Chronic Fatigue Syndrome – What drugs can I use?

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Therapeutic aims

- Alter natural history
  - Improve prognosis/outcome
- Control symptoms

(Some therapeutic approaches may address both areas)

Medically unexplained symptoms

- More difficult to affect natural history
  - Mechanism ill/not understood
  - Natural history not well established
  - No objective biological marker
  - Trials difficult
- May have to address symptoms alone

CFS – a medically unexplained syndrome (MUS)?

- Underlying mechanism not understood
- Parallel with other MUS
  - Irritable bowel syndrome
  - Tension headache
  - Fibro myalgia (FMS)
  - Chronic pain syndromes

Aetiology

- WHO defines as “neurological illness”
- Numerous suggestions of mechanism
  - Infective
  - Immunological
  - Endocrine/neuro endocrine
  - Genetic
  - Psychological

NICE view

"… best regarded as a spectrum of illness that is triggered by a variety of factors in people who have an underlying predisposition"

NICE 2007

Drugs affecting natural history

"There is no known pharmacological treatment or cure for CFS/ME. However,

symptoms of CFS/ME should be managed as in usual clinical practice."

- None confirmed as providing benefit
- None recommended by NICE

Suggested therapies

- Anti infective
  - Anti virals – herpes therapy
  - Anti bacterials – tetracyclines, cephalosporins
  - Antifungals
- Immunological
  - Immunoglobulin, interferon, ampliglen
- Endocrine
  - Thyroxine, steroids
- Psychological
  - TCAs, SSRIs

Supplements

- Magnesium, fatty acids, carnitine

Reviews of Pharmacological Therapy

- JAMA meta analysis 2001
- York CRD 2002
- York CRD 2007 (Feb)
  - Chambers D et al. Interventions for the treatment, management and rehabilitation of patients with CFS/ME: an updated systematic review.

J R Soc Med 2006; 99: 506-520

Only significant evidence is for CBT and GET

York CRD 2007

- 70 studies included (out of 10768!)
  - 59 were RCTs

" GET and CBT appeared to reduce symptoms and improve function based on evidence from RCTs. For most other interventions, evidence of effectiveness was inconclusive and some interventions were associated with significant adverse events"

www.york.ac.uk/inst/crd/pdf/crdreport35.pdf

Anti infectives

- Suggested infective aetiologies
  - Herpes viruses (EBV, HCMV, HHV6)
  - Candida
  - Borrelia burgdorferri (Lyme disease)
  - Enteroviruses
  - Mycoplasma
  - Coxiella
  - Rickettsia
  - Strongyloides

No evidence for any of these

Aciclovir study

- RCT n=27
- Anxiety, depression, confusion better in control group
- No other differences
- 3 reversible renal failure
  - *Straus NEJM 1988*

Ganciclovir

- RCT n=11
- Symptomatic benefit suggested by authors
- 2 patients bled during myocardial Bx
- Study terminated prematurely

Lerner. CID 2001

Galantamine

- Acetylcholinesterase inhibitor
- RCT n=434
- 130 withdrawals
- 389 reported adverse events (88 withdrew)
- No sig diff for fatigue symptoms, global impression or cognitive function

Blacker JAMA 2004

Steroids

- Hydrocortisone RCT n=?120
  - Sig improvement in fatigue in Rx group

Cleare. Int J Neurpsychopharm 2002

- HC + FC RCT (DB cross over) n=80
  - No sig diff in fatigue, well being, anxiety/depression

Blackman. Am j Med 2003

- No benefit from nasal steroids RCT n=28

Kakumanu. J All Clin Imm 2001

Immunological studies

- Inosine pranobex
  - CCT (n=16)
  - Improvement in NK function. No symptomatic improvement

Diaz-Mitoma J CFS 2003

- Staph toxoid
  - RCT (n=98)
  - Some symptomatic improvement (low validity)

Zachrisson. Eur J Pain 2002

Older studies

- 5 studies of immune globulin – no definite benefit
- Ampligen 1994 – n=92 some improvements in cognitive function and exercise scores

Strayer. Clin Inf Dis 1994

- Interferon
  - n=20 No major benefit

Brooke. J Inf Dis 1993

  - n=30 Improved NK. No QoL diff

See. Imm inv 1996

Magnesium

- RCT n=34
- IM magnesium for 6 weeks
- Significant benefit in a number of QoL measures
- Never repeated

Cox. Lancet 1991

No evidence

- No appropriate trials
  - Expert patient programme
  - Amitriptylline
  - Gabapentin
  - Baclofen
  - Injectable Vitamin B12

What is the way ahead for cures

- More studies?
  - How to fund
  - How to recruit
- Subtyping of CFS/ME
  - Difficult
  - ?Has to be symptom based
  - No consistent biological marker

Symptomatic Treatments

- General principles
  - Identify, quantify and treat specific symptoms
  - Patients often tolerate drugs poorly
  - Use minimum effective dose for minimum time required
  - Withdraw treatment that is having no benefit

Outcome with symptomatic treatments

- Worsening of symptoms/adverse drug reaction
  - Probably withdraw drug depending on severity
- No symptomatic benefit
  - Withdraw after “decent” trial period
- Some benefit
  - Continue. Consider dose increment
- Symptom relieved
  - Continue. Consider withdrawal at some stage

Symptoms not amenable to pharmacological relief

- Fatigue
- Payback
- Brain fog
- Lymphadenopathy
- Recurrent URTIs

Symptoms potentially amenable to pharmacological relief

- Pain
  - Headache
  - Arthralgia/Myalgia
  - Neuralgia
  - Hyperasethesia
- Depression
- Sleepiness
- Insomnia

Pain

- Usual analgesic approach
  - Paracetamol, NSAID, opioid
- Consider neuropathic pain early
  - Amitryptilline may benefit insomnia and pain
  - Start with low doses
  - Gabapentin, pregabalin and carbamazepine
- Other approaches
  - TCNS, Physio
  - Acupuncture

Depression

- RCTs have been disappointing
  - Phenelzine and fluoxetine
- Many have used
  - 30% at time of referral
  - 20% previous use
- Start with low dose ?TCA ?SSRI

Insomnia

- Sleep hygiene advice
- Proprietary remedies (antihistamines etc)
- TCAs
- Short term use of zopiclone/zolpidem?
- Melatonin
    - Widely used in children
    - One study shows benefit (Non RCT n=29)

Van Heukelom Eur J Neur 1991

Sleepiness

- Unusual symptom
- Epworth scoring
- Consider SAS
- Try modafanil
  - Recent adverse effects (Skin, anxiety)
  - No prognostic benefit
  - 1 placebo controlled crossover study (n=14)
  - Modafanil not helpful in 1 study

Randall . J Psychpharm 2005

Problems

- Non evidence based practitioners
  - Medically/non medically qualified
  - NHS/private
- Non evidence based information
  - Books
  - Internet
- Patient beliefs
- Paradox
  - “Not a psychological condition but we are going to give you a psychological treatment”
- Continuity of care

One patient

- Before breakfast
  - L glutathione 3 tabs daily
  - L carnitine 1000 mg daily
  - Zinc citrate 15 mg daily

With breakfast

- Insulin
- Levothyroxine T4 100 mcg
- Liothyronine T3 5mcg
- Selenium 200 mg
- B50 complex 1 tablet
- Nicotinamide 500 mg
- Coenzyme Q10 100 mg
- Magnesium citrate 150 mg
- Fish oil
- Creon 1 tablet
- D ribose 6G

With lunch

- Insulin
- Fish oil
- Creon

With evening meal

- Insulin
- Fish oil
- Creon

Bedtime

- Magnesium citrate 150 mg
- Vit D/Cal (12.5 elemental calcium)
- Vitamin D3 400 iu
- Bromocriptine 1.25 mg

Summary – what drugs can I use?

- None for prognostic benefit (? Yet)
- Huge amount of self medication
- Several options for symptomatic improvement
- Problems with evidence gathering
- More and better studies needed
- ?Role of subtyping

Thank you