom, Canada, Australia and many other markets. It is slightly more expensive than the SSRI drugs. In some countries normal tablets are no longer sold, only extended release formulations. Desvenlafaxine is only available in the United States and is more costly.

duloxetine (Cymbalta, Yentreve)

milnacipran (Ixel)

Norepinephrine reuptake inhibitors (NRIs)

See also: protriptyline, desipramine (CHAPTER 5)

reboxetine (Edronax, Vestra, Norebox, Solvex, Prolift)

atomoxetine (Strattera, Attentin)

bupropion (Wellbutrin, Zyban, Quomem)

Bupropion is often claimed to be an SSRI, but in reality it inhibits the reuptake of norepinephrine and dopamine with barely any effect on serotonin. It also has some action on the nicotinic cholinergic receptors. It is used as an antidepressant (Wellbutrin) and as a smoking cessation aid (Zyban), though both of these formulations contain the same active ingredient and can be used interchangeably. It is considered a good anti depressant for bipolar disorder, especially for rapid cycling.⁸⁴

Bupropion has been used to relieve many different kinds of fatigue and tiredness, e.g. in cancer patients. Besides the noradrenergic and dopaminergic effects, it suppresses the inflammatory cytokine TNF alpha⁸⁵, which may be pertinent in reducing fatigue and other symptoms of CFS/ME and fibromyalgia. Studies have demonstrated efficacy in the treatment of neuropathic pain⁸⁶ and restless legs syndrome.⁸⁷

One small study about the successful use of the drug in CFS/ME⁸⁸ as well as one case report, which describes the use of bupropion in combination with paroxetine⁸⁹, have been published. Lucinda Bateman prescribes her CFS/ME patients slow release tablets with the dosage 100– 300 mg a day.⁹⁰ Others suggest doses from 75 mg once a day to 150 mg three times a day.⁹¹ The CFS/ME study used 300 mg a day, which is probably suitable for FM as well.

Bupropion lacks most of the side effects of SSRIs except for dry mouth. Instead of weight gain it tends to cause weight loss. Sexual side effects are rare—in fact it can help with sexual problems caused by SSRIs or other reasons. Because of its stimulating nature bupropion can cause insomnia. Other common side effects include fever, tremor, impaired concentration, headache, dizziness, stomach upset and altered taste.

Bupropion increases the risk of seizures. This risk is generally negligible without other precipitating factors, but it means the drug cannot be used in patients with epilepsy or a history of seizures. Fluoxetine, orphenadrine, carbamazepine, valproate, cimetidine and oral contraceptives can affect the metabolism of the drug. Levodopa and amantadine may worsen the side effects of bupropion

Bupropion is available in the United States, the United Kingdom, Canada, Australia and some other markets. In some countries it is only approved for smoking cessation. It is more expensive than the SSRIs, but cheaper than most other noradrenergic drugs. There are different modified release formulations available depending on the country. Some need to be taken twice a day, but Wellbutrin XL is only taken once.

Monoamine oxidase inhibitors (MAOI)

moclobemide (Manerix, Aurorix)

phenelzine (Nardil)

tranylcypromine (Parnate)

selegiline (Eldepryl, Deprenyl, Jumex, Niar, Emsam)

Selegiline is an irreversible inhibitor of MAO-B (though large doses also inhibit MAO-A), so it mostly affects dopamine. It also has some effect on dopamine reuptake independent of the MAO inhibition. Because of its dopaminergic mode of action selegiline was originally approved as a treatment for Parkinson's disease. More recently a transdermal selegiline patch (Emsam) has been approved in the treatment of clinical depression.

Selegiline is stimulating and energizing and is sometimes used to treat narcolepsy. It is widely considered a nootropic and is purported to be a "life extension" drug used in tiny doses. It has some anticonvulsant action as well.¹⁰⁰ One small study compared oral selegiline to placebo on 25 CFS/ME patients.¹⁰¹ It concluded that selegiline had a "small but significant" therapeutic effect in CFS/ME, though it was not found to act as an antidepressant.

In most patients selegiline is well tolerated. It is not as strict with dietary restrictions as other MAOIs and with the lowest dose of the Emsam patch no such restrictions are considered necessary. Dry mouth, orthostatic hypotension and insomnia are possible adverse effects. The patch may cause skin irritation.

Oral forms of selegiline are available almost everywhere. The Emsam patch is not yet available outside of the United States. It is also highly expensive, most likely being the most expensive antidepressant at the moment. Oral selegiline in contrast is very inexpensive.

rasagiline (Azilect, Agilect)

Other antidepressants

trazodone (Desyrel, Molipaxin, Trazolan, Trazone, Trittico)

nefazodone (Serzone, Dutonin, Nefadar)

mirtazapine (Remeron, Zispin)

mianserin (Tolvon, Bolvidon, Norval, Lerivon)

bupirone (Buspar, Anxiron, Spitomin, Buspiron)

tianeptine (Stablon, Coaxil)

Tianeptine has a novel action as an antidepressant. It enhances the reuptake of serotonin, so it essentially works the opposite from SSRI drugs. It is an effective antidepressant and anxiolytic lacking most of the side effects of other antidepressants. It has also been used for various off-label indications, such as erectile dysfunction¹²⁸, asthma¹²⁹, and ADHD¹³⁰, making it an intriguing treatment choice for those patients with many comorbid conditions.

Tianeptine appears to be generally neuroprotective, though it does not protect against glutamate excitotoxicity.¹³¹ It stabilizes the HPA axis¹³² and acts as an analgesic.¹³³ A clinical trial is currently trying it for fibromyalgia.¹³⁴ There is a U.S. patent that proposes tianeptine as a treatment for a myriad of neurological conditions, including “chronic fatigue syndrome, [and] myalgic encephalomyelitis post-viral fatigue syndrome.”¹³⁵ Another patented use is that of IBS and dyspepsia.¹³⁶ Insomnia, nightmares and headache are fairly common side effects.

Nausea, constipation, drowsiness, dizziness and dry mouth can occur, but are less frequent than with most other antidepressants. There are no known drug interactions. Tianeptine is taken more frequently than most antidepressants, usually three times a day. Abrupt discontinuation can cause insomnia, nausea and other symptoms.

Tianeptine is currently available in France and some other European countries and in parts of Asia and South America, but not in the United States, United Kingdom, Canada or Australia. It no longer enjoys patent protection, which makes it very inexpensive, but unlikely to be licensed to new markets.

S-adenosylmethionine/ademetionine (Transmetil)*

L-tryptophan (Tryptan, Optimax)* 5-hydroxytryptophan (Levotonine, Cincofarm)*

Neuroleptics and lithium

olanzapine (Zyprexa)

risperidone (Risperdal, Rispolept, Belivon)

amisulpride (Solian)

sulpiride (Dolmatil, Sulpor, Meresa, Sulpitol, Dogmatil)

ziprasidone (Geodon, Zeldox)

quetiapine (Seroquel)

Quetiapine is indicated in the treatment of schizophrenia and mania and used for a variety of off-label indications. One study found it effective for the fatigue and stiffness associated with fibromyalgia, but not for pain.¹⁵⁸ A second fibromyalgia trial augmented it with pregabalin with good results, though a fairly large proportion of participants withdrew from the study.¹⁵⁹

Because of its extreme sedative qualities quetiapine is commonly utilized as a sleep aid. As one person using it as described, “it is not a sleeping pill but an elephant tranquilizer.” It is often used by people with CFS/ME for this purpose, but they usually require very small doses to avoid excessive daytime sedation and “feeling like a zombie.”

Other side effects include constipation, headache and weight gain, though it is less pronounced than with many other antipsychotics and weight loss is also possible. Quetiapine may lower seizure threshold. Animal studies have found that in long-term use quetiapine can cause cataracts. It is not known whether this is applicable to humans, but in prolonged use eye examinations are recommended.

Quetiapine is available in the United States, the United Kingdom, Canada, Australia and some other markets. Even in the smallest 25 mg dose it is somewhat expensive compared to most other sleep inducing agents.

lithium (Eskalith, Carbolith, Camcolit, Priadel, Neurolithium)

CHAPTER 6.

Stimulants and nootropics

Sympathomimetic and dopaminergic drugs

See also: protriptyline, desipramine, norepinephrine reuptake inhibitors, selegiline (CHAPTER 5), amantadine (CHAPTER 9), naphazoline (CHAPTER 10)

methylphenidate (Ritalin, Concerta, Rubifen, Equasym, Ritalina)

amphetamine salts (Adderall)
dexamphetamine/dextroamphetamine (Dexedrine)
lisdexamphetamine (Vyvanse)

midodrine (ProAmatine, Amatine, Gutron)

Midodrine is an alpha-sympathomimetic drug (not an alpha blocker, as some sources mistakenly list it, but the exact opposite) used to treat orthostatic hypotension. It acts as a vasoconstrictor and may improve cerebral circulation, which may in turn improve attention.²⁰ Midodrine has a fairly short half-life and needs to be taken three times a day. It is not recommended for use before bedtime or before lying down.

Mark Alexander reports improvement from midodrine in adolescents with orthostatic intolerance and CFS/ME.²¹ He reports serious side effects to be uncommon. One case report²² and one small study²³ on the use of midodrine in CFS/ME have been published, providing very encouraging results. Dr. Jay Goldstein believes that the positive effects of midodrine are not a result of the raised blood pressure, but due to the stimulation of oxytocin release.²⁴

Side effects may include tingling, itching and other sensations of skin, cardiac symptoms and problems urinating. There can be drug interactions with e.g. other sympathomimetics, heart medications, cimetidine, ranitidine, metformin and ergotamine derivatives. Midodrine should not be used in persons with hypertension. It can elevate blood pressure too much even in hypotensive persons. Concomitant use of fludrocortisone increases this risk.

Midodrine is available e.g. in the United States, Canada and some other countries, but not in the United Kingdom or Australia. The high price no doubt limits its availability to many patients.

etilefrine (Effortil)

ephedrine (Efedrin)

phentermine (Ionamin, Adipex-P, Adipex, Duromine)

levodopa and carbidopa (Sinemet)

pramipexole (Mirapex, Mirapexin, Sifrol)

Pramipexole is a dopamine agonist used in the treatment of Parkinson's disease and RLS, sometimes also for cluster headaches, bipolar disorder and sexual side effects of SSRIs. Besides the D₂ receptor, it also binds to the D₃ receptor, which provides neuroprotection.²⁹ Pramipexole has shown significant benefit in fibromyalgia in a double-blinded trial.³⁰ Pain, fatigue and functionality were improved with 4.5 mg dose. Many other variables also showed a trend for improvement, but did not reach statistical significance.

Pramipexole may also be useful in CFS/ME. Dr. Lucinda Bateman uses a low dose of 0.125–1.5 mg in the evening to treat sleep problems in her patients.³¹ A patient has given an anecdotal account about recovering from CFS/ME after 15 years of severe illness with the drug.³² There are also anecdotal reports of significant relief of myofascial pain. Pramipexole can also help depression and anxiety.³³ Usually the drug is taken three times a day.

Pramipexole can cause sleep disturbances, sedation (even suddenly falling asleep), nausea and stomach upset. In the aforementioned fibromyalgia study the most common side effects were anxiety and weight loss. No patient discontinued the study because of side effects and serious adverse reactions were actually reported more frequently in the placebo arm. Amantadine and cimetidine may affect the plasma levels of pramipexole.

Pramipexole is available in the United States, the United Kingdom, Canada, Australia and many other countries. In low doses it is inexpensive, but higher doses can get costly.

ropinirole (Requip, Repreve, Adartrel)

rotigotine (Neupro)

bromocriptine (Parlodel, Apo-Bromocriptine, Bromergon, Serocryptin, Pravidel)

modafinil (Provigil, Modasomil, Modiodal, Alertec)

armodafinil (Nuvigil)

adrafinil (Olmifon)

Nootropics

See also: alprazolam, clonazepam (CHAPTER 1), atomoxetine, selegiline (CHAPTER 5), modafinil/armodafinil/adrafinil (CHAPTER 6), pindolol, nimodipine (CHAPTER 7), desmopressin, estrogen (CHAPTER 8), NMDA antagonists, cholinesterase inhibitors, cinnarizine (CHAPTER 9)

piracetam (Nootropil, Nootrop, Cerebryl)*

aniracetam (Ampamet)*

Piracetam and aniracetam are derivatives of GABA, but are not thought to have GABAergic effects. They are cholinergic and may possibly act at NMDA receptors and ion channels. Additionally piracetam decreases the viscosity of blood and reduces platelet aggregation. Aniracetam also modulates AMPA receptors and may have dopaminergic action.

The racetams have neuroprotective and anticonvulsive properties. They are used to treat a variety of cognitive and neurological problems, such as stroke, dyslexia, dementia and vertigo. Both drugs but especially aniracetam are thought to have antidepressant and anxiolytic effects. In animal studies

aniracetam has also improved neurogenic bladder overactivity. ⁵¹ Piracetam appears to work well for Raynaud's phenomenon.⁵²

CFS/ME patients have reported decreased cognitive fatigability and improved cognition, especially in verbal areas like word recall. The racetams can also alleviate physical fatigue. In one study the combination of piracetam and the antihistamine cinnarizine produced good results in the treatment of chronic fatigue.⁵³ Piracetam has shown efficacy in "soft tissue rheumatism," an old term which includes fibromyalgia. ⁵⁴

The racetams do not normally have any adverse effects. Drug monographs may list plenty of side effects for piracetam, but they are applicable for use in myoclonus, which requires very large doses (up to 20 grams a day). In nootropic use the dose is usually 800–4,800 mg a day in 2–3 doses, sometimes less. Normal dose for aniracetam is 500– 1,500 mg a day in 1–2 doses. Too large doses may cause headache, restlessness and insomnia, sometimes sedation. There are no known drug interactions.

Piracetam is considered an over-the-counter supplement in many countries, but a prescription drug in e.g. Australia, and many European and Asian countries. It is also sold in combination products with ergoloid, other nootropics and cinnarizine. In the United States it can be prepared by a compounding pharmacy. Aniracetam is a prescription drug in Italy, Greece and Argentina. They are fairly inexpensive.

ergoloid (Hydergin, Hydergine, Gerimal, Niloric, Redergin)

nicergoline (Sermion, Cebran, Ergotop, Varson)*

vinpocetine (Cavinton)*

sulbutiamine (Arcalion)*

pyritinol (Enerbol, Encephabol)

meclofenoxate (Helfergin, Cerutil, Cetrexin)*

CHAPTER 7.

Heart and blood pressure drugs

Antiadrenergic drugs

clonidine (Catapres, Catapresan, Dixarit, Isoglaucon, Aruclonin)

moxonidine (Physiotens, Fisiotens, Normatens, Moxon)

prazosin (Minipress, Minipres, Apo–Prazo, Pratsiol, Pressin)

tamsulosin (Flomax, Flomaxtra, Omnic, Secotex, Alna)

Tamsulosin is an antagonist of the alpha₁ receptor. It is fairly selective for the alpha_{1A} receptor subtype, which is mostly found in the prostate and the urinary tract. It is usually only used to treat prostrate hypertrophy, but may sometimes be prescribed for urinary problems in women. A large trial did not find it effective for overactive bladder in women¹⁴, but it was found helpful for female lower urinary tract symptoms in another study.¹⁵

Professor and sleep researcher Olli Polo has tried tamsulosin in many of his patients who suffer from chronic fatigue or CFS/ME, noting that it can improve sleep, circulatory problems and urinary frequency.¹⁶ Some of his patients have even described it as a stimulant, which he believes may result from improved sleep quality. He prescribes 0.4 mg for either daily use or to be taken every other day (tamsulosin has a long half-life).

Tamsulosin is the least prone of the alpha blockers to causing orthostatic hypotension, sedation and reflex tachycardia, but these are still possible side effects. Nasal congestion is fairly common. Men can experience problems with sexual function, especially ejaculation. Tamsulosin should not be used by those allergic to sulfa drugs. Many other drugs, such as some SSRI antidepressants, ropinirole, azole antifungals, macrolide antibiotics, diclofenac, verapamil and doxycycline can affect blood levels of tamsulosin.

Tamsulosin is available in the United States, the United Kingdom, Canada, Australia and some other countries. It is only available as 0.4 mg extended release capsules. It is very inexpensive.

Beta blockers

propranolol (Inderal, Dociton, Detensol, Novopropanol)

atenolol (Tenormin, Blokium, Atenolol, Atehexal, Vascoten)

metoprolol (Lopressor, Lopresor, Betaloc, Beloc, Seloken)

pindolol (Visken, Apo–Pindol, Barbloc)

Pindolol is a less commonly used beta blocker with significant sympathomimetic activity. A small open trial tried pindolol for fibromyalgia with encouraging results.²¹ Especially tender point scores improved

and scores in FIQ (fibromyalgia impact questionnaire, which mostly measures functionality) also significantly increased.

Dr. Jay Goldstein prescribes pindolol in doses of 5 mg 2–3 times a day for cognitive impairment, especially memory problems. Apparently the effect is mediated by pindolol's blockage of the 5-HT_{1A} serotonin receptor and not antiadrenergic action. Because of this receptor antagonism pindolol can be used to augment the antidepressive effect of SSRI drugs and speed up their onset of action.²²

Pindolol is available in the United States, the United Kingdom, Canada, Australia and some other countries. It is very inexpensive.

Calcium channel blockers

See also: cyproheptadine, pizotifen (CHAPTER 2), neomycin (CHAPTER 4), nicergoline (CHAPTER 6), dextromethorphan, cinnarizine, parenteral magnesium, flavoxate (CHAPTER 9)

verapamil (Calan, Isoptin, Verpamil, Cordilox, Verahexal)

nimodipine (Nimotop, Tropocer, Brainal, Nemotan, Eugerial)

Nimodipine mainly has a vasodilatory effect on the cerebral arteries. It is indicated for the treatment of post-stroke cerebral vasospasm in very large doses, up to 12 tablets a day. It is a promising treatment for CFS/ME with relatively few side effects. Jay Goldstein believes that nimodipine is one of the most useful treatments for CFS/ME and fibromyalgia. ²⁸ About 40% of his patients have experienced increased energy, exercise tolerance and mental clarity as well as decreased tender point sensitivity.

Andrew J. Wright prescribes nimodipine to treat orthostatic hypotension in CFS/ME. He starts with a very low dose of 7.5 mg which is Heart and blood pressure drugs 179 slowly titrated up.²⁹ The usual maintenance dose is 30 mg twice a day. Dr. Mason Brown recommends starting with a much lower dose—as little as 1/8 or 1/16 of a tablet every 3–4 days, if the patient has severe CFS/ME.³⁰

Nimodipine is a good migraine prophylactic. One study found its efficacy comparable to the common prophylactic agent pizotifen, but it was better tolerated.³¹ It has sometimes been used for psychiatric problems and seems to be helpful for bipolar disorder, especially the troublesome and hard-to-treat ultra rapid cycling.³² It may be effective in refractory panic disorder.³³ Nimodipine also greatly helps a minority of people with tinnitus.³⁴

Unlike verapamil, nimodipine can be taken in the morning, as it is not so prone to causing lightheadedness. Even small doses can nonetheless cause headache. Nimodipine has potential interactions with many other medications. Especially concurrent use ofazole antifungals and many psychiatric drugs and anticonvulsants can affect the blood levels of either or both drugs. In general use with anticonvulsants is not recommended. Grapefruit juice can dangerously elevate blood levels of nimodipine.

Nimodipine is widely available. Unfortunately it is quite expensive to extremely expensive, depending on the country. Usually 30 mg is the only available size, and in some markets the only available form is capsules, making it difficult to administer smaller doses. Tablets are usually not scored, but still easy to split.

nifedipine (Adalat, Nifelat, Nifecard, Nifedin, Nifehexal)

nilvadipine (Escor, Nivadil)

Other cardiovascular medications

See also: phenytoin (CHAPTER 3), tadalafil, theophylline, statins, angiotensin II receptor blockers, ACE inhibitors, isoxsuprine, buphenine, epoetin (CHAPTER 10)

glyceryl trinitrate (Minitran, Deponit, Nitro–Dur, Nitroderm, Nitrolingual)

disopyramide (Norpace, Rythmodan, Disomet)

pentoxifylline/oxpentifylline (Trental, Artal, Pentoxin, Pentoxil)

Pentoxifylline is a xanthine derivative (remotely similar to caffeine) and a phosphodiesterase–4 (PDE4) inhibitor. It increases the deformability of red blood cells and is primarily used to improve circulation. People with CFS/ME generally suffer from poor circulation and SPECT scans have demonstrated hypoperfusion in the brains of the patients.⁵⁰ According to doctor Leslie O. Simpson red blood cells are often deformed in CFS/ME, which impairs the circulation in capillaries.^{51,52} Simpson has found pentoxifylline helpful in relieving dizziness and cognitive problems in CFS/ME.

In addition pentoxifylline downregulates some major inflammatory pathways, such as TNF alpha⁵³, IL–2⁵⁴ and NF–kappa B.⁵⁵ This is another good rationale for using the drug in CFS/ME. Pentoxifylline appears to possess some other immunomodulatory and antiviral properties as well and as a result it is sometimes used as a supportive treatment for HIV/AIDS.⁵⁶ It can also reduce the malaise and loss of appetite associated with HIV infection.⁵⁷

Pentoxifylline works for both inflammatory and neuropathic pain. One study found it helpful in rheumatoid arthritis⁵⁸ and another one successfully combined it with beta interferon in multiple sclerosis.⁵⁹ Pentoxifylline may also be of use in the treatment of endometriosis and aphthous ulcers (mouth ulcers), but the studies of these uses have been inconclusive.

Pentoxifylline cannot be used in patients who cannot tolerate stimulants, who have a major risk of hemorrhage or who suffer from a peptic ulcer. Possible side effects include nausea, stomach upset, pruritus (itching), cardiac arrhythmias, insomnia, headache and dizziness. Weight loss may occur sometimes. Pentoxifylline may potentiate the effects of antihypertensive and blood sugar lowering drugs, including insulin. It also appears to increase the replication of cytomegalovirus.⁶⁰

Pentoxifylline is available almost everywhere. In some countries it is even an over–the–counter drug, but most places (including the United States, the United Kingdom and Australia) require a prescription. In Australia and some other countries the drug is known as oxpentifylline. It is inexpensive.

mexiletine (Mexitil, Katen, Ritalmex)

hydralazine (Apresoline, Hydrapres, Alphapress)

hydrochlorothiazide (Hydrodiuril, Microzide, Apo– Hydro, Esidrex)

spironolactone (Aldactone, Spirolone, Spiractin, Spirix)

heparin (Calciparine, Monoparin, Multiparin, Minihep) enoxaparin (Lovenox, Clexane, Klexane)

CHAPTER 8.

Hormones and immunomodulators

Several hormonal deficiencies have been associated with CFS/ME and fibromyalgia. Many of the symptoms can be corrected simply by fixing the deficiency, providing a justified and safe way to treat the patient. Occasionally there may be even complete symptom relief. Because many of these hormones have a profound effect on the immune system, they can also alleviate the immune dysfunction.

This chapter also includes other immunomodulatory drugs. Almost all drugs have some effect on the immune system, but immunomodulators are drugs that are primarily used for these effects. Traditionally immunomodulators have been grouped into immunostimulants (drugs that upregulate the immune system) and immunosuppressants (drugs that downregulate the immune system), but all immunomodulators do not conveniently fit into this scheme and may have both kinds of properties.

There is no consensus whether CFS/ME and fibromyalgia are caused by underactive or overactive immune system (if either), or whether there are different subsets. Both immunostimulants and immunosuppressants have been used to treat CFS/ME and to some extent also FM, though immunostimulants have been more popular. Immunosuppressants have been traditionally used to treat autoimmunity, but immunostimulants (such as IVIG and LDN, both reviewed later in this chapter) may offer a safer alternative.

Both kinds of immunomodulators may be able to treat the root cause of CFS/ME and fibromyalgia, if it is immune dysfunction, and to stop illness progression which is sometimes present. Immunostimulants are also very helpful in the treatment of viral infections. Immunostimulants are usually safer, but they can cause fever and other flu-like symptoms. Immunosuppressants are often lower on side effects, but they increase the risk of infections and even cancer.

CFS/ME is generally considered a Th2 illness, which means that the cellular immune system is overactive and the humoral immune system (Th1) side is suppressed. Many of the immunomodulators used to treat CFS/ME are thought to switch the immune system from excessive Th2 domination to Th1 side. Th2 domination has generally been associated with allergic conditions and Th1 with autoimmunity, though the latter is increasingly being disputed. As a whole this model is probably inadequate to explain the full complexity of the immune system.

Corticosteroids

See also: corticosteroid pulse (CHAPTER 10)

prednisone (Deltasone, Orasone, Meticorten, Panafcort) prednisolone (Orapred, Prelone, Prednisolon, Deltacortril)

hydrocortisone (Cortef, Hydrocortison, Hydrocortone)

fludrocortisone (Florinef, Astonin H)

Fludrocortisone is the synthetic equivalent of aldosterone, the most important mineralocorticoid in the human body. It only has minor glucocorticoid action. Administration causes fluid retention and thus raises blood volume. Hypovolemia is very common in CFS/ME²⁴ and patients appear to have lower

aldosterone levels than healthy controls.²⁵ A Japanese case report describes a CFS/ME patient whose illness went into remission for six years when she suffered from hyperaldosteronism due to an adrenal adenoma.²⁶

Measuring aldosterone levels is probably not necessary; the symptoms are more useful in determining whether a patient might benefit from fludrocortisone. Most people with CFS/ME suffer from orthostatic hypotension, sometimes so severe that the patient cannot even stand upright. Even in milder cases treating the problem can relieve the symptoms in general. Other circulation problems may also stem from hypovolemia.

Not all studies have shown benefit from fludrocortisone in CFS/ME, but one got very impressive results, even a full remission in some of the patients using fludrocortisone in combination with other treatments for orthostatic hypotension.²⁷ The treatment is also endorsed by the CFS/ME specialists Richard Podell²⁸ and Charles Lapp.²⁹ Dr. David Bell has found fludrocortisone beneficial for 1/3 to 1/2 of his patients, noting that it is most helpful for adolescents and the lesser ill.³⁰

Many CFS/ME doctors recommend beginning the treatment with a very small dose, such as only one fourth of a tablet for the first four nights and then increasing the dose by one fourth of a tablet every four days. Andrew J. Wright, however, does not recommend increasing the dose beyond one fourth of a tablet.³¹ Some doctors think it is important to always take the medication at the same time of the day.

Potassium supplementation may be warranted and it is important that the patient ingests plenty of fluids and an adequate amount of protein. If the drug causes headache or stomach upset, taking it with a glass of water may help. Fludrocortisone can cause depression (sometimes even severe) or an excessive surge in blood pressure. CFS/ME expert Paul Cheney does not recommend fludrocortisone and believes it can actually exacerbate the illness in long-term use.³²

Fludrocortisone is available in the United States, the United Kingdom, Canada, Australia and some other countries. Like the other corticosteroids it is very inexpensive. The potassium supplementation will likely cost more, though it is by no means expensive either.

Other hormones

See also: spironolactone (CHAPTER 7), raloxifene (CHAPTER 10)

thyroxine (Synthroid, Eltroxin, Euthyrox, Levotheroid, Thyrax)

liothyronine (Cytomel, Tertroxin)

thyroxine and liothyronine (Thyrolar, Novothyral)

thyroid (Armour thyroid, Westhroid, Thyrar)

estrogen

estrogen and progesterone

testosterone

DHEA/prasterone

Dehydroepiandrosterone (DHEA) is an important natural steroid hormone which is e.g. a precursor to testosterone and estrogens. Levels decline with age and have been associated with the negative effects of aging. There is conflicting information about the levels of DHEA in CFS/ME—some studies have

concluded there is too little of it^{61,62}, but one study found elevated levels.⁶³ In fibromyalgia both normal⁶⁴ and low⁶⁵ levels have been reported.

DHEA does not just affect the levels of sex steroids, but also appears to have anti-inflammatory, neuroprotective and even anti-cancer effects. It inhibits the secretion of IL-6, a major inflammatory cytokine, which has been associated with fibromyalgia pain.⁶⁶ DHEA has been successfully used to treat e.g. SLE⁶⁷ and HIV infection.⁶⁸ Higher DHEAS levels have been associated with better cognition in women.⁶⁹

Two studies have found DHEA effective for CFS/ME.^{70,71} A double-blind trial trying 50 mg of DHEA for postmenopausal women with fibromyalgia found no improvement in any of the studied variables, but DHEA did cause some side effects typical of the androgens.⁷²

Small doses do not usually cause side effects, but long-term use of larger, over 50 mg doses may cause acne, cardiac arrhythmias, weight gain, menstrual problems, hair loss, hirsutism, insulin resistance, other lipid changes and possibly increase the risk of hormonal cancers. Even smaller doses can decrease the amount of HDL (good cholesterol). DHEA is not recommended for those with a history of PTSD, psychosis or bipolar disorder. Some people think that DHEA may cause CFS/ME relapses.

DHEA is available in most countries. It is usually a prescription drug, but in the United States it is available over the counter.

oxytocin (Syntocinon, Pitocin)

growth hormone (Genotropin, Humatrope, Norditropin, Nutropin, Saizen)

desmopressin (DDAVP, Minirin, Octostim, Desmospray, Desmotabs)

Biological immunosuppressants

infliximab (Remicade)

Infliximab is a mouse-human chimeric antibody against the major inflammatory cytokine TNF alpha. It has been successfully tried for many different ailments from ulcerative colitis to prolapsed discs. There are no studies about its use in CFS/ME yet, but Jonathan Kerr plans to conduct one as soon as he gets the required funding.⁹² Andrew J. Wright proposed infliximab as a CFS/ME treatment back in 2002.⁹³ Professor Olli Polo has also made a similar proposal.⁹⁴

Infliximab is given as an infusion in a hospital first every few weeks, then usually every 4–8 weeks. The method of administration is not the most convenient one, but on the other hand it does not need to be done very often. Infliximab does not usually cause major side effects, though infections are common. There can be flu-like symptoms during the infusion and rarely allergic symptoms between the treatments. Infliximab may also increase the risk of lymphoma.

Infliximab is available in the United States, the United Kingdom, Canada, Australia and many other countries. It is extremely expensive.

etanercept (Enbrel)

adalimumab (Humira)

omalizumab (Xolair)

anakinra (Kineret)

Other immunomodulators

See also: benzodiazepines, dantrolene (CHAPTER 1), tetracyclines, macrolides (CHAPTER 4), SSRIs, lithium (CHAPTER 5), pyritinol (CHAPTER 6), pentoxifylline (CHAPTER 7), cannabinoids, ranitidine/ cimetidine (CHAPTER 9), pioglitazone/rosiglitazone, sizofiran, montelukast, angiotensin II receptor blockers, pegademase, ACE inhibitors, statins (CHAPTER 10)

immunoglobulin (Flebogamma, Gammagard, Endobulin, Intragam, Beriglobin)

interferon alfa (Intron A, Pegasys, PegIntron, Roferon– A, Infergen)

interferon beta (Avonex, Betaseron, Betaferon, Rebif, Serobif)

interferon gamma (Actimmune, Imukin, Immukin, Immukine)

liver derivative complex (Nexavir)

inosine pranobex (Isoprinosine, Immunovir, Delimmun)

thymalfasin (Zadaxin)

hydroxychloroquine (Plaquenil, Plaquinol)

acetylcysteine (Mucomyst, Parvolex, ACC, Solmucol, Fluimucil)*

Staphylococcus toxoid (Staphypan)

Toxoid refers to inactivated bacterial toxin. For example the tetanus vaccine is a toxoid vaccine; it does not offer protection from *Clostridium tetani*, only from its deadly toxin. Staphylococcus toxoid has been used to treat both CFS/ME and fibromyalgia. Some doctors think its benefits are due to immunomodulation, whereas others believe that staphylococci may actually be involved in the pathogenesis of the illness.^{143,144} The injections are given about once a month.

Several studies have tried staphylococcus toxoid in CFS/ME and fibromyalgia. In the first trial fatigability improved the most.¹⁴⁵ Half of the participants were able to resume working. In another study 65% of patients with CFS/ME or FM reported improvement compared to only 18% in the placebo arm.¹⁴⁶ The largest trial so far included 160 patients with fibromyalgia or CFS/ME on long-term treatment with staphylococcus toxoid for one year.¹⁴⁷ Of particular importance in that study was the reduced incidence of infections reported by patients.

Even though vaccinations in general have caused problems in this population, treatment with the staphylococcus toxoid appears to be well-tolerated. Local reactions are common but usually mild. Headache is possible. In the long-term study only 9 out of 160 patients withdrew from the study because of side effects, two because they developed an allergy to preservative in the vaccine. Nonetheless, the therapy may not be appropriate for those who have reacted severely to vaccinations.

Staphylococcus toxoid is currently only available in Switzerland. It is likely difficult to acquire outside of clinical trials.

Mycobacterium vaccae

naltrexone (Revia, Nalorex, Antaxone, Nemexin)

polyI:polyC12U (Ampligen)

mycophenolate (CellCept, Myfortic)

thalidomide (Thalomid)

CHAPTER 9.

Other medications

NMDA receptor antagonists

See also: orphenadrine, dantrolene (CHAPTER 1), methadone, dextropropoxyphene/propoxyphene, flupirtine, nefopam (CHAPTER 2), anticonvulsants (CHAPTER 3), cycloserine (CHAPTER 4), calcium channel blockers (CHAPTER 7), progesterone (CHAPTER 8), parenteral magnesium (CHAPTER 9), guaifenesin, acamprosate, isoxsuprine, buphenine (CHAPTER 10)

dextromethorphan (Robitussin, DexAlone, Romilar, Benylin)*

amantadine (Symmetrel, Symadine, Atarin)

riluzole (Rilutek)

memantine (Namenda, Ebixa, Akatinol, Axura)

ketamine (Ketalar, Ketanest, Calypsol)

S–ketamine (Ketanest–S)

Ketamine is an anesthetic which is usually given parenterally, but sometimes orally too, usually in conjunction with other analgesics. Besides its non-competitive NMDA receptor antagonism it blocks sodium channels and binds to mu opioid receptors and sigma receptors. Ketamine has been shown to work for many refractory cases of major depression²⁴ and migraine.²⁵ It also has some anti-inflammatory activity by inhibiting activation of NF-kappa B.²⁶

As could be expected, ketamine works well in fibromyalgia (and likely in CFS/ME as well, but clinical trials have not been performed). Several studies have demonstrated its efficacy.^{27,28} Jay Goldstein believes ketamine to be the most useful agent in neurosomatic medicine (in the treatment of CFS/ME and fibromyalgia).²⁹ If it makes the patient worse, he thinks topiramate might be a good candidate to try next, because its mode of action is somewhat opposite.

Ketamine can be administered as either a racemic mixture, or as the S-enantiomer, S-ketamine or esketamine. The S-form is a stronger analgesic and less likely to cause hallucinations, but also more prone to causing drowsiness. Oral ketamine is usually given every day, whereas intravenous ketamine generally only needs to be administered a few times a month. One study demonstrated good efficacy in using a topical cream with 2% ketamine and 1% amitriptyline for neuropathic pain.³⁰

Ketamine is widely available, but the availability of S-ketamine is more limited. Treatment is usually fairly expensive.

Cholinesterase inhibitors

See also: carbamazepine (CHAPTER 3), atomoxetine (CHAPTER 5), nootropics (CHAPTER 6), hydroxychloroquine (CHAPTER 8)

pyridostigmine (Mestinon, Kalymin)

Pyridostigmine is a peripherally acting cholinesterase inhibitor. It is used in the treatment of e.g. myasthenia gravis. According to CFS/ME expert Jay Goldstein pyridostigmine can help with muscle weakness, muscle aches, fatigue and brainfog.⁴⁰ Pyridostigmine does not normally cross the blood–brain barrier, so some of these benefits may be mediated by the increase in growth hormone secretion effected by the drug.⁴¹ In animal studies pyridostigmine has also elevated brain serotonin and dopamine levels.⁴²

As fibromyalgia patients are often deficient in growth hormone, pyridostigmine has sparked interest as a treatment. In one study FM patients were shown to have a significantly reduced growth hormone response to exercise.⁴³ In 19 out of the 20 patients a 30 mg dose of pyridostigmine normalized the secretion of growth hormone, but the study did not examine the resulting clinical effects. A later study did not find pyridostigmine helpful in fibromyalgia, except for anxiety and sleep.⁴⁴

Pyridostigmine has been shown to significantly raise blood levels of growth hormone in CFS/ME using a dose of 120 mg, but again clinical effects were not reported.⁴⁵ A case series has been published on the successful use of pyridostigmine in CFS/ME in three patients using a dose of 10–30 mg.⁴⁶ This is significantly smaller than the dose used to treat myasthenia gravis, which may be even more than 500 mg.

Pyridostigmine is considered a promising treatment for orthostatic hypotension and postural orthostatic tachycardia syndrome (POTS).⁴⁷ It may also be helpful for cases of chronic Lyme disease with symptoms of myasthenia (muscle weakness).⁴⁸

Possible cholinergic side effects include nausea, vomiting, stomach upset, muscle weakness and increased secretion of saliva, mucus and tears. Pyridostigmine should be used with caution in patients with asthma or diabetes. The bromide part of the compound may cause an allergic rash requiring discontinuation of the drug. People who have previously experienced a rash with bromide containing drugs should not use pyridostigmine.

Pyridostigmine is available virtually everywhere and is very inexpensive.

donepezil (Aricept)

galantamine (Reminyl, Razadyne, Nivalin)

tacrine (Cognex)

Antihistamines

See also: orphenadrine (CHAPTER 1), pizotifen, cyproheptadine (CHAPTER 2), doxepin, mirtazapine, mianserin, olanzapine (CHAPTER 5), ranitidine/cimetidine (CHAPTER 9), montelukast (CHAPTER 10)

hydroxyzine (Atarax, Vistaril)

cetirizine (Zyrtec, Reactine, Virlix, Cidron, Alerid)*

levocetirizine (Xyzal, Xyzall)*

chlorphenamine/chlorpheniramine (Trimeton, Chlor–Trimeton, Polaramine, Polaramin, Piriton)*

diphenhydramine (Benadryl, Nytol, Unisom)*

Diphenhydramine is a sedative first-generation antihistamine with significant anticholinergic effects. It also inhibits the reuptake of serotonin and in fact some SSRIs were developed based on diphenhydramine. It is very effective for allergic symptoms and also works as an antiemetic, but it is even more commonly used as a sleep aid. Small 25 mg doses may be useful for severe pain in patients who have not responded to other treatments.⁶⁴

Besides sedation, diphenhydramine can have significant anticholinergic side effects, such as dry mouth, tachycardia, constipation, urinary retention, confusion, cognitive problems and even hallucinations. Obviously some of these effects can also be beneficial, but diphenhydramine should not be combined with other anticholinergic drugs.

Diphenhydramine is available in the United States, the United Kingdom, Canada, Australia and many other countries. In these four markets it is available without prescription. A cream is also available on some markets. The tablet form is very inexpensive.

doxylamine (Unisom SleepTabs, Unisom-2, Dozile)*

meclozine/meclizine (Antivert, Bonamine, Postafen, Agyrax, Sea-legs)*

cinnarizine (Stugeron, Mitronal, Cinna)*

Cannabinoids

nabilone (Cesamet)

Nabilone is a synthetic cannabinoid similar to THC, but with less intoxicating effects. It is administered as tablets. It is approved for the treatment of nausea, anorexia and weight loss in patients with cancer or AIDS, but is also sometimes used for chronic pain. It has been reported to be helpful in fibromyalgia.⁹² A recent double-blind study tried nabilone for this indication with very beneficial results.⁹³

Nabilone is available in the United States, the United Kingdom, Canada and Australia. It is very expensive.

Parenteral supplements

parenteral magnesium

intramuscular vitamin B12

A deficiency of vitamin B12 usually cannot be demonstrated in the bloodwork of patients with CFS/ME, but elevated levels of homocysteine have been found in the cerebrospinal fluid of patients who had both CFS/ME and fibromyalgia. Elevated homocysteine can be caused by a deficiency of vitamin B12 and in the study the levels of homocysteine correlated significantly with fatigue, with the CSF B12 levels having an inverse correlation (higher B12 levels meant less fatigue).¹¹¹

Intramuscular administration of vitamin B12 is not a very common treatment for fibromyalgia, but it is one of the most popular CFS/ME treatments and considered one of the most effective. Oral and

sublingual forms of the vitamin help many, but the absorption is low. B12 injections can contain thousands of times the RDA of the vitamin. Opinions differ as to which is the best form of B12.

CFS/ME specialist Charles Lapp believes there is enough vitamin in the blood, but it is not properly taken into the cells.¹¹² According to him as many as 80% of CFS/ME patients benefit from large doses of B12. He uses a dose of 3 mg, which the patient administers himself 2–3 times a week. The effects are noticeable in a few weeks, often almost immediately. Kenny De Meirleir recommends a 10 mg injection twice a week.¹¹³

Dr. Sarah Myhill too considers B12 injections to be an essential part of treatment of CFS/ME.¹¹⁴ She prescribes a weekly dose of 2 mg. In her experience B12 helps fatigue, muscle weakness and cognitive problems. Paul Cheney goes as far as prescribing 10–25 mg daily doses.¹¹⁵ Martin Pall believes that B12 works because it scavenges nitric oxide.¹¹⁶ Dr. Leslie O. Simpson on the other hand thinks the benefits result from improved deformability of red blood cells.¹¹⁷

B12 also has some analgesic effects, especially in the treatment of neuropathic pain.¹¹⁸ It is sometimes used as a treatment of multiple sclerosis. Many patients with multiple chemical sensitivity benefit from B12 injections. Even healthy people often note that B12 supplements ameliorate tiredness and impaired concentration. A study using vitamin B12 for tiredness in the 1970s found it very helpful.¹¹⁹

B12 is very safe even in massive doses. Side effects are extremely rare aside from harmless discoloration of the urine. Rarely there may be an acne-like rash, which usually disappears by lowering the dose. It is possible to be allergic to B12, but it is very uncommon. Some patients have reported increased anxiety from B12.

B12 is available everywhere, though doses larger than 1 mg may have to be compounded. Cost depends on dose and injection frequency.

Myers' cocktail

intravenous vitamin C

intravenous saline

Treatments for bladder and bowel dysfunction

See also: diazepam, melatonin, baclofen, cyclobenzaprine (CHAPTER 1), flupirtine, triptans, codeine (CHAPTER 2), anticonvulsants (CHAPTER 3), metronidazole, rifaximin, antifungals (CHAPTER 4), tricyclic antidepressants, SSRIs, mianserin, mirtazapine, tianeptine (CHAPTER 5), midodrine, etilefrine, ephedrine, aniracetam (CHAPTER 6), alpha blockers, beta blockers, calcium channel blockers, nitrates (CHAPTER 7), naltrexone (CHAPTER 8), memantine, hydroxyzine, diphenhydramine, cannabinoids, ranitidine/cimetidine, misoprostol, granisetron/tropisetron/ondansetron (CHAPTER 9), aprepitant, scopolamine (CHAPTER 10)

oxybutynin (Ditropan, Cystrin, Driptane, Lyrinel, Dridase)

tolterodine (Detrol, Detrusitol, Unidet)

tropium (Sanctura, Spasmex, Spasmo-lyt, Trosec, Regurin)

darifenacin (Enblex, Emselex)

solifenacin (VESicare)

flavoxate (Urispas, Bladuril)

dicycloverine/dicyclomine (Bentyl, Antispas, Dibent, Bentlyl, Merbentyl)

hyoscyamine (Anaspaz, Egazil, Levsin)

hyoscyamine, atropine, methenamine, methylene blue, phenyl salicylate and benzoic acid (Urised, Uriseptic)

phenazopyridine (Uristat, Prodiem, Pyridium, Phenazo)

pentosan polysulfate (Elmiron)

Pentosan polysulfate is a heparin-like drug which is used to treat interstitial cystitis. It is believed to work by creating a protective coating on the bladder wall and possibly by mast cell inhibition. Unfortunately the oral bioavailability is extremely low—only 6% is excreted through urine. The drug needs to be taken for weeks, three times a day, to be effective. Alternatively it can be used as a bladder instillation during a flare of the symptoms.

Pentosan polysulfate has some antiviral action similar to heparin.¹³⁶ It has been suggested to possess migraine-prophylactic action¹³⁷ and neuroprotective properties.¹³⁸ Pentosan polysulfate can be used to treat osteoarthritis, but for some reason is only used for this purpose in animals. ¹³⁹

Pentosan polysulfate is usually well-tolerated. Side effects can include headache, hair loss, skin rashes, rectal hemorrhage (bleeding from the rectum), diarrhea and nausea, but they are all fairly rare. No other drug interactions are known, but other anticoagulant drugs can increase the risk of bleeding. Pentosan polysulfate should not be used in patients with a peptic ulcer.

Pentosan polysulfate is available in the United States, Canada, and a few other countries, but not in the United Kingdom or Australia. It is quite expensive.

Other drugs

acetazolamide (Diamox, Sequels, Glaupax, Diuramid)

sibutramine (Meridia, Reductil)

misoprostol (Cytotec)

ranitidine (Zantac, Histac, Ranitic, Ranix, Ranitin)*

cimetidine (Tagamet, Cimehexal, Histodil, Dyspamet, Ulcedine)*

Ranitidine and cimetidine are antagonists of the H₂ histamine receptor. Because of this they are often called antihistamines, though their effects are quite different from the antiallergic drugs (which act on the H₁ receptor). They are used to reduce the secretion of stomach acid in ulcer prevention and treatment, but

have largely been surpassed by the proton pump inhibitors. They may be useful for allergic symptoms in conjunction with H₁ antagonists (“normal” antihistamines).¹⁵²

Dr. Jay Goldstein discovered in the 1980s that H₂ receptor antagonists can be very effective against infectious mononucleosis.¹⁵³ Because at the time CFS/ME was thought to be a form of chronic mononucleosis, he also tried them in CFS/ME patients, often with good results. He believes the effects may result from the cholinergic and NMDA antagonist properties of the drugs. Devin Starlanyl notes these drugs may be useful in fibromyalgia for promoting stage 4 sleep, especially with amitriptyline.¹⁵⁴

The H₂ antagonists have some immunostimulatory properties.^{155,156} They can be used to treat interstitial cystitis¹⁵⁷ and painful bladder disease.¹⁵⁸ There is some evidence H₂ antagonists are helpful for weight loss.^{159,160} They have shown some efficacy in reducing the weight gain caused by olanzapine (an antipsychotic).¹⁶¹ This might apply to other medications that cause weight gain, as well. Additionally they potentiate opioid analgesia.¹⁶²

According to Goldstein H₂ antagonists may cause restlessness and overstimulation in patients with CFS/ME and fibromyalgia. Headache is also possible and rarely may be severe. Occasionally H₂ antagonists cause allergic reactions. People with SLE may experience lupus flares. The H₂ antagonists may also increase the requirements of folic acid, vitamin B12 and zinc. Cimetidine may interact with phenytoin, carbamazepine, lidocaine, opioids, theophylline and tricyclic antidepressants.

Cimetidine and ranitidine are widely available. Low doses of cimetidine are available over-the-counter in the United States and some other countries. Ranitidine is available without prescription in the United States, the United Kingdom and Australia.

folinic acid/leucovorin (Leucovorin, Lederfoline, Lederfolin, Rescuvolin)*
levofolinic acid/levoleucovorin (Isovorin, Antrex, Calcifolin)

granisetron (Kytril)
tropisetron (Navoban)
ondansetron (Zofran, Emeset, Emetron)

CHAPTER 10.

Experimental therapies

cholestyramine (Questran, Prevalite)

pioglitazone (Actos)
rosiglitazone (Avandia)

calcitonin (Miacalcin, Miacalcic, Osteocalcin, Calco, Calsynar)

tadalafil (Cialis)

sizofiran (Sonifilan)

ibudilast (Ketas)

montelukast (Singulair)

neurotropin

erdosteine (Vectrine, Flusten, Dostein, Erdomed, Erdotin)

theophylline (Euphyllin, Nuelin, Theo–Dur, Theolair, Xanthium)

naphazoline (Albalon, Allersol, Naphcon Forte)*

raloxifene (Evista, Optruma)

scopolamine/hyoscine (Transderm Scop, Scopoderm, Scopace, Buscopan, Transderm–V)

aprepitant (Emend)

valsartan (Diovan, Tareg)
losartan (Cozaar, Cormac, Lortaan, Lorista)
telmisartan (Micardis, Pritor, Kinzalmono)
olmesartan (Benicar, Olmetec)

guaifenesin (Humibid, Mucinex)

probenecid (Benemid, Benuryl, Probecid, Benemid, Pro–Cid)

flavocoxid (Limbrel)

pegademase (Adagen)

captopril (Capoten, Captopril, Tensiomin, Cptohehexal, Lopirin)
enalapril (Vasotec, Renitec, Enap, Ednyt, Enalapril)

Captopril and enalapril are ACE (angiotensin converting enzyme) inhibitors. They are used to treat e.g. hypertension, congestive heart failure and diabetic nephropathy. ACE levels have been found to be elevated in the majority of patients of CFS/ME.⁶⁷ Interestingly gene polymorphisms which increase ACE levels have been associated with GWS.⁶⁸ Dr. David Moskowitz believes that ACE inhibitors can be very useful in both CFS/ME and fibromyalgia.⁶⁹

Besides inducing vasodilation ACE inhibitors inhibit some other enzymes, such as dipeptidyl carboxypeptidase, which breaks down opioid peptides like beta endorphin. They appear to reduce the secretion of Th2 cytokines, TGF-beta, NF-kappa B and NO, all of which are thought to be elevated in CFS/ME and fibromyalgia.^{70,71}

ACE inhibitors can also help orthostatic hypotension.⁷² They improve cerebral blood flow which may be beneficial in the treatment of cognitive problems.⁷³ Captopril significantly reduces platelet aggregation (similar to the “blood thinning” effect of aspirin), but enalapril does not.⁷⁴

In animal studies captopril has demonstrated analgesic properties.⁷⁵ It has shown efficacy against migraine and other headaches.^{76,77} Captopril is sometimes used to treat chronic pain in CFS/ME in conjunction with other drugs.⁷⁸ Jay Goldstein notes captopril and possibly enalapril to have antidepressive action.⁷⁹

Enalapril is taken once a day, captopril 2–3 times a day. Even healthy people are often recommended to start with just half of the smallest tablet size, so this is especially important in CFS/ME to avoid hypotension. Other side effects include cough, hypoglycemia, skin eruptions and dizziness. With captopril there should be regular bloodwork to monitor for neutropenia and agranulocytosis. Both drugs can have interactions with a wide range of medications, but different ones for each.

Both medications are available everywhere. Enalapril is usually cheaper, but both are very inexpensive.

atorvastatin (Lipitor, Sortis, Torvast, Torvacard, Zarator)
simvastatin (Zocor, Vasilip, Kavelor, Belmalip, Simvor)
lovastatin (Mevacor, Lovacol, Medostatin, Mevlor, Nergadan)
fluvastatin (Lescol, Canef, Locol, Vastin, Digaril)

omeprazole (Prilosec, Losec, Ortanol, Ulcuprazol, Omeprazol)
esomeprazole (Nexium)
lansoprazole (Prevacid, Zoton, Ogastro, Monolimum, Lanzo)
rabeprazole (Aciphex, Pariet)

acamprosate (Campral)

isoxsuprine (Duvadil)
buphenine (Arlidin)

streptokinase (Streptase, Kabikinase)
urokinase (Abbokinase, Ukidan)
alteplase (Activase, Actilyse)

epoetin (Procrit, Eprex, Recormon, NeoRecormon, Epogen)

corticosteroid pulse