Table 32: Clinical evidence profile: Antiviral drugs (IV acyclovir or oral valganciclovir) versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antiviral drugs (IV acyclovir or oral valganciclovir) versus placebo	Control	Relative (95% CI)	Absolute		
Fatigue: Multidimensional fatigue inventory (MFI-20) (follow-up 9 months; range of scores; 20-100; Better indicated by lower values)												
1 [original analysis]	randomised trials	very serious[1]	no serious inconsistency	very serious[2]	serious[3]	none	20 (oral valganciclovir)	10	-	MD 5.05 lower (11.48 lower to 1.38 higher)	⊕OOO VERY LOW	CRITICAL
1 [PEM reanalysis]	randomised trials	very serious[1]	no serious inconsistency	serious[4]	serious[3]	none						
Fatigue: POMS fatigue (follow-up 37 days; range of scores: 0-28; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	27 (IV acyclovir)	27	-	MD 1.26 higher (1.01 lower to 3.53 higher)	⊕OOO VERY LOW	CRITICAL
Fatigue: POMS vigour (follow-up 37 days; range of scores: 0-32; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	27 (IV acyclovir)	27	-	MD 2.05 lower (4.65 lower to 0.55 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status: POMS anxiety (follow-up 37 days; range of scores: 0-36; Better indicated by lower values)												

1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	27 (IV acyclovir)	27	-	MD 2.92 higher (0.63 to 5.21 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status: POMS depression (follow-up 37 days; range of scores: 0-60; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	27 (IV acyclovir)	27	-	MD 3.97 higher (0.69 to 7.25 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status: POMS anger (follow-up 37 days; range of scores: 0-48; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	27 (IV acyclovir)	27	-	MD 2.3 higher (0.13 lower to 4.73 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status: POMS confusion (follow-up 37 days; range of scores: 0-28; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	27 (IV acyclovir)	27	-	MD 1.83 higher (0.57 to 3.09 higher)	⊕OOO VERY LOW	CRITICAL
Adverse events: treatment-related adverse events (follow-up 9 months)												
1 [original analysis]	randomised trials	very serious[1]	no serious inconsistency	very serious[2]	no serious imprecision	none	0/20 (0%) (oral valganciclovir)	0/10 (0%)	RD 0.00 (-0.14 to 0.14)	0 more per 1000 (from 140 fewer to 140 more)	⊕OOO VERY LOW	CRITICAL
1 [PEM reanalysis]	randomised trials	very serious[1]	no serious inconsistency	serious[4]	no serious imprecision	none						
Adverse events: reversible renal failure (follow-up 37 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	3/27 (11.1%) (IV acyclovir)	0/27 (0%)	Peto OR 7.99 (0.8 to 80.28)	11 more per 1000 (from 20 fewer to 240 more)	⊕OOO VERY LOW	CRITICAL
Activity levels: rest (hours/day) (follow-up 37 days; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	27 (IV acyclovir)	27	-	MD 0.05 lower (0.83 lower to 0.73 higher)	⊕OOO VERY LOW	CRITICAL
Symptom scales: Wellness score (follow-up 37 days; range of scores: not reported; Better indicated by higher values)												

1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	27 (IV acyclovir)	27	-	MD 1.08 lower (7.28 lower to 5.12 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments). Populations were downgraded if the ME/CFS diagnostic criteria used did not include PEM as a compulsory feature (one increment). Montoya 2013 was additionally downgraded due to population having suspected viral onset and requirement to have elevated antibody titres. [original analysis]
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] The majority of the evidence included an indirect population (downgraded by one increment): requirement for suspected viral onset and elevated viral antibody tiers (Montoya 2013). [PEM reanalysis]