

Evidence Review F - Pharmacological Interventions

Review Question - What is the clinical and cost effectiveness of pharmacological interventions for people with ME/CFS? What are the experiences of people who have had interventions for ME/CFS?

There are two questions here, perhaps reflecting the call for evidence regarding experience of interventions, which did not specify whether pharmacological or non-pharmacological evidence was sought, or both. However there is no reference to the call for evidence in the body of the Evidence Review and it would appear that none was forthcoming regarding pharmacological interventions. So the second part of this question does not appear to have been considered.

On the other hand, that a call for evidence on patient experience went out and garnered considerable response regarding *non-pharmacological* interventions has provided a curious platform to mention these here. As in: 1.1.1 Introduction (page 6):

The committee evaluated evidence from clinical effectiveness studies and patient experience from a wide range of non-pharmacological management strategies to inform the recommendation in these areas.

The clinical and cost effectiveness methods and evidence found are outlined Evidence review G: Non pharmacological management as well as the methods and evidence found for the review on the experiences of people who have had interventions for ME/CFS.

Also, while no health economic studies emerged - neither for inclusion nor for exclusion - Appendix G presents a platform for “flow chart of health economic study selection for the guideline” (P324) - none of which is relevant to pharmacological evidence . (This is in fact exactly the same flow chart as is presented in respect of non-pharmacological interventions: Appendix G - Figure 369, Evidence review H)

Arguably, a potentially valuable opportunity has been lost to obtain information about patient experiences specifically of pharmacological interventions.

What follows relates to the presentation regarding clinical evidence on Pharmacological Interventions

Downgrading

Populations were downgraded if the ME/CFS diagnostic criteria used did not include PEM as a compulsory feature. While identifying PEM as a compulsory feature represents a step forward for future work, it must be recognised that it has simply not been possible to publish research that selected participants on this basis. Researchers wishing to study people with ME - *i.e.* people who experience PEM - had no choice but to use an existing set of CFS research criteria - normally Fukada *et al.* 1994. Research on these patients had nowhere else to ‘go’. Patients are experiencing a most unpleasant illness and need relief. Downgrading the pharmacological research in this way is not helpful to this end and is likely to continue for the foreseeable future as we do not have accepted research criteria that include PEM as essential feature.

To further downgrade a study of an anti-viral therapy by Montoya *et al.* (Reference 53) on the basis that the patients receiving the anti-viral therapy had had a suspected viral onset

and confirmed elevated antibody titers would appear to be quite illogical. A synopsis of this study is set out below.

Similarly, Kakumanu 2003 [Ref 36: Kakumanu S, Mende C, Lehman E, Yeageer M, Craig T. *The effect of topical nasal corticosteroids in patients with chronic fatigue syndrome and rhinitis*. Journal of Allergy and Clinical Immunology. 2001; 107(2): S153 was additionally downgraded due to all participants having rhinitis and Rowe 2001 [Ref 77 Rowe PC, Calkins H, DeBusk K, McKenzie R, Anand R, Sharma G *et al*. *Fludrocortisone acetate to treat neurally mediated hypotension in chronic fatigue syndrome: A randomized controlled trial*. JAMA. 2001; 285(1): 52-59 was additionally downgraded due to all participants having neurally-mediated hypotension.

Thus an opportunity is lost to consider subgrouping within the 'CFS' construct, which is viewed as overly inclusive in terms of recruitment to research (else why downgrade evidence due to lack of specificity i.e. no 'PEM'). It runs counter to this to then further downgrade studies specifically because an attempt was made made to investigate patients and treat accordingly.

Exclusions

The reason cited for excluding Rowe's work on use of immunoglobulin in adolescents [(74) Rowe KS. *Double-blind randomized controlled trial to assess the efficacy of intravenous gammaglobulin for the management of chronic fatigue syndrome in adolescents*. Journal of Psychiatric Research. 1997; 31(1): 133-147] is "no relevant extractable outcomes". This study employed an extensive range of outcome measures. These included at least one of those listed on page 7 of the evidence review as 'Critical Outcomes'.

Rowe's follow up study [(75) Rowe KS. *Five-year follow-up of young people with chronic fatigue syndrome following the double blind randomised controlled intravenous gammaglobulin trial*. Journal of Chronic Fatigue Syndrome. 1999; 5(3-4): 97-107] also excluded on a basis that appears quite unfounded - in this case "not all participants were randomised". This is a follow up study to the 1997 paper. We have brought this to the attention of the author and been assured: *The patients were definitely randomized during the trial*.

Montoya JG, Kogelnik AM, Bhangoo M, Lunn MR, Flamand L, Merrihew LE *et al*. *Randomized clinical trial to evaluate the efficacy and safety of valganciclovir in a subset of patients with chronic fatigue syndrome*. Journal of Medical Virology. 2013; 85(12): 2101-2109

Thirty CFS patients with elevated IgG antibody titers against HHV-6 and EBV were randomized 2:1 to receive valganciclovir (VGCV) or placebo for 6 months in a double-blind, placebo-controlled trial.

Clinical endpoints aimed at measuring physical and mental fatigue included the Multidimensional Fatigue Inventory (MFI-20) and Fatigue Severity Scale (FSS) scores, self-reported cognitive function, and physician-determined responder status.

Biological endpoints included monocyte and neutrophil counts and cytokine levels.

VGCV patients experienced a greater improvement by MFI-20 at 9 months from baseline compared to placebo patients but this difference was not statistically significant.

However, statistically significant differences in trajectories between groups were observed in MFI-20 mental fatigue subscore ($P = 0.039$), FSS score ($P = 0.006$), and cognitive function ($P = 0.025$).

VGCV patients experienced these improvements within the first 3 months and maintained that benefit over the remaining 9 months.

Patients in the VGCV arm were 7.4 times more likely to be classified as responders ($P = 0.029$).

In the VGCV arm, monocyte counts decreased ($P < 0.001$), neutrophil counts increased ($P = 0.037$) and cytokines were more likely to evolve towards a Th1-profile ($P < 0.001$). Viral IgG antibody titers did not differ between arms.

VGCV may have clinical benefit in a subset of CFS patients independent of placebo effect, possibly mediated by immunomodulation and/or antiviral effect. Further investigation with longer treatment duration and a larger sample size is warranted. *J. Med. Virol.* 85:2101–2109, 2013

To assess the safety of the drug, complete blood cell counts with leukocyte differential, renal function tests, and liver function tests were performed per protocol. In addition, safety issues were assessed at each visit.

VGCV was well-tolerated and was not discontinued due to hematologic or hepatic adverse events. Two patients were diagnosed with cancer during the study period: in the VGCV arm, one patient was removed from the study at week 16 due to the diagnosis of ovarian cancer; in the placebo arm, one patient was diagnosed with breast cancer at week 36. These two serious adverse events were deemed unrelated to VGCV.

The 25% ME Group

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