Table 23: Clinical evidence profile: Antidepressants (duloxetine, fluoxetine, moclobemide) versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antidepressants (duloxetine, fluoxetine, moclobemide) versus placebo	Control	Relative (95% CI)	Absolute		
Quality of Life: SF36 vitality (follow-up 12 weeks; range of scores: 0-100; Better indicated by higher values)												

1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	20 (duloxetine)	26	-	MD 3.3 higher (10.3 lower to 16.9 higher)	⊕OOO VERY LOW	CRITICAL
Quality of Life: SF-36 physical functioning (follow-up 12 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	20 (duloxetine)	26	-	MD 6.8 higher (8.5 lower to 22.1 higher)	⊕OOO VERY LOW	CRITICAL
Quality of Life: SF-36 role physical (follow-up 12 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	20 (duloxetine)	26	-	MD 11 higher (9 lower to 31 higher)	⊕OOO VERY LOW	CRITICAL
Quality of Life: SF36 mental health (follow-up 12 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	20 (duloxetine)	26	-	MD 1.1 lower (11.8 lower to 9.6 higher)	⊕OOO VERY LOW	CRITICAL
Quality of Life: SF36 role emotional (follow-up 12 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	20 (duloxetine)	26	-	MD 4.4 higher (24.2 lower to 33 higher)	⊕OOO VERY LOW	CRITICAL
Quality of Life: SF36 bodily pain (follow-up 12 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	20 (duloxetine)	26	-	MD 11.4 higher (0.5 lower to 23.3 higher)	⊕OOO VERY LOW	CRITICAL
Quality of Life: SF36 general health (follow-up 12 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	20 (duloxetine)	26	-	MD 0 higher (10.8 lower to 10.8 higher)	⊕OOO VERY LOW	CRITICAL
Quality of Life: SF36 social functioning (follow-up 12 weeks; range of scores: 0-100; Better indicated by higher values)												

1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	20 (duloxetine)	26	-	MD 0.7 higher (14.7 lower to 16.1 higher)	⊕OOO VERY LOW	CRITICAL
Fatigue: 14-item Chalder fatigue scale at 26 weeks (follow-up 26 weeks; range of scores: not reported; Better indicated by lower values)												
1	randomised trials	very serious[3]	no serious inconsistency	serious[2]	serious[3]	none	35 (fluoxetine)	34	-	MD 0.3 lower (4.06 lower to 3.46 higher)	⊕OOO VERY LOW	CRITICAL
Fatigue: MFI-20 general fatigue (follow-up 12 weeks; range of scores: not reported; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	27 (duloxetine)	30	-	MD 1 lower (2.8 lower to 0.8 higher)	⊕OOO VERY LOW	CRITICAL
Fatigue: MFI-20 physical fatigue (follow-up 12 weeks; range of scores: not reported; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	27 (duloxetine)	30	-	MD 0.9 lower (2.7 lower to 0.9 higher)	⊕OOO VERY LOW	CRITICAL
Fatigue: MFI-20 reduced activity (follow-up 12 weeks; range of scores: not reported; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	27 (duloxetine)	30	-	MD 0 higher (1.8 lower to 1.8 higher)	⊕OOO VERY LOW	CRITICAL
Fatigue: MFI-20 reduced motivation (follow-up 12 weeks; range of scores: not reported; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	27 (duloxetine)	30	-	MD 0.8 lower (2.6 lower to 1 higher)	⊕OOO VERY LOW	CRITICAL
Fatigue: MFI-20 mental fatigue (follow-up 12 weeks; range of scores: not reported; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	27 (duloxetine)	30	-	MD 2.5 lower (4.4 to 0.6 lower)	⊕OOO VERY LOW	CRITICAL
Fatigue: Checklist Individual Strength (CIS) fatigue (follow-up 16 weeks; range of scores: 8-56; Better indicated by lower values)												

1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	52 (fluoxetine)	45	-	MD 0.16 lower (0.64 lower to 0.31 higher)	⊕OOO VERY LOW	CRITICAL
Physical functioning: Karnofsky Performance Index (measured in units of standard deviation at baseline) (follow-up 6 weeks; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	40 (moclobemide)	37	-	MD 0.28 higher (0.28 lower to 0.84 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status: Profile of mood states (POMS) fatigue (follow-up 6 weeks; range of scores: 0-28; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	40 (moclobemide)	37	-	MD 0.04 lower (0.2 lower to 0.12 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status: Profile of mood states (POMS) vigour (follow-up 6 weeks; range of scores: 0-32; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	40 (moclobemide)	37	-	MD 0.51 higher (0 to 1.02 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status: Profile of mood states (POMS) depression (follow-up 6 weeks; range of scores: 0-60; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	40 (moclobemide)	37	-	MD 0.02 higher (0.36 lower to 0.4 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status: HADS depression change scores (follow-up 12-26 weeks; range of scores: 0-21; Better indicated by lower values)												
2	randomised trials	very serious[1]	serious[4]	serious[2]	serious[3]	none	62 (fluoxetine or duloxetine)	64	-	MD 0.51 higher (0.72 lower to 1.74 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status: HADS anxiety (follow-up 12 weeks; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	27 (duloxetine)	30	-	MD 0.9 lower (2.4 lower to 0.6 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status: Beck Depression Inventory (follow-up 16 weeks; range of scores: 0-63; Better indicated by lower values)												

1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	52 (fluoxetine)	45	-	MD 0.19 lower (0.35 to 0.02 lower)	⊕OOO VERY LOW	CRITICAL
Pain: Brief Pain Inventory severity (follow-up 12 weeks; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	27 (duloxetine)	30	-	MD 0.73 lower (1 to 0.46 lower)	⊕OOO VERY LOW	CRITICAL
Pain: Brief Pain Inventory interference (follow-up 12 weeks; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	27 (duloxetine)	30	-	MD 0.7 lower (0.96 to 0.44 lower)	⊕OOO VERY LOW	CRITICAL
Adverse events: tremor (follow-up 16 weeks)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	18/45 (40%) (fluoxetine)	13/51 (25.5%)	RR 1.57 (0.87 to 2.83)	145 more per 1000 (from 33 fewer to 466 more)	⊕OOO VERY LOW	CRITICAL
Adverse events: perspiration (follow-up 16 weeks)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	30/45 (66.7%) (fluoxetine)	20/51 (39.2%)	RR 1.7 (1.14 to 2.53)	275 more per 1000 (from 55 more to 600 more)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure: VO2 max (mL O2/kg/min) (follow-up 26 weeks; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	35 (fluoxetine)	34	-	MD 1.1 higher (1.43 lower to 3.63 higher)	⊕OOO VERY LOW	CRITICAL
Symptom scales: Clinical Global Impression of Severity (follow-up 12 weeks; range of scores: 1-7; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	27 (duloxetine)	30	-	MD 0.1 lower (0.3 lower to 0.1 higher)	⊕OOO VERY LOW	CRITICAL
Symptom scales: Clinical Global Impression of Improvement (follow-up 12 weeks; range of scores: 1-7; Better indicated by lower values)												

1	randomised trials	very serious[3]	no serious inconsistency	serious[2]	serious[3]	none	27 (duloxetine)	30	-	MD 0.8 lower (1.7 lower to 0.1 higher)	⊕OOO VERY LOW	CRITICAL
Symptom scales: CDC symptom inventory (follow-up 12 weeks; range of scores: not reported; Better indicated by lower values)												
1	randomised trials	very serious[3]	no serious inconsistency	serious[2]	serious[3]	none	20 (duloxetine)	26	-	MD 2.7 lower (15.5 lower to 10.1 higher)	⊕OOO VERY LOW	CRITICAL
Symptom scales: Improvement of symptoms (patient-reported) (follow-up 6-16 weeks)												
2	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	32/92 (34.8%) (fluoxetine or moclobemide)	19/94 (20.2%)	RR 1.63 (1.02 to 2.59)	127 more per 1000 (from 4 more to 321 more)	⊕OOO VERY LOW	CRITICAL
Symptom scales: Worsening of symptoms (patient-reported) (follow-up 16 weeks)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	7/45 (15.6%) (fluoxetine)	12/51 (23.5%)	RR 0.66 (0.28 to 1.53)	80 fewer per 1000 (from 169 fewer to 125 more)	⊕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
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] Downgraded for inconsistency. I^2=63%