Evidensprofiler for NKR for farmakologisk behandling af bipolar lidelse – supplerende vedligeholdelsesbehandling efter depression

Question: Should Lithium vs Placebo be used for Bipolar Disorder?

Bibliography: NKR Bipolar Lidelse

Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Placebo	With Lithium		Risk with Placebo	Risk difference with Lithium (95% CI)
Ny affektiv episode - Lithium (CRITICAL OUTCOME)											
1802 (7 studies)	no serious risk of bias	no serious inconsistency	serious[1,2,3]	no serious imprecision	undetected	⨁⨁⨁⊖ **MODERATE**[1,2,3] due to indirectness	548/936 (58.5%)	317/866 (36.6%)	**RR 0.65** (0.54 to 0.77)	**585 per 1000**	**205 fewer per 1000** (from 135 fewer to 269 fewer)
Ny depressiv episode - Lithium (IMPORTANT OUTCOME)											
1597 (6 studies)	no serious risk of bias	no serious inconsistency	serious[1,2,3]	no serious imprecision	undetected	⨁⨁⨁⊖ **MODERATE**[1,2,3] due to indirectness	228/832 (27.4%)	161/765 (21%)	**RR 0.78** (0.65 to 0.92)	**274 per 1000**	**60 fewer per 1000** (from 22 fewer to 96 fewer)
Ny manisk episode - Lithium (NOT IMPORTANT OUTCOME)											
1358 (5 studies)	no serious risk of bias	no serious inconsistency	serious[1,2,3]	no serious imprecision	undetected	⨁⨁⨁⊖ **MODERATE**[1,2,3] due to indirectness	240/713 (33.7%)	113/645 (17.5%)	**RR 0.55** (0.41 to 0.73)	**337 per 1000**	**151 fewer per 1000** (from 91 fewer to 199 fewer)
Drop-out - Lithium (CRITICAL OUTCOME)											

1736 (6 studies)	no serious risk of bias	no serious inconsistency	serious[1,2,4]	serious[5]	undetected	⨁⨁⨀⨀ **LOW**[1,2,4,5] due to indirectness, imprecision	668/903 (74%)	501/833 (60.1%)	**RR 0.86** (0.74 to 0.99)	**740 per 1000**	**104 fewer per 1000** (from 7 fewer to 192 fewer)
Død - Lithium (CRITICAL OUTCOME)											
988 (2 studies)	no serious risk of bias	no serious inconsistency	serious[6]	serious[5,7]	undetected	⨁⨁⨀⨀ **LOW**[5,6,7] due to indirectness, imprecision	3/514 (0.58%)	1/474 (0.21%)	**RR 0.33** (0.04 to 3.16)	**6 per 1000**	**4 fewer per 1000** (from 6 fewer to 13 more)
Serious adverse event - Lithium (CRITICAL OUTCOME)											
1103 (3 studies)	no serious risk of bias	no serious inconsistency	serious[1,2,3]	serious[5,8]	undetected	⨁⨁⨀⨀ **LOW**[1,2,3,5,8] due to indirectness, imprecision	29/583 (5%)	20/520 (3.8%)	**RR 0.83** (0.48 to 1.44)	**50 per 1000**	**8 fewer per 1000** (from 26 fewer to 22 more)
Weight gain events - Lithium (IMPORTANT OUTCOME)											
1361 (4 studies)	no serious risk of bias	no serious inconsistency	serious[2,9,10]	no serious imprecision	undetected	⨁⨁⨁⨀ **MODERATE**[2,9,10] due to indirectness	26/688 (3.8%)	51/673 (7.6%)	**RR 1.97** (1.24 to 3.12)	**38 per 1000**	**37 more per 1000** (from 9 more to 80 more)
Sedation - Lithium (IMPORTANT OUTCOME)											
1361 (4 studies)	no serious risk of bias	no serious inconsistency	serious[1]	serious[5]	undetected	⨁⨁⨀⨀ **LOW**[1,5] due to indirectness, imprecision	63/688 (9.2%)	57/673 (8.5%)	**RR 1.05** (0.59 to 1.86)	**92 per 1000**	**5 more per 1000** (from 38 fewer to 79 more)
Selvmord - Lithium (CRITICAL OUTCOME)											
1343 (4 studies)	no serious risk of	no serious inconsistency	serious[1,2,6]	no serious imprecision	undetected	⨁⨁⨁⨀ **MODERATE**[1,2,6]	11/703 (1.6%)	5/640 (0.78%)	**RR 0.55** (0.19 to	**16 per 1000**	**7 fewer per 1000** (from 13 fewer to 10 more)

	bias					due to indirectness		1.61)		
Kidney failure - Lithium (CRITICAL OUTCOME)										
1003368 (1 study)	no serious risk of bias[11]	no serious inconsistency	serious[12]	no serious imprecision	undetected	⨁⊖⊖⊖ **VERY LOW**[11,12] due to indirectness	2202/999999 (0.22%)	18/3369 (0.53%)	-	**Swedish background population**
										2 per 1000
										2 fewer per 1000 (from 2 fewer to 2 fewer)
Glomerular Filtration Rate (GFR) (CRITICAL OUTCOME; Better indicated by lower values)										
679 (6 studies)	no serious risk of bias	serious[13]	serious[14]	serious[5]	undetected	⨁⊖⊖⊖ **VERY LOW**[5,13,14] due to inconsistency, indirectness, imprecision	307	372	-	The mean glomerular filtration rate (gfr) in the control groups was **GFR (ml/min)**
										The mean glomerular filtration rate (gfr) in the intervention groups was **6.22 lower** (14.65 lower to 2.2 higher)

[1] Both monotherapy and add-on studies
[2] Patients index episodes of both manic, depressive and mixed type
[3] Majority of studies non-enriched
[4] The majority of studies enriched for study drug
[5] Wide CI crossing the decision threshold
[6] Both enrichment and non-enrichment study
[7] No events in one of the two studies
[8] One study with no events
[9] Only non-enrichment studies
[10] Only monotherapy studies
[11] Data for renal failure not based on renal biopsies in alle cases.
[12] Not certain that patients were bipolar disorder patients.
[13] Heterogeneity across studies, effect sizes differ in direction.
[14] GFR is a surrogate outcome in relation to kidney failure

Question: Should Aripiprazol vs Placebo be used for Bipolar Disorder?

Bibliography: NKR Bipolar lidelse½

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Placebo	**With Aripiprazol**		**Risk with Placebo**	**Risk difference with Aripiprazol** (95% CI)
Ny affektiv episode - Aripiprazol (CRITICAL OUTCOME)											
927 (4 studies) 24-52 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	no serious imprecision	undetected	⨁⨁⨁⨀ **MODERATE**[1,2,3] due to indirectness	149/465 (32%)	90/462 (19.5%)	**RR 0.61** (0.49 to 0.77)	**320 per 1000**	**125 fewer per 1000** (from 74 fewer to 163 fewer)
Drop-out - Aripiprazol (CRITICAL OUTCOME)											
161 (1 study) 24-52 weeks	no serious risk of bias	no serious inconsistency	serious[2,3,4]	serious[5,6]	undetected	⨁⨁⨀⨀ **LOW**[2,3,4,5,6] due to indirectness, imprecision	55/83 (66.3%)	39/78 (50%)	**RR 0.75** (0.58 to 0.99)	**663 per 1000**	**166 fewer per 1000** (from 7 fewer to 278 fewer)
Død - Aripiprazol (CRITICAL OUTCOME)											
416 (2 studies) 24-52 weeks	no serious risk of bias	no serious inconsistency	serious[2,3,7]	serious[8,9]	undetected	⨁⨁⨀⨀ **LOW**[2,3,7,8,9] due to indirectness, imprecision	1/209 (0.48%)	1/207 (0.48%)	**See comment**[10]	**5 per 1000**	**0 fewer per 1000** (from 20 fewer to 20 more)
Selvmord - Aripiprazol (CRITICAL OUTCOME)											
834 (3 studies)	no serious risk of bias	no serious inconsistency	serious[1,2,3]	serious[8,11]	undetected	⨁⨁⨀⨀ **LOW**[1,2,3,8,11] due to indirectness,	1/414 (0.24%)	1/420 (0.24%)	**See comment**[10]	**2 per 1000**	**1 more per 1000** (from 10 fewer to 10 more)

24-52 weeks						imprecision					
Serious adverse event - Aripiprazol (CRITICAL OUTCOME)											
917 (4 studies) 24-52 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	serious[12]	undetected	⨁⨁⨀⨀ **LOW**[1,2,3,12] due to indirectness, imprecision	33/457 (7.2%)	24/460 (5.2%)	**RR 0.74** (0.44 to 1.25)	**72 per 1000**	**19 fewer per 1000** (from 40 fewer to 18 more)
Ny depressiv episode - Aripiprazol (IMPORTANT OUTCOME)											
927 (4 studies) 24-52 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	serious[9]	undetected	⨁⨁⨀⨀ **LOW**[1,2,3,9] due to indirectness, imprecision	61/465 (13.1%)	47/462 (10.2%)	**RR 0.77** (0.54 to 1.1)	**131 per 1000**	**30 fewer per 1000** (from 60 fewer to 13 more)
Ny manisk episode - Aripiprazol (NOT IMPORTANT OUTCOME)											
924 (4 studies) 24-52 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	no serious imprecision	undetected	⨁⨁⨁⨀ **MODERATE**[1,2,3] due to indirectness	68/462 (14.7%)	35/462 (7.6%)	**RR 0.52** (0.36 to 0.77)	**147 per 1000**	**71 fewer per 1000** (from 34 fewer to 94 fewer)
Weight gain events - Aripiprazol (IMPORTANT OUTCOME)											
873 (4 studies) 24-52 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	serious[9,12]	undetected	⨁⨁⨀⨀ **LOW**[1,2,3,9,12] due to indirectness, imprecision	19/434 (4.4%)	44/439 (10%)	**RR 2.1** (0.86 to 5.09)	**44 per 1000**	**48 more per 1000** (from 6 fewer to 179 more)
Sedation - Aripiprazol (IMPORTANT OUTCOME)											
834 (3 studies) 24-52 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	serious[12,13]	undetected	⨁⨁⨀⨀ **LOW**[1,2,3,12,13] due to indirectness, imprecision	9/414 (2.2%)	6/420 (1.4%)	**RR 0.7** (0.25 to 1.94)	**22 per 1000**	**7 fewer per 1000** (from 16 fewer to 20 more)

[1] Co-medication in add-on studies was lithium/valproate in one study, lamotrigene in one study and valproate in one study.

[2] Enriched discontinuation study design

[3] Patients with a manic/mixed index episode
[4] Monotherapy
[5] Small sample size
[6] Wide CI
[7] Co-medication was lithium/valproate in one study and valproate in one study
[8] Only one event in each group combined
[9] CI crosses zero
[10] Based on too few events to calculate relative difference
[11] Wide CI, the true effect may be higher rates of suicide in drug group
[12] Wide CI, crossing decision threshold
[13] Very few events in each study

Question: Should Olanzapin vs Placebo be used for Bipolar Disorder?

Bibliography: NKR bipolar lidelse

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Placebo	**With Olanzapin**		**Risk with Placebo**	**Risk difference with Olanzapin** (95% CI)
Ny affektiv episode - Olanzapin (CRITICAL OUTCOME)											
723 (3 studies) 48-78 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	no serious imprecision	undetected	⊕⊕⊕⊖ **MODERATE**[1,2,3] due to indirectness	199/317 (62.8%)	151/406 (37.2%)	**RR 0.57** (0.41 to 0.79)	**628 per 1000**	**270 fewer per 1000** (from 132 fewer to 370 fewer)
Drop-out - Olanzapin (CRITICAL OUTCOME)											
627 (3 studies) 48-78 weeks	no serious risk of bias	no serious inconsistency[4]	serious[3,5,6]	serious[7,8]	undetected	⊕⊕⊖⊖ **LOW**[3,4,5,6,7,8] due to indirectness, imprecision	224/271 (82.7%)	237/356 (66.6%)	**RR 0.72** (0.48 to 1.08)	**827 per 1000**	**231 fewer per 1000** (from 430 fewer to 66 more)
Død - Olanzapin (CRITICAL OUTCOME)											
460 (2 studies) 48-78 weeks	no serious risk of bias	no serious inconsistency	serious[1,5,9]	serious[10,11]	undetected	See comment	0/184 (0%)	0/276 (0%)	**See comment**[12]	See comment	**0 fewer per 1000** (from 11.3 fewer to 11.3 more)
Selvmord - Olanzapin (CRITICAL OUTCOME)											
266 (1 study) 78 weeks	no serious risk of bias	no serious inconsistency	serious[1,13]	very serious[14,15,16]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,13,14,15,16] due to indirectness, imprecision	3/135 (2.2%)	0/131 (0%)	**See comment**[12]	**22 per 1000**	**22 fewer per 1000** (from 50 fewer to 10 more)

Serious adverse event - Olanzapin (CRITICAL OUTCOME)											
627 (2 studies) 48-78 weeks	no serious risk of bias	no serious inconsistency	serious[17]	serious[14,18]	undetected	⊕⊕⊖⊖ **LOW**[14,17,18] due to indirectness, imprecision	42/271 (15.5%)	20/356 (5.6%)	**RR 0.42** (0.25 to 0.7)	**155 per 1000**	**90 fewer per 1000** (from 46 fewer to 116 fewer)
Ny depressiv episode - Olanzapin (IMPORTANT OUTCOME)											
723 (3 studies) 48-78 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	serious[16]	undetected	⊕⊕⊖⊖ **LOW**[1,2,3,16] due to indirectness, imprecision	88/317 (27.8%)	95/406 (23.4%)	**RR 0.78** (0.56 to 1.1)	**278 per 1000**	**61 fewer per 1000** (from 122 fewer to 28 more)
Ny manisk episode - Olanzapin (NOT IMPORTANT OUTCOME)											
723 (3 studies) 48-78 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	no serious imprecision	undetected	⊕⊕⊕⊖ **MODERATE**[1,2,3] due to indirectness	91/317 (28.7%)	45/406 (11.1%)	**RR 0.38** (0.27 to 0.53)	**287 per 1000**	**178 fewer per 1000** (from 135 fewer to 210 fewer)
Weight gain events - Olanzapin											
719 (3 studies) 48-78 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	no serious imprecision	undetected	⊕⊕⊕⊖ **MODERATE**[1,2,3] due to indirectness	18/314 (5.7%)	85/405 (21%)	**RR 3.73** (2.28 to 6.09)	**57 per 1000**	**156 more per 1000** (from 73 more to 292 more)
Sedation - Olanzapin											
723 (3 studies) 48-78 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	no serious imprecision	undetected	⊕⊕⊕⊖ **MODERATE**[1,2,3] due to indirectness	8/317 (2.5%)	28/406 (6.9%)	**RR 3.12** (1.49 to 6.53)	**25 per 1000**	**54 more per 1000** (from 12 more to 140 more)

[1] Patients with a manic/mixed index episode
[2] Two monotherapy studies and one add-on study where co-medication was lithium/valproate
[3] The majority of patients originate from enriched discontinuation design studies
[4] Inconsistecy between the two studies, but not impacting decision
[5] Enriched discontinuation study design
[6] Monotherapy studies
[7] CI crossing zero, but not substantially against intervention

[8] Wide CI overlapping no effect
[9] One monotherapy study and one add-on study with co-medication lithium/valproate
[10] CI crosses zero
[11] No events in either group
[12] Based on too few events to calculate relative difference
[13] Monotherapy
[14] Small sample size
[15] Only one study with very few events
[16] Wide CI, crossing decision threshold
[17] Both enrichment and non-enrichment design studies
[18] Wide CI

Question: Should Lamotrigin vs Placebo be used for Bipolar Disorder?

Bibliography: NKR Bipolar lidelse

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Placebo	**With Lamotrigin**		**Risk with Placebo**	**Risk difference with Lamotrigin** (95% CI)
Ny affektiv episode - Lamotrigin (CRITICAL OUTCOME)											
878 (5 studies) 26-76 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	no serious imprecision[4]	undetected	⨁⨁⨁⨀ **MODERATE**[1,2,3,4] due to indirectness	231/402 (57.5%)	235/476 (49.4%)	**RR 0.85** (0.74 to 0.97)	**575 per 1000**	**86 fewer per 1000** (from 17 fewer to 149 fewer)
Drop-out - Lamotrigin (CRITICAL OUTCOME)											
653 (3 studies) 26-76 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,5]	no serious imprecision	undetected	⨁⨁⨁⨀ **MODERATE**[1,2,5] due to indirectness	245/280 (87.5%)	295/373 (79.1%)	**RR 0.93** (0.88 to 0.98)	**875 per 1000**	**61 fewer per 1000** (from 17 fewer to 105 fewer)
Død - Lamotrigin (CRITICAL OUTCOME)											
137 (1 study) 32 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,6]	very serious[7,8,9]	undetected	⨁⨀⨀⨀ **VERY LOW**[1,2,6,7,8,9] due to indirectness, imprecision	0/69 (0%)	0/68 (0%)	**See comment**[10]	See comment	-
Selvmord - Lamotrigin (CRITICAL OUTCOME)											
600 (3 studies) 32-76 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,11]	serious[12,13]	undetected	⨁⨁⨀⨀ **LOW**[1,2,11,12,13] due to indirectness, imprecision	3/258 (1.2%)	6/342 (1.8%)	**See comment**[10]	**12 per 1000**	**8 more per 1000** (from 10 fewer to 30 more)

Serious adverse event - Lamotrigin (CRITICAL OUTCOME)											
549 (4 studies) 26-76 weeks	no serious risk of bias	no serious inconsistency	serious[1,3,6]	serious[14]	undetected	⊕⊕⊖⊖ **LOW**[1,3,6,14] due to indirectness, imprecision	25/285 (8.8%)	21/264 (8%)	**RR 0.92** (0.54 to 1.58)	**88 per 1000**	**7 fewer per 1000** (from 40 fewer to 51 more)
Ny depressiv episode - Lamotrigin (IMPORTANT OUTCOME)											
701 (4 studies) 26-76 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3,6]	no serious imprecision	undetected	⊕⊕⊕⊖ **MODERATE**[1,2,3,6] due to indirectness	127/315 (40.3%)	76/386 (19.7%)	**RR 0.51** (0.4 to 0.65)	**403 per 1000**	**198 fewer per 1000** (from 141 fewer to 242 fewer)
Ny manisk episode - Lamotrigin (NOT IMPORTANT OUTCOME)											
701 (4 studies) 26-76 weeks	no serious risk of bias	no serious inconsistency[15]	serious[1,2,3,6]	serious[16]	undetected	⊕⊕⊖⊖ **LOW**[1,2,3,6,15,16] due to indirectness, imprecision	65/315 (20.6%)	119/386 (30.8%)	**RR 1.33** (0.71 to 2.48)	**206 per 1000**	**68 more per 1000** (from 60 fewer to 305 more)
Weight gain events - Lamotrigin (IMPORTANT OUTCOME)											
392 (2 studies) 76 weeks	no serious risk of bias	no serious inconsistency	serious[1,5]	serious[17]	undetected	⊕⊕⊖⊖ **LOW**[1,5,17] due to indirectness, imprecision	11/165 (6.7%)	18/227 (7.9%)	**RR 1.19** (0.58 to 2.46)	**67 per 1000**	**13 more per 1000** (from 28 fewer to 97 more)
Sedation - Lamotrigin (IMPORTANT OUTCOME)											
417 (2 studies) 76 weeks	no serious risk of bias	no serious inconsistency	serious[1,5]	serious[18]	undetected	⊕⊕⊖⊖ **LOW**[1,5,18] due to indirectness, imprecision	13/190 (6.8%)	21/227 (9.3%)	**RR 1.36** (0.69 to 2.7)	**68 per 1000**	**25 more per 1000** (from 21 fewer to 116 more)

[1] Enriched discontinuation study design
[2] Patients with index episodes of various polarity
[3] All monotherapy studies but one
[4] Wide CI, upper CI boundary close to zero (no effect)
[5] Monotherapy

[6] Add-on study not specifying co-medication
[7] Small sample size
[8] No events in either group
[9] Wide CI, crossing decision threshold
[10] Based on too few events to calculate relative difference
[11] Two monotherapy studies and one add-on study not specifying co-medication
[12] Very few events in each study
[13] Wide CI, the true effect may be higher rates of suicide in drug group
[14] Wide CI overlapping no effect
[15] Some, but not crucial heterogeneity across studies
[16] Wide CI, true effect may be higher incidence of manic relapse in drug group
[17] Wide CI, true effect may be much higher incidence of weight gain events in drug group
[18] Wide CI, true effect may be much higher incidence of sedation in drug group

Question: Should Valproat vs Placebo be used for Bipolar Disorder?

Bibliography: NKR Bipolar lidelse

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Placebo	**With Valproat**		**Risk with Placebo**	**Risk difference with Valproat** (95% CI)
Ny affektiv episode - Valproat (CRITICAL OUTCOME)											
587 (3 studies) 24-52 weeks	serious[1]	no serious inconsistency	serious[2,3,4,5]	no serious imprecision	undetected	⨁⨁⨀⨀ **LOW**[1,2,3,4,5] due to risk of bias, indirectness	140/249 (56.2%)	127/338 (37.6%)	**RR 0.73** (0.57 to 0.94)	**562 per 1000**	**152 fewer per 1000** (from 34 fewer to 242 fewer)
Drop-out - Valproat (CRITICAL OUTCOME)											
501 (2 studies) 24-52 weeks	no serious risk of bias	no serious inconsistency	serious[6,7]	serious[8,9]	undetected	⨁⨁⨀⨀ **LOW**[6,7,8,9] due to indirectness, imprecision	115/204 (56.4%)	162/297 (54.5%)	**RR 0.89** (0.71 to 1.11)	**564 per 1000**	**62 fewer per 1000** (from 163 fewer to 62 more)
Død - Valproat (CRITICAL OUTCOME)											
220 (1 study) 24 weeks	serious[10]	no serious inconsistency	serious[3,11,12]	very serious[13,14]	undetected	⨁⨀⨀⨀ **VERY LOW**[3,10,11,12,13,14] due to risk of bias, indirectness, imprecision	2/110 (1.8%)	1/110 (0.91%)	**See comment**[15]	**18 per 1000**	**9 fewer per 1000** (from 40 fewer to 20 more)
Selvmord - Valproat (CRITICAL OUTCOME)											
220 (1 study)	serious[10]	no serious inconsistency	serious[3,12]	very serious[8,14,16]	undetected	⨁⨀⨀⨀ **VERY LOW**[3,8,10,12,14,16] due to risk of bias,	0/110 (0%)	0/110 (0%)	**See comment**[15]	See comment	-

24 weeks						indirectness, imprecision				
Serious adverse event - Valproat (CRITICAL OUTCOME)										
220 (1 study) 24 weeks	serious[17]	no serious inconsistency	serious[3,11,12]	very serious[9,18]	undetected	⨁⨀⨀⨀ **VERY LOW**[3,9,11,12,17,18] due to risk of bias, indirectness, imprecision	5/110 (4.5%)	4/110 (3.6%)	**RR 0.8** (0.22 to 2.9)	**45 per 1000**	**9 fewer per 1000** (from 35 fewer to 86 more)
Ny depressiv episode - Valproat (IMPORTANT OUTCOME)										
587 (3 studies) 24-52 weeks	no serious risk of bias	no serious inconsistency	serious[1,4,5,11]	serious[9,19]	undetected	⨁⨁⨀⨀ **LOW**[1,4,5,9,11,19] due to indirectness, imprecision	80/249 (32.1%)	69/338 (20.4%)	**RR 0.71** (0.42 to 1.2)	**321 per 1000**	**93 fewer per 1000** (from 186 fewer to 64 more)
Ny manisk episode - Valproat (NOT IMPORTANT OUTCOME)										
587 (3 studies) 32-52 weeks	no serious risk of bias	no serious inconsistency	serious[7,20,21]	serious[9]	undetected	⨁⨁⨀⨀ **LOW**[7,9,20,21] due to indirectness, imprecision	30/139 (21.6%)	38/228 (16.7%)	**RR 0.75** (0.56 to 1.01)	**281 per 1000**	**70 fewer per 1000** (from 124 fewer to 3 more)
Weight gain events - Valproat (IMPORTANT OUTCOME)										
281 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	serious[22,23,24]	no serious imprecision[25]	undetected	⨁⨁⨁⨀ **MODERATE**[22,23,24,25] due to indirectness	7/94 (7.4%)	39/187 (20.9%)	**RR 2.8** (1.3 to 6.02)	**74 per 1000**	**134 more per 1000** (from 22 more to 374 more)
Sedation - Valproat (CRITICAL OUTCOME)										
281 (1 study) 32 weeks	no serious risk of bias	no serious inconsistency	serious[22,23,24]	very serious[8,14]	undetected	⨁⨀⨀⨀ **VERY LOW**[8,14,22,23,24] due to indirectness, imprecision	33/94 (35.1%)	78/187 (41.7%)	**RR 1.19** (0.86 to 1.64)	**351 per 1000**	**67 more per 1000** (from 49 fewer to 225 more)

[1] 40% of total study population from open-label trial

[2] The majority of patients originate from enriched discontinuation design studies

[3] Patients with index episodes of various polarity
[4] One monotherapy study and two add-on studies
[5] Co-medication lithium in one add-on study and lamotrigine in another
[6] One add-on and one monotherapy study
[7] Majority of participants from non-enriched study
[8] Small sample size
[9] Wide CI overlapping no effect
[10] Open-label trial
[11] Enriched discontinuation study design
[12] Co-medication with lithium
[13] Only one study with very few events
[14] Wide CI, crossing decision threshold
[15] Based on too few events to calculate relative difference
[16] No events in either group
[17] No explanation was provided
[18] Very few events in each group
[19] Some, but not crucial heterogeneity across studies
[20] Index episode manic in majority of patients
[21] Co-medication in add-on study lamotrigine
[22] Patients with a manic/mixed index episode
[23] Monotherapy
[24] Non-enriched study
[25] Wide CI

Question: Should Quetiapin vs Placebo be used for Bipolar Disorder?

Bibliography: NKR bipolar lidelse

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Placebo	**With Quetiapin**		**Risk with Placebo**	**Risk difference with Quetiapin** (95% CI)
Ny affektiv episode - Quetiapin (CRITICAL OUTCOME)											
2718 (4 studies) 52-104 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	no serious imprecision	undetected	⊕⊕⊕⊖ **MODERATE**[1,2,3] due to indirectness	670/1378 (48.6%)	287/1340 (21.4%)	**RR 0.44** (0.36 to 0.54)	**486 per 1000**	**272 fewer per 1000** (from 224 fewer to 311 fewer)
Drop-out - Quetiapin (CRITICAL OUTCOME)											
2719 (4 studies) 52-104 weeks	no serious risk of bias	no serious inconsistency[4]	serious[1,2,3]	no serious imprecision	undetected	⊕⊕⊕⊖ **MODERATE**[1,2,3,4] due to indirectness	946/1378 (68.7%)	615/1341 (45.9%)	**RR 0.67** (0.54 to 0.82)	**687 per 1000**	**227 fewer per 1000** (from 124 fewer to 316 fewer)
Død - Quetiapin (CRITICAL OUTCOME)											
2096 (3 studies) 52-104 weeks	no serious risk of bias	no serious inconsistency	serious[1,5,6]	serious[7]	undetected	⊕⊕⊖⊖ **LOW**[1,5,6,7] due to indirectness, imprecision	4/1065 (0.38%)	2/1031 (0.19%)	**See comment**[8]	**4 per 1000**	**1 fewer per 1000** (from 0 more to 0 more)
Selvmord - Quetiapin (CRITICAL OUTCOME)											
2096 (3 studies) 52-104	no serious risk of bias	no serious inconsistency	serious[1,5,6]	serious[9]	undetected	⊕⊕⊖⊖ **LOW**[1,5,6,9] due to indirectness,	15/1065 (1.4%)	6/1031 (0.58%)	**See comment**[8]	**14 per 1000**	**7 fewer per 1000** (from 20 fewer to 10 more)

weeks						imprecision				
Serious adverse event - Quetiapin (IMPORTANT OUTCOME)										
2719 (4 studies) 52-104 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	serious[10]	undetected	⊕⊕⊖⊖ **LOW**[1,2,3,10] due to indirectness, imprecision	54/1378 (3.9%)	36/1341 (2.7%)	**RR 0.65** (0.24 to 1.74)	**39 per 1000**	**14 fewer per 1000** (from 30 fewer to 29 more)
Ny depressiv episode - Quetiapine (IMPORTANT OUTCOME)										
2718 (4 studies) 52-104 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	no serious imprecision	undetected	⊕⊕⊕⊖ **MODERATE**[1,2,3] due to indirectness	358/1378 (26%)	146/1340 (10.9%)	**RR 0.42** (0.35 to 0.5)	**260 per 1000**	**151 fewer per 1000** (from 130 fewer to 169 fewer)
Ny manisk episode - Quetiapine (NOT IMPORTANT OUTCOME)										
2718 (4 studies) 52-104 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	no serious imprecision	undetected	⊕⊕⊕⊖ **MODERATE**[1,2,3] due to indirectness	312/1378 (22.6%)	141/1340 (10.5%)	**RR 0.48** (0.35 to 0.67)	**226 per 1000**	**118 fewer per 1000** (from 75 fewer to 147 fewer)
Weight gain events - Quetiapin (IMPORTANT OUTCOME)										
2719 (4 studies) 52-104 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	no serious imprecision	undetected	⊕⊕⊕⊖ **MODERATE**[1,2,3] due to indirectness	38/1378 (2.8%)	111/1341 (8.3%)	**RR 2.93** (2.03 to 4.21)	**28 per 1000**	**53 more per 1000** (from 28 more to 89 more)
Sedation - Quetiapin (IMPORTANT OUTCOME)										
2719 (4 studies) 52-104 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	no serious imprecision	undetected	⊕⊕⊕⊖ **MODERATE**[1,2,3] due to indirectness	52/1378 (3.8%)	88/1341 (6.6%)	**RR 1.31** (1.35 to 3.94)	**31 per 1000**	**41 more per 1000** (from 11 fewer to 92 more)

[1] Enriched discontinuation study design
[2] Two monotherapy studies and two add-on studies, co-medication lithium/valproate
[3] Depressive index episode in one study and index episode of various polarity in three studies
[4] Significant heterogeneity but all results favoring drug
[5] Two monotherapy studies and one add-on study, co-medication lithium/valproate
[6] Index episode depression in one study and of various polarities in two studies
[7] CI crosses zero
[8] Based on too few events to calculate relative difference
[9] Wide CI, the true effect may be higher rates of suicide in drug group
[10] Wide CI, crossing decision threshold

Question: Should Risperidon vs Placebo be used for Bipolar Disorder?

Bibliography: NKR bipolar lidelse

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Placebo	**With Risperidon**		**Risk with Placebo**	**Risk difference with Risperidon** (95% CI)
Ny affektiv episode - Risperidon (CRITICAL OUTCOME)											
663 (3 studies) 52-104 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	no serious imprecision	undetected	⊕⊕⊕⊖ **MODERATE**[1,2,3] due to indirectness	178/327 (54.4%)	108/336 (32.1%)	**RR 0.6** (0.49 to 0.73)	**544 per 1000**	**218 fewer per 1000** (from 147 fewer to 278 fewer)
Drop-out - Risperidon (CRITICAL OUTCOME)											
694 (3 studies) 52-104 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	no serious imprecision	undetected	⊕⊕⊕⊖ **MODERATE**[1,2,3] due to indirectness	251/343 (73.2%)	186/351 (53%)	**RR 0.73** (0.61 to 0.86)	**732 per 1000**	**198 fewer per 1000** (from 102 fewer to 285 fewer)
Død - Risperidon (CRITICAL OUTCOME)											
124 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	serious[1,4,5]	very serious[6,7,8]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,4,5,6,7,8] due to indirectness, imprecision	2/59 (3.4%)	1/65 (1.5%)	**See comment**[9]	**34 per 1000**	**19 fewer per 1000** (from 70 fewer to 40 more)
Selvmord - Risperidon (CRITICAL OUTCOME)											
694 (3 studies) 52-104	no serious risk of bias	no serious inconsistency	serious[1,2,3]	serious[7,10]	undetected	⊕⊕⊖⊖ **LOW**[1,2,3,7,10] due to indirectness,	7/343 (2%)	3/351 (0.85%)	**See comment**[9]	**20 per 1000**	**9 fewer per 1000** (from 20 fewer to 10 more)

weeks						imprecision					
Serious adverse event - Risperidon (IMPORTANT OUTCOME)											
570 (2 studies) 78-104 weeks	no serious risk of bias	no serious inconsistency	serious[1,11,12]	serious[6,13]	undetected	⨁⨁⨀⨀ **LOW**[1,6,11,12,13] due to indirectness, imprecision	57/284 (20.1%)	32/286 (11.2%)	**RR 0.56** (0.38 to 0.84)	**201 per 1000**	**88 fewer per 1000** (from 32 fewer to 124 fewer)
Ny depressiv episode - Risperidon (IMPORTANT OUTCOME)											
663 (3 studies) 52-104 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	serious[8]	undetected	⨁⨁⨀⨀ **LOW**[1,2,3,8] due to indirectness, imprecision	48/327 (14.7%)	53/336 (15.8%)	**RR 1.08** (0.75 to 1.55)	**147 per 1000**	**12 more per 1000** (from 37 fewer to 81 more)
Ny manisk episode - Risperidon (NOT IMPORTANT OUTCOME)											
663 (3 studies) 52-104 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	no serious imprecision	undetected	⨁⨁⨁⨀ **MODERATE**[1,2,3] due to indirectness	115/327 (35.2%)	43/336 (12.8%)	**RR 0.36** (0.27 to 0.5)	**352 per 1000**	**225 fewer per 1000** (from 176 fewer to 257 fewer)
Weight gain events - Risperidon (IMPORTANT OUTCOME)											
691 (3 studies) 52-104 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	serious[14]	undetected	⨁⨁⨀⨀ **LOW**[1,2,3,14] due to indirectness, imprecision	34/341 (10%)	59/350 (16.9%)	**RR 1.79** (0.79 to 4.08)	**100 per 1000**	**79 more per 1000** (from 21 fewer to 307 more)
Sedation - Risperidon (IMPORTANT OUTCOME)											
388 (2 studies) 52-78 weeks	no serious risk of bias	no serious inconsistency	serious[1,15,16]	serious[14]	undetected	⨁⨁⨀⨀ **LOW**[1,14,15,16] due to indirectness, imprecision	4/192 (2.1%)	12/196 (6.1%)	**RR 2.47** (0.83 to 7.35)	**21 per 1000**	**31 more per 1000** (from 4 fewer to 132 more)

[1] Enriched discontinuation study design
[2] Two monotherapy studies and one add-on study not specifying co-medication
[3] Index episode manic/mixed in two studies and various polarities in one study
[4] Add-on study not specifying co-medication
[5] Patients with index episodes of various polarity
[6] Small sample size
[7] Very few events in each group
[8] Wide CI, crossing decision threshold
[9] Based on too few events to calculate relative difference
[10] Wide CI, the true effect may be higher rates of suicide in drug group
[11] Patients with a manic/mixed index episode
[12] Monotherapy
[13] Wide CI
[14] CI crosses zero
[15] One add-on and one monotherapy study
[16] Manic/mixed index episode in majority of patients

Question: Should Perphenazin vs Placebo be used for Bipolar Disorder?

Bibliography: NKR bipolar lidelse

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Placebo	**With Perphenazin**		**Risk with Placebo**	**Risk difference with Perphenazin** (95% CI)
Ny affektiv episode - Perphenazin (CRITICAL OUTCOME)											
37 (1 study) 26 weeks	no serious risk of bias	no serious inconsistency[1]	serious[2,3,4]	very serious[5,6,7]	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2,3,4,5,6,7] due to indirectness, imprecision	2/18 (11.1%)	5/19 (26.3%)	**RR 2.37** (0.52 to 10.7)	**111 per 1000**	**152 more per 1000** (from 53 fewer to 1000 more)
Drop-out - Perphenazin (CRITICAL OUTCOME)											
37 (1 study) 26 weeks	no serious risk of bias	no serious inconsistency	serious[2,3,4]	serious[5,8]	undetected	⨁⨁⊖⊖ **LOW**[2,3,4,5,8] due to indirectness, imprecision	3/18 (16.7%)	10/19 (52.6%)	**RR 3.16** (1.03 to 9.66)	**167 per 1000**	**360 more per 1000** (from 5 more to 1000 more)
Død - Perphenazin - not reported											
-	-	-	-	-	-	See comment	-	-	**See comment**	See comment	See comment
Selvmord - Perphenazin - not reported											
-	-	-	-	-	-	See comment	-	-	**See comment**	See comment	See comment
Serious adverse event - Perphenazin - not reported											

-	-	-	-	-	-	See comment	-	-	-	See comment	See comment
Ny depressiv episode - Perphenazin (CRITICAL OUTCOME)											
37 (1 study) 26 weeks	no serious risk of bias	no serious inconsistency	serious[2,3,4]	very serious[5,7]	undetected	⨁⊖⊖⊖ **VERY LOW**[2,3,4,5,7] due to indirectness, imprecision	0/18 (0%)	4/19 (21.1%)	**RR 8.55** (0.49 to 148.33)	**0 per 1000**	-
Ny manisk episode - Perphenazin (IMPORTANT OUTCOME)											
37 (1 study) 26 weeks	no serious risk of bias	no serious inconsistency	serious[2,3,4]	very serious[5,7]	undetected	⨁⊖⊖⊖ **VERY LOW**[2,3,4,5,7] due to indirectness, imprecision	2/18 (11.1%)	1/19 (5.3%)	**RR 0.47** (0.05 to 4.78)	**111 per 1000**	**59 fewer per 1000** (from 106 fewer to 420 more)
Weight gain events - Perphenazin - not reported											
-	-	-	-	-	-	See comment	-	-	-	See comment	See comment
Sedation - Perphenazin - not reported											
-	-	-	-	-	-	See comment	-	-	-	See comment	See comment

[1] Only one trial with few number of patients.
[2] Enriched discontinuation study design
[3] Patients with a manic/mixed index episode
[4] Co-medication various 'mood stabilizers'
[5] Small sample size
[6] Very few events in each group
[7] Wide CI, crossing decision threshold
[8] Wide CI

Question: Should Ziprasidon vs Placebo be used for Bipolar Disorder?

Bibliography: NKR bipolar lidelse

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Placebo	**With Ziprasidon**		**Risk with Placebo**	**Risk difference with Ziprasidon** (95% CI)
Ny affektiv episode - Ziprasidon (CRITICAL OUTCOME)											
238 (1 study) 26 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	serious[4,5]	undetected	⨁⨁⨀⨀ **LOW**[1,2,3,4,5] due to indirectness, imprecision	36/111 (32.4%)	25/127 (19.7%)	**RR 0.61** (0.39 to 0.94)	**324 per 1000**	**126 fewer per 1000** (from 19 fewer to 198 fewer)
Drop-out - Ziprasidon - not reported											
-	-	-	-	-	-	See comment	-	-	**-**	See comment	See comment
Død - Ziprasidon - not reported											
-	-	-	-	-	-	See comment	-	-	**See comment**	See comment	See comment
Selvmord - Ziprasidon - not reported											
-	-	-	-	-	-	See comment	-	-	**See comment**	See comment	See comment
Serious adverse event - Ziprasidon (CRITICAL OUTCOME)											
238 (1 study)	no serious	no serious	serious[1,2,3]	very	undetected	⨁⨀⨀⨀ **VERY LOW**[1,2,3,4,6,7]	2/111	3/127	**RR 1.31**	**18 per 1000**	**6 more per 1000** (from 14 fewer to 121 more)

26 weeks	risk of bias	inconsistency		serious[4,6,7]		due to indirectness, imprecision	(1.8%)	(2.4%)	(0.22 to 7.7)		
Ny depressiv episode - Ziprasidon (IMPORTANT OUTCOME)											
238 (1 study) 26 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	very serious[4,7]	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2,3,4,7] due to indirectness, imprecision	16/111 (14.4%)	16/127 (12.6%)	**RR 0.87** (0.46 to 1.66)	**144 per 1000**	**19 fewer per 1000** (from 78 fewer to 95 more)
Ny manisk episode - Ziprasidon (NOT IMPORTANT OUTCOME)											
238 (1 study) 26 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	very serious[4,7]	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2,3,4,7] due to indirectness, imprecision	20/111 (18%)	9/127 (7.1%)	**RR 0.39** (0.19 to 0.83)	**180 per 1000**	**110 fewer per 1000** (from 31 fewer to 146 fewer)
Weight gain events - Ziprasidon (IMPORTANT OUTCOME)											
239 (1 study) 26 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	very serious[4,7]	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2,3,4,7] due to indirectness, imprecision	6/112 (5.4%)	7/127 (5.5%)	**RR 1.03** (0.36 to 2.97)	**54 per 1000**	**2 more per 1000** (from 34 fewer to 106 more)
Sedation - Ziprasidon - not reported											
-	-	-	-	-	-	See comment	-	-	**-**	See comment	See comment

[1] Enriched discontinuation study design
[2] Patients with a manic/mixed index episode
[3] Co-medication with valproate/lithium
[4] Small sample size
[5] Wide CI, upper CI boundary close to zero (no effect)
[6] Only one study with very few events
[7] Wide CI, crossing decision threshold

Question: Should Paliperidon vs Placebo be used for Bipolar Disorder?

Bibliography: NKR bipolar lidelse

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Placebo	**With Paliperidon**		**Risk with Placebo**	**Risk difference with Paliperidon** (95% CI)
Ny affektiv episode - Paliperidon (CRITICAL OUTCOME)											
290 (1 study) 104 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	serious[4,5]	undetected	⨁⨁⨀⨀ **LOW**[1,2,3,4,5] due to indirectness, imprecision	104/144 (72.2%)	85/146 (58.2%)	**RR 0.81** (0.68 to 0.96)	**722 per 1000**	**137 fewer per 1000** (from 29 fewer to 231 fewer)
Drop-out - Paliperidon - not reported											
-	-	-	-	-	-	See comment	-	-	**-**	See comment	See comment
Død - Paliperidon (CRITICAL OUTCOME)											
296 (1 study) 104 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	very serious[6,7]	undetected	⨁⨀⨀⨀ **VERY LOW**[1,2,3,6,7] due to indirectness, imprecision	0/147 (0%)	2/149 (1.3%)	**See comment**[8]	**0 per 1000**	**-**
Selvmord - Paliperidon (CRITICAL OUTCOME)											
295 (1 study) 104 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	very serious[4,7,9]	undetected	⨁⨀⨀⨀ **VERY LOW**[1,2,3,4,7,9] due to indirectness, imprecision	0/147 (0%)	0/148 (0%)	**See comment**[8]	See comment	**-**

Serious adverse event - Paliperidon (CRITICAL OUTCOME)											
296 (1 study) 104 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	very serious[4,7]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2,3,4,7] due to indirectness, imprecision	33/147 (22.4%)	16/149 (10.7%)	**RR 0.48** (0.28 to 0.83)	**224 per 1000**	**117 fewer per 1000** (from 38 fewer to 162 fewer)
Ny depressiv episode - Paliperidon - not reported											
-	-	-	-	-	-	See comment	-	-	**-**	See comment	See comment
Ny manisk episode - Paliperidon - not reported											
-	-	-	-	-	-	See comment	-	-	**-**	See comment	See comment
Weight gain events - Paliperidon (IMPORTANT OUTCOME)											
296 (1 study) 104 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,10]	very serious[4,7]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2,4,7,10] due to indirectness, imprecision	10/147 (6.8%)	12/149 (8.1%)	**RR 1.18** (0.53 to 2.66)	**68 per 1000**	**12 more per 1000** (from 32 fewer to 113 more)
Sedation - Paliperidon - not reported											
-	-	-	-	-	-	See comment	0/147 (0%)	0/149 (0%)	**-**	See comment	See comment

[1] Enriched discontinuation study design
[2] Patients with a manic/mixed index episode
[3] Monotherapy
[4] Small sample size
[5] Wide CI, upper CI boundary close to zero (no effect)
[6] Only one study with very few events
[7] Wide CI, crossing decision threshold
[8] Based on too few events to calculate relative difference
[9] No events in either group
[10] Co-medication in add-on studies was lithium/valproate in one study, lamotrigene in one study and valproate in one study.

Question: Should Lamotrigin vs Placebo be used for Bipolar Disorder?

Bibliography: NKR bipolar lidelse

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Placebo	**With Lamotrigin**		**Risk with Placebo**	**Risk difference with Lamotrigin** (95% CI)
Ny affektiv episode - Lamotrigin (CRITICAL OUTCOME)											
878 (5 studies) 26-76 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	no serious imprecision[4]	undetected	⨁⨁⨁⨀ **MODERATE**[1,2,3,4] due to indirectness	231/402 (57.5%)	235/476 (49.4%)	**RR 0.85** (0.74 to 0.97)	**575 per 1000**	**86 fewer per 1000** (from 17 fewer to 149 fewer)
Drop-out - Lamotrigin (CRITICAL OUTCOME)											
653 (3 studies) 26-76 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,5]	no serious imprecision	undetected	⨁⨁⨁⨀ **MODERATE**[1,2,5] due to indirectness	245/280 (87.5%)	295/373 (79.1%)	**RR 0.93** (0.88 to 0.98)	**875 per 1000**	**61 fewer per 1000** (from 17 fewer to 105 fewer)
Død - Lamotrigin (CRITICAL OUTCOME)											
137 (1 study) 32 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,6]	very serious[7,8,9]	undetected	⨁⨀⨀⨀ **VERY LOW**[1,2,6,7,8,9] due to indirectness, imprecision	0/69 (0%)	0/68 (0%)	**See comment**[10]	See comment	-
Selvmord - Lamotrigin (CRITICAL OUTCOME)											
600 (3 studies) 32-76 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,11]	serious[12,13]	undetected	⨁⨁⨀⨀ **LOW**[1,2,11,12,13] due to indirectness, imprecision	3/258 (1.2%)	6/342 (1.8%)	**See comment**[10]	**12 per 1000**	**8 more per 1000** (from 10 fewer to 30 more)

Serious adverse event - Lamotrigin (CRITICAL OUTCOME)											
549 (4 studies) 26-76 weeks	no serious risk of bias	no serious inconsistency	serious[1,3,6]	serious[14]	undetected	⊕⊕⊖⊖ **LOW**[1,3,6,14] due to indirectness, imprecision	25/285 (8.8%)	21/264 (8%)	**RR 0.92** (0.54 to 1.58)	**88 per 1000**	**7 fewer per 1000** (from 40 fewer to 51 more)
Ny depressiv episode - Lamotrigin (IMPORTANT OUTCOME)											
701 (4 studies) 26-76 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3,6]	no serious imprecision	undetected	⊕⊕⊕⊖ **MODERATE**[1,2,3,6] due to indirectness	127/315 (40.3%)	76/386 (19.7%)	**RR 0.51** (0.4 to 0.65)	**403 per 1000**	**198 fewer per 1000** (from 141 fewer to 242 fewer)
Ny manisk episode - Lamotrigin (NOT IMPORTANT OUTCOME)											
701 (4 studies) 26-76 weeks	no serious risk of bias	no serious inconsistency[15]	serious[1,2,3,6]	serious[16]	undetected	⊕⊕⊖⊖ **LOW**[1,2,3,6,15,16] due to indirectness, imprecision	65/315 (20.6%)	119/386 (30.8%)	**RR 1.33** (0.71 to 2.48)	**206 per 1000**	**68 more per 1000** (from 60 fewer to 305 more)
Weight gain events - Lamotrigin (IMPORTANT OUTCOME)											
392 (2 studies) 76 weeks	no serious risk of bias	no serious inconsistency	serious[1,5]	serious[17]	undetected	⊕⊕⊖⊖ **LOW**[1,5,17] due to indirectness, imprecision	11/165 (6.7%)	18/227 (7.9%)	**RR 1.19** (0.58 to 2.46)	**67 per 1000**	**13 more per 1000** (from 28 fewer to 97 more)
Sedation - Lamotrigin (IMPORTANT OUTCOME)											
417 (2 studies) 76 weeks	no serious risk of bias	no serious inconsistency	serious[1,5]	serious[18]	undetected	⊕⊕⊖⊖ **LOW**[1,5,18] due to indirectness, imprecision	13/190 (6.8%)	21/227 (9.3%)	**RR 1.36** (0.69 to 2.7)	**68 per 1000**	**25 more per 1000** (from 21 fewer to 116 more)

[1] Enriched discontinuation study design
[2] Patients with index episodes of various polarity
[3] All monotherapy studies but one
[4] Wide CI, upper CI boundary close to zero (no effect)
[5] Monotherapy

[6] Add-on study not specifying co-medication
[7] Small sample size
[8] No events in either group
[9] Wide CI, crossing decision threshold
[10] Based on too few events to calculate relative difference
[11] Two monotherapy studies and one add-on study not specifying co-medication
[12] Very few events in each study
[13] Wide CI, the true effect may be higher rates of suicide in drug group
[14] Wide CI overlapping no effect
[15] Some, but not crucial heterogeneity across studies
[16] Wide CI, true effect may be higher incidence of manic relapse in drug group
[17] Wide CI, true effect may be much higher incidence of weight gain events in drug group
[18] Wide CI, true effect may be much higher incidence of sedation in drug group

Question: Should Valproate vs Placebo be used for Bipolar Disorder?

Bibliography: NKR bipolar lidelse

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Placebo	**With Valproate**		**Risk with Placebo**	**Risk difference with Valproate** (95% CI)
Ny affektiv episode - Valproat (CRITICAL OUTCOME)											
587 (3 studies) 24-52 weeks	serious[1]	no serious inconsistency	serious[2,3,4,5]	no serious imprecision	undetected	⨁⨁⨀⨀ **LOW**[1,2,3,4,5] due to risk of bias, indirectness	140/249 (56.2%)	127/338 (37.6%)	**RR 0.73** (0.57 to 0.94)	**562 per 1000**	**152 fewer per 1000** (from 34 fewer to 242 fewer)
Drop-out - Valproat (CRITICAL OUTCOME)											
501 (3 studies) 24-52 weeks	no serious risk of bias	no serious inconsistency	serious[6,7]	serious[8,9]	undetected	⨁⨁⨀⨀ **LOW**[6,7,8,9] due to indirectness, imprecision	115/204 (56.4%)	162/297 (54.5%)	**RR 0.89** (0.71 to 1.11)	**564 per 1000**	**62 fewer per 1000** (from 163 fewer to 62 more)
Død - Valproat (CRITICAL OUTCOME)											
220 (1 study) 24 weeks	serious[10]	no serious inconsistency	serious[3,11,12]	very serious[13,14]	undetected	⨁⨀⨀⨀ **VERY LOW**[3,10,11,12,13,14] due to risk of bias, indirectness, imprecision	2/110 (1.8%)	1/110 (0.91%)	**See comment**[15]	**18 per 1000**	**9 fewer per 1000** (from 40 fewer to 20 more)
Selvmord - Valproat (CRITICAL OUTCOME)											
220 (1 study)	serious[10]	no serious inconsistency	serious[3,12]	very serious[8,14,16]	undetected	⨁⨀⨀⨀ **VERY LOW**[3,8,10,12,14,16] due to risk of bias,	0/110 (0%)	0/110 (0%)	**See comment**[15]	See comment	-

24 weeks						indirectness, imprecision					
Serious adverse event - Valproat (CRITICAL OUTCOME)											
220 (1 study) 24 weeks	serious[17]	no serious inconsistency	serious[3,11,12]	very serious[9,18]	undetected	⨁⊖⊖⊖ **VERY LOW**[3,9,11,12,17,18] due to risk of bias, indirectness, imprecision	5/110 (4.5%)	4/110 (3.6%)	**RR 0.8** (0.22 to 2.9)	**45 per 1000**	**9 fewer per 1000** (from 35 fewer to 86 more)
Ny depressiv episode - Valproat (IMPORTANT OUTCOME)											
587 (3 studies) 24-52 weeks	no serious risk of bias	no serious inconsistency	serious[1,4,5,11]	serious[9,19]	undetected	⨁⨁⊖⊖ **LOW**[1,4,5,9,11,19] due to indirectness, imprecision	80/249 (32.1%)	69/338 (20.4%)	**RR 0.71** (0.42 to 1.2)	**321 per 1000**	**93 fewer per 1000** (from 186 fewer to 64 more)
Ny manisk episode - Valproat (NOT IMPORTANT OUTCOME)											
367 (2 studies) 32-52 weeks	no serious risk of bias	no serious inconsistency	serious[7,20,21]	serious[9]	undetected	⨁⨁⊖⊖ **LOW**[7,9,20,21] due to indirectness, imprecision	30/139 (21.6%)	38/228 (16.7%)	**RR 0.75** (0.48 to 1.17)	**216 per 1000**	**54 fewer per 1000** (from 112 fewer to 37 more)
Weight gain events - Valproat (IMPORTANT OUTCOME)											
281 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	serious[22,23,24]	no serious imprecision[25]	undetected	⨁⨁⨁⊖ **MODERATE**[22,23,24,25] due to indirectness	7/94 (7.4%)	39/187 (20.9%)	**RR 2.8** (1.3 to 6.02)	**74 per 1000**	**134 more per 1000** (from 22 more to 374 more)
Sedation - Valproat (CRITICAL OUTCOME)											
281 (1 study) 32 weeks	no serious risk of bias	no serious inconsistency	serious[22,23,24]	very serious[8,14]	undetected	⨁⊖⊖⊖ **VERY LOW**[8,14,22,23,24] due to indirectness, imprecision	33/94 (35.1%)	78/187 (41.7%)	**RR 1.19** (0.86 to 1.64)	**351 per 1000**	**67 more per 1000** (from 49 fewer to 225 more)

[1] 40% of total study population from open-label trial

[2] The majority of patients originate from enriched discontinuation design studies

[3] Patients with index episodes of various polarity
[4] One monotherapy study and two add-on studies
[5] Co-medication lithium in one add-on study and lamotrigine in another
[6] One add-on and one monotherapy study
[7] Majority of participants from non-enriched study
[8] Small sample size
[9] Wide CI overlapping no effect
[10] Open-label trial
[11] Enriched discontinuation study design
[12] Co-medication with lithium
[13] Only one study with very few events
[14] Wide CI, crossing decision threshold
[15] Based on too few events to calculate relative difference
[16] No events in either group
[17] No explanation was provided
[18] Very few events in each group
[19] Some, but not crucial heterogeneity across studies
[20] Index episode manic in majority of patients
[21] Co-medication in add-on study lamotrigine
[22] Patients with a manic/mixed index episode
[23] Monotherapy
[24] Non-enriched study
[25] Wide CI

Question: Should Oxcarbazepine vs Placebo be used for Bipolar Disorder?

Bibliography: NKR bipolar lidelse

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Placebo	**With Oxcarbazepine**		**Risk with Placebo**	**Risk difference with Oxcarbazepine** (95% CI)
Ny affektiv episode - Oxcarbazepin (CRITICAL OUTCOME)											
55 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness[1,2]	serious[3,4]	undetected	⨁⨁⨁⊖ **MODERATE**[1,2,3,4] due to imprecision	18/29 (62.1%)	8/26 (30.8%)	**RR 0.5** (0.26 to 0.94)	**621 per 1000**	**310 fewer per 1000** (from 37 fewer to 459 fewer)
Drop-out - Oxcarbazepin - not reported											
-	-	-	-	-	-	See comment	-	-	**-**	See comment	See comment
Død - Oxcarbazepin - not reported											
-	-	-	-	-	-	See comment	-	-	**See comment**	See comment	See comment
Selvmord - Oxcarbazepin - not reported											
-	-	-	-	-	-	See comment	-	-	**See comment**	See comment	See comment
Ny depressiv episode - Oxcarbazepin (IMPORTANT OUTCOME)											
55 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness[1,2]	very serious[3,5]	undetected	⨁⨁⊖⊖ **LOW**[1,2,3,5] due to imprecision	9/29 (31%)	3/26 (11.5%)	**RR 0.37** (0.11 to 1.23)	**310 per 1000**	**196 fewer per 1000** (from 276 fewer to 71 more)

Ny manisk episode - Oxcarbazepin (NOT IMPORTANT OUTCOME)											
55 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness[1,2]	very serious[3,6]	undetected	⨁⨁⨀⨀ **LOW**[1,2,3,6] due to imprecision	8/29 (27.6%)	4/26 (15.4%)	**RR 0.56** (0.19 to 1.64)	**276 per 1000**	**121 fewer per 1000** (from 223 fewer to 177 more)
Serious adverse event - Oxcarbazepin (CRITICAL OUTCOME)											
55 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness[1,2]	very serious[5,7]	undetected	⨁⨁⨀⨀ **LOW**[1,2,5,7] due to imprecision	3/29 (10.3%)	3/26 (11.5%)	**RR 1.12** (0.25 to 5.05)	**103 per 1000**	**12 more per 1000** (from 78 fewer to 419 more)
Weight gain events - Oxcarbazepin (IMPORTANT OUTCOME)											
55 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness[1,2]	very serious[3,6]	undetected	⨁⨁⨀⨀ **LOW**[1,2,3,6] due to imprecision	2/29 (6.9%)	5/26 (19.2%)	**RR 2.79** (0.59 to 13.16)	**69 per 1000**	**123 more per 1000** (from 28 fewer to 839 more)
Sedation - Oxcarbazepin - not reported											
-	-	-	-	-	-	See comment	-	-	**-**	See comment	See comment

[1] Index episode not specified
[2] Co-medication with lithium
[3] Small sample size
[4] Wide CI, upper CI boundary close to zero (no effect)
[5] Wide CI overlapping no effect
[6] Wide CI, crossing decision threshold
[7] Very few events in each group

Question: Should Imipramine vs Placebo be used for Bipolar Disorder?

Bibliography: NKR bipolar lidelse

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Placebo	**With Imipramine**		**Risk with Placebo**	**Risk difference with Imipramine** (95% CI)
Ny affektiv episode - Imipramin (CRITICAL OUTCOME)											
153 (2 studies) 24-104 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	very serious[4,5]	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2,3,4,5] due to indirectness, imprecision	31/80 (38.8%)	30/73 (41.1%)	**RR 1.07** (0.67 to 1.71)	**388 per 1000**	**27 more per 1000** (from 128 fewer to 275 more)
Drop-out - Imipramin (CRITICAL OUTCOME)											
75 (1 study) 24 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,6]	very serious[4,7]	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2,4,6,7] due to indirectness, imprecision	29/38 (76.3%)	32/37 (86.5%)	**RR 1.13** (0.91 to 1.41)	**763 per 1000**	**99 more per 1000** (from 69 fewer to 313 more)
Død - Imipramin - not reported											
-	-	-	-	-	-	See comment	-	-	**See comment**	See comment	See comment
Selvmord - Imipramin - not reported											
-	-	-	-	-	-	See comment	-	-	**See comment**	See comment	See comment
Serious adverse event - Imipramin - not reported											

-	-	-	-	-	-	See comment	-	-	-	See comment	See comment
Ny depressiv episode - Imipramin (IMPORTANT OUTCOME)											
153 (2 studies) 24-104 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	very serious[8,9]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2,3,8,9] due to indirectness, imprecision	16/80 (20%)	11/73 (15.1%)	**RR 0.78** (0.39 to 1.53)	**200 per 1000**	**44 fewer per 1000** (from 122 fewer to 106 more)
Ny manisk episode - Imipramin (NOT IMPORTANT OUTCOME)											
153 (2 studies) 24-104 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	serious[10]	undetected	⊕⊕⊖⊖ **LOW**[1,2,3,10] due to indirectness, imprecision	15/80 (18.8%)	19/73 (26%)	**RR 1.41** (0.67 to 2.92)	**188 per 1000**	**77 more per 1000** (from 62 fewer to 360 more)
Weight gain events - Imipramin - not reported											
-	-	-	-	-	-	See comment	-	-	-	See comment	See comment
Sedation - Imipramin - not reported											
-	-	-	-	-	-	See comment	-	-	-	See comment	See comment

[1] Enriched discontinuation study design
[2] Co-medication with lithium
[3] Patients with both manic/mixed and depressive index episodes in both stuides
[4] Small sample size
[5] Wide CI, true effect may be higher incidence of new affective episodes in drug group
[6] Patients with index episodes of various polarity
[7] Wide CI overlapping no effect
[8] Very few events in each group
[9] Wide CI, true effect may bemore depressive relapses in drug group
[10] Wide CI, true effect may be higher incidence of manic relapse in drug group

Question: Should Olanzapin vs Lithium be used for Bipolar Disorder?

Bibliography: NKR bipolar lidelse

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Lithium	**With Olanzapin**		**Risk with Lithium**	**Risk difference with Olanzapin** (95% CI)
Ny affektiv episode - Olanzapin (CRITICAL OUTCOME)											
395 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness[1,2,3]	serious[4]	undetected	⊕⊕⊕⊖ **MODERATE**[1,2,3,4] due to imprecision	69/193 (35.8%)	53/202 (26.2%)	**RR 0.73** (0.54 to 0.99)	**358 per 1000**	**97 fewer per 1000** (from 4 fewer to 164 fewer)
Drop-out - Olanzapin - not reported											
-	-	-	-	-	-	See comment	-	-	**-**	See comment	See comment
Død - Olanzapin (CRITICAL OUTCOME)											
431 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness[1,2,3]	serious[5,6]	undetected	⊕⊕⊕⊖ **MODERATE**[1,2,3,5,6] due to imprecision	2/214 (0.93%)	0/217 (0%)	**See comment**[7]	**9 per 1000**	**9 fewer per 1000** (from 30 fewer to 10 more)
Selvmord - OLA (CRITICAL OUTCOME)											
431 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness[2,3]	serious[5]	undetected	⊕⊕⊕⊖ **MODERATE**[2,3,5] due to imprecision	1/214 (0.47%)	0/217 (0%)	**RR 0.33** (0.01 to 8.03)	**5 per 1000**	**3 fewer per 1000** (from 5 fewer to 33 more)
Serious adverse event - Olanzapin - not reported											

-	-	-	-	-	-	See comment	-	-	**See comment**	See comment	See comment
Ny depressiv episode - Olanzapin (IMPORTANT OUTCOME)											
395 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness[1,2,3]	serious[5]	undetected	⊕⊕⊕⊖ **MODERATE**[1,2,3,5] due to imprecision	16/193 (8.3%)	28/202 (13.9%)	**RR 1.67** (0.93 to 2.99)	**83 per 1000**	**56 more per 1000** (from 6 fewer to 165 more)
Ny manisk episode - Olanzapin (NOT IMPORTANT OUTCOME)											
395 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness[1,2,3]	serious[8]	undetected	⊕⊕⊕⊖ **MODERATE**[1,2,3,8] due to imprecision	49/193 (25.4%)	24/202 (11.9%)	**RR 0.47** (0.3 to 0.73)	**254 per 1000**	**135 fewer per 1000** (from 69 fewer to 178 fewer)
Sedation - Olanzapin - not reported											
-	-	-	-	-	-	See comment	-	-	**-**	See comment	See comment
Weight gain events - OLA (IMPORTANT OUTCOME)											
341 (1 study) 52 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness[1,2,3]	serious[8]	undetected	⊕⊕⊕⊖ **MODERATE**[1,2,3,8] due to imprecision	21/214 (9.8%)	64/127 (50.4%)	**RR 5.14** (3.3 to 7.98)	**98 per 1000**	**406 more per 1000** (from 226 more to 685 more)

[1] Study non-enriched for study drug
[2] Patients with manic index episode
[3] Monotherapy
[4] Wide CI, close to no effect
[5] Wide CI, crossing decision threshold
[6] Low event rate
[7] Based on too few events to estimate relative difference
[8] Small total sample size

Question: Should Quetiapine vs Lithium be used for Bipolar Disorder?

Bibliography: NKR bipolar lidelse

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Lithium	**With Quetiapine**		**Risk with Lithium**	**Risk difference with Quetiapine** (95% CI)
Ny affektiv episode - Quetiapin (CRITICAL OUTCOME)											
768 (1 study) 104 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	serious[4]	undetected	⨁⨁⨀⨀ **LOW**[1,2,3,4] due to indirectness, imprecision	95/364 (26.1%)	91/404 (22.5%)	**RR 0.86** (0.67 to 1.11)	**261 per 1000**	**37 fewer per 1000** (from 86 fewer to 29 more)
Drop-out - Quetiapin (CRITICAL OUTCOME)											
768 (1 study) 104 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	serious[5,6]	undetected	⨁⨁⨀⨀ **LOW**[1,2,3,5,6] due to indirectness, imprecision	188/364 (51.6%)	152/404 (37.6%)	**RR 0.73** (0.62 to 0.85)	**516 per 1000**	**139 fewer per 1000** (from 77 fewer to 196 fewer)
Død - Quetiapin (CRITICAL OUTCOME)											
768 (1 study) 104 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	serious[7]	undetected	⨁⨁⨀⨀ **LOW**[1,2,3,7] due to indirectness, imprecision	0/364 (0%)	0/404 (0%)	**See comment**[8]	See comment	-
Selvmord - Quetiapin (CRITICAL OUTCOME)											
768 (1 study) 104 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	serious[4,9]	undetected	⨁⨁⨀⨀ **LOW**[1,2,3,4,9] due to indirectness,	3/364 (0.82%)	3/404 (0.74%)	**RR 0.9** (0.18 to 4.44)	**8 per 1000**	**1 fewer per 1000** (from 7 fewer to 28 more)

						imprecision				
Serious adverse event - Quetiapin (CRITICAL OUTCOME)										
768 (1 study) 104 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	serious[4,9]	undetected	⊕⊕⊖⊖ **LOW**[1,2,3,4,9] due to indirectness, imprecision	10/364 (2.7%)	5/404 (1.2%)	**See comment**[8]	**27 per 1000**	**15 fewer per 1000** (from 40 fewer to 0 more)
Ny depressiv episode - Quetiapin (IMPORTANT OUTCOME)										
768 (1 study) 104 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	serious[10]	undetected	⊕⊕⊖⊖ **LOW**[1,2,3,10] due to indirectness, imprecision	49/364 (13.5%)	36/404 (8.9%)	**RR 0.66** (0.44 to 0.99)	**135 per 1000**	**46 fewer per 1000** (from 1 fewer to 75 fewer)
Ny manisk episode - Quetiapin (NOT IMPORTANT OUTCOME)										
768 (1 study) 104	no serious risk of bias	no serious inconsistency	serious[1,2,3]	serious[4]	undetected	⊕⊕⊖⊖ **LOW**[1,2,3,4] due to indirectness, imprecision	46/364 (12.6%)	55/404 (13.6%)	**RR 1.08** (0.75 to 1.55)	**126 per 1000**	**10 more per 1000** (from 32 fewer to 70 more)
Weight gain events - Quetiapin (IMPORTANT OUTCOME)										
822 (1 study) 104 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	serious[5,6]	undetected	⊕⊕⊖⊖ **LOW**[1,2,3,5,6] due to indirectness, imprecision	23/418 (5.5%)	43/404 (10.6%)	**RR 1.93** (1.19 to 3.15)	**55 per 1000**	**51 more per 1000** (from 10 more to 118 more)
Sedation - Quetiapin (IMPORTANT OUTCOME)										
822 (1 study) 104 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	serious[5,6]	undetected	⊕⊕⊖⊖ **LOW**[1,2,3,5,6] due to indirectness, imprecision	11/418 (2.6%)	27/404 (6.7%)	**RR 2.54** (1.28 to 5.05)	**26 per 1000**	**41 more per 1000** (from 7 more to 107 more)

[1] Monotherapy
[2] Study enriched for study drug
[3] Patients with index episode of various polarity
[4] Wide CI, crossing decision threshold
[5] Small total sample size
[6] Wide CI
[7] No events in either study group
[8] Based on too few events to estimate relative difference
[9] Low event rate
[10] Wide CI, close to no effect

Question: Should Lamotrigine vs Lithium be used for Bipolar Disorder?

Bibliography: NKR bipolar lidelse

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Lithium	**With Lamotrigine**		**Risk with Lithium**	**Risk difference with Lamotrigine** (95% CI)
Ny affektiv episode - Lamotrigin (CRITICAL OUTCOME)											
437 (2 studies) 52-76 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	serious[4,5]	undetected	⨁⨁⨀⨀ **LOW**[1,2,3,4,5] due to indirectness, imprecision	74/164 (45.1%)	143/273 (52.4%)	**RR 1.15** (0.94 to 1.41)	**451 per 1000**	**68 more per 1000** (from 27 fewer to 185 more)
Drop-out - Lamotrigin (CRITICAL OUTCOME)											
447 (2 studies) 52-76 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	no serious imprecision[5]	undetected	⨁⨁⨁⨀ **MODERATE**[1,2,3,5] due to indirectness	146/167 (87.4%)	239/280 (85.4%)	**RR 0.98** (0.92 to 1.04)	**874 per 1000**	**17 fewer per 1000** (from 70 fewer to 35 more)
Død - Lamotrigin - not reported											
-	-	-	-	-	-	See comment	-	-	**See comment**	See comment	See comment
Selvmord - Lamotrigin (CRITICAL OUTCOME)											
463 (2 studies) 52-76 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	serious[4,5,6]	undetected	⨁⨁⨀⨀ **LOW**[1,2,3,4,5,6] due to indirectness, imprecision	3/189 (1.6%)	5/274 (1.8%)	**RR 1.37** (0.32 to 5.92)	**16 per 1000**	**6 more per 1000** (from 11 fewer to 78 more)

Serious adverse event - Lamotrigin - not reported											
-	-	-	-	-	-	See comment	-	-	**See comment**	See comment	See comment
Ny depressiv episode - Lamotrigin (IMPORTANT OUTCOME)											
437 (2 studies) 52-76 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	serious[5,7]	undetected	⨁⨁⨀⨀ **LOW**[1,2,3,5,7] due to indirectness, imprecision	56/164 (34.1%)	46/273 (16.8%)	**RR 0.48** (0.34 to 0.67)	**341 per 1000**	**178 fewer per 1000** (from 113 fewer to 225 fewer)
Ny manisk episode - Lamotrigin (NOT IMPORTANT OUTCOME)											
102 (1 study) 76 weeks	no serious risk of bias	no serious inconsistency	serious[1,8,9]	serious[4,5]	undetected	⨁⨁⨀⨀ **LOW**[1,4,5,8,9] due to indirectness, imprecision	8/44 (18.2%)	20/58 (34.5%)	**RR 1.9** (0.92 to 3.9)	**182 per 1000**	**164 more per 1000** (from 15 fewer to 527 more)
Weight gain events - Lamotrigin (IMPORTANT OUTCOME)											
391 (2 studies) 52-76 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	serious[4,5]	undetected	⨁⨁⨀⨀ **LOW**[1,2,3,4,5] due to indirectness, imprecision	16/164 (9.8%)	18/227 (7.9%)	**RR 0.81** (0.43 to 1.55)	**98 per 1000**	**19 fewer per 1000** (from 56 fewer to 54 more)
Sedation - Lamotrigin (IMPORTANT OUTCOME)											
391 (2 studies) 52-76 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	serious[4,5]	undetected	⨁⨁⨀⨀ **LOW**[1,2,3,4,5] due to indirectness, imprecision	22/164 (13.4%)	21/227 (9.3%)	**RR 0.69** (0.39 to 1.21)	**134 per 1000**	**42 fewer per 1000** (from 82 fewer to 28 more)

[1] Monotherapy
[2] Patients with manic index episode in one study and depressive index episode in one study
[3] Studies enriched for study drug
[4] Wide CI, crossing decision threshold
[5] Small total sample size
[6] Low event rate

[7] Wide CI
[8] Patients with manic index episode
[9] Study enriched for study drug

Question: Should Valproate vs Lithium be used for Bipolar Disorder?

Bibliography: NKR bipolar lidelse

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Lithium	**With Valproate**		**Risk with Lithium**	**Risk difference with Valproate** (95% CI)
Ny affektiv episode - Valproat (CRITICAL OUTCOME)											
558 (3 studies) 24-80 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	serious[4,5]	undetected	⨁⨁⨀⨀ **LOW**[1,2,3,4,5] due to indirectness, imprecision	111/233 (47.6%)	135/325 (41.5%)	**RR 0.99** (0.75 to 1.29)	**476 per 1000**	**5 fewer per 1000** (from 119 fewer to 138 more)
Drop-out - Valproat (CRITICAL OUTCOME)											
558 (3 studies) 24-80 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	no serious imprecision	undetected	⨁⨁⨁⨀ **MODERATE**[1,2,3] due to indirectness	140/233 (60.1%)	179/325 (55.1%)	**RR 0.85** (0.75 to 0.96)	**601 per 1000**	**90 fewer per 1000** (from 24 fewer to 150 fewer)
Død - Valproat (CRITICAL OUTCOME)											
220 (1 study) 24 weeks	no serious risk of bias	no serious inconsistency	serious[1,2]	serious[4,5,6]	undetected	⨁⨁⨀⨀ **LOW**[1,2,4,5,6] due to indirectness, imprecision	2/110 (1.8%)	3/110 (2.7%)	**See comment**	**18 per 1000**	**9 more per 1000** (from 30 fewer to 50 more)
Selvmord - Valproat (CRITICAL OUTCOME)											
220 (1 study) 24 weeks	no serious risk of bias	no serious inconsistency	serious[1,2]	serious[5,7]	undetected	⨁⨁⨀⨀ **LOW**[1,2,5,7] due to indirectness, imprecision	0/110 (0%)	0/110 (0%)	-	See comment	-

Serious adverse event - Valproat (CRITICAL OUTCOME)											
220 (1 study) 24 weeks	no serious risk of bias	no serious inconsistency	serious[1,2]	serious[4,5,6]	undetected	⊕⊕⊖⊖ **LOW**[1,2,4,5,6] due to indirectness, imprecision	5/110 (4.5%)	7/110 (6.4%)	**See comment**	**45 per 1000**	**18 more per 1000** (from 40 fewer to 80 more)
Ny depressiv episode - Valproat (IMPORTANT OUTCOME)											
558 (3 studies) 24-80 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	serious[4,5]	undetected	⊕⊕⊖⊖ **LOW**[1,2,3,4,5] due to indirectness, imprecision	55/233 (23.6%)	70/325 (21.5%)	**RR 1.03** (0.62 to 1.7)	**236 per 1000**	**7 more per 1000** (from 90 fewer to 165 more)
Ny manisk episode - Valproat (NOT IMPORTANT OUTCOME)											
558 (3 studies) 24-80 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	serious[4,5]	undetected	⊕⊕⊖⊖ **LOW**[1,2,3,4,5] due to indirectness, imprecision	60/233 (25.8%)	85/325 (26.2%)	**RR 1.1** (0.78 to 1.55)	**258 per 1000**	**26 more per 1000** (from 57 fewer to 142 more)
Weight gain events - Valproat (IMPORTANT OUTCOME)											
338 (2 studies) 52-80 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,8]	serious[4,5]	undetected	⊕⊕⊖⊖ **LOW**[1,2,4,5,8] due to indirectness, imprecision	13/123 (10.6%)	40/215 (18.6%)	**RR 1.56** (0.87 to 2.79)	**106 per 1000**	**59 more per 1000** (from 14 fewer to 189 more)
Sedation - Valproat (IMPORTANT OUTCOME)											
338 (2 studies) 52-80 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,8]	serious[5,9]	undetected	⊕⊕⊖⊖ **LOW**[1,2,5,8,9] due to indirectness, imprecision	26/123 (21.1%)	79/215 (36.7%)	**RR 1.54** (1.06 to 2.25)	**211 per 1000**	**114 more per 1000** (from 13 more to 264 more)

[1] Monotherapy
[2] Patients with index episode of various polarity
[3] Two studies with non-enriched design, one study with enrichment for study drug
[4] Wide CI, crossing decision threshold

[5] Small total sample size
[6] Low event rate
[7] No events in either study group
[8] One study with enrichment design, one study with non-enrichment design
[9] Wide CI

Question: Should Imipramine vs Lithium be used for Bipolar Disorder?

Bibliography: NKR bipolar lidelse

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Lithium	**With Imipramine**		**Risk with Lithium**	**Risk difference with Imipramine** (95% CI)
Ny affektiv episode - Imipramin (CRITICAL OUTCOME)											
78 (1 study) 104 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	serious[4,5]	undetected	⨁⨁⨀⨀ **LOW**[1,2,3,4,5] due to indirectness, imprecision	23/42 (54.8%)	29/36 (80.6%)	**RR 1.47** (1.07 to 2.02)	**548 per 1000**	**257 more per 1000** (from 38 more to 559 more)
Drop-out - Imipramin - not reported											
-	-	-	-	-	-	See comment	-	-	**-**	See comment	See comment
Død - Imipramin - not reported											
-	-	-	-	-	-	See comment	-	-	**See comment**	See comment	See comment
Selvmord - Imipramin - not reported											
-	-	-	-	-	-	See comment	-	-	**-**	See comment	See comment
Serious adverse event - Imipramin - not reported											
-	-	-	-	-	-	See comment	-	-	**See comment**	See comment	See comment

Ny depressiv episode - Imipramin - not reported											
-	-	-	-	-	-	See comment	-	-	-	See comment	See comment
Ny manisk episode - Imipramin (NOT IMPORTANT OUTCOME)											
78 (1 study) 104 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	serious[4,5]	undetected	⨁⨁⨀⨀ **LOW**[1,2,3,4,5] due to indirectness, imprecision	11/42 (26.2%)	19/36 (52.8%)	**RR 2.02** (1.11 to 3.65)	**262 per 1000**	**267 more per 1000** (from 29 more to 694 more)
Weight gain events - Imipramin - not reported											
-	-	-	-	-	-	See comment	-	-	-	See comment	See comment
Sedation - Imipramin - not reported											
-	-	-	-	-	-	See comment	-	-	-	See comment	See comment

[1] Study non-enriched for study drug
[2] Monotherapy
[3] Patients with index episode of various polarity
[4] Small total sample size
[5] Wide CI

Question: Should Carbamazepine vs Lithium be used for Bipolar Disorder?

Bibliography: NKR bipolar lidelse

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Lithium	**With Carbamazepine**		**Risk with Lithium**	**Risk difference with Carbamazepine** (95% CI)
Ny affektiv episode - Carbamazepin (CRITICAL OUTCOME)											
228 (3 studies) 52-130 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	serious[4,5]	undetected	⨁⨁⨀⨀ **LOW**[1,2,3,4,5] due to indirectness, imprecision	37/120 (30.8%)	47/108 (43.5%)	**RR 1.38** (0.94 to 2.02)	**308 per 1000**	**117 more per 1000** (from 18 fewer to 314 more)
Drop-out - Carbamazepin (CRITICAL OUTCOME)											
228 (3 studies) 52-130 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,3]	serious[4,5]	undetected	⨁⨁⨀⨀ **LOW**[1,2,3,4,5] due to indirectness, imprecision	55/113 (48.7%)	75/115 (65.2%)	**RR 1.22** (0.86 to 1.74)	**487 per 1000**	**107 more per 1000** (from 68 fewer to 360 more)
Død - Carbamazepin (CRITICAL OUTCOME)											
103 (1 study) 130 weeks	no serious risk of bias	no serious inconsistency	serious[1,2,6]	serious[4,5,7]	undetected	⨁⨁⨀⨀ **LOW**[1,2,4,5,6,7] due to indirectness, imprecision	1/43 (2.3%)	0/60 (0%)	**See comment**[8]	**23 per 1000**	**23 fewer per 1000** (from 80 fewer to 30 more)
Selvmord - Carbamazepin (CRITICAL OUTCOME)											
103 (3 studies)	no serious	no serious	serious[1,2,6]	serious[4,5,7]	undetected	⨁⨁⨀⨀ **LOW**[1,2,4,5,6,7]	0/60	2/43	**RR 6.93** (0.34 to	**0 per 1000**	-

130 weeks	risk of bias	inconsistency				due to indirectness, imprecision	(0%) (4.7%)	140.84)		
Serious adverse event - Carbamazepin - not reported										
-	-	-	-	-	-	See comment	- -	**See comment**	See comment	See comment
Ny depressiv episode - Carbamazepin - not reported										
-	-	-	-	-	-	See comment	- -	**-**	See comment	See comment
Ny manisk episode - Carbamazepin - not reported										
-	-	-	-	-	-	See comment	- -	**-**	See comment	See comment
Weight gain events - Carbamazepin - not reported										
-	-	-	-	-	-	See comment	- -	**-**	See comment	See comment
Sedation - Carbamazepin - not reported										
-	-	-	-	-	-	See comment	- -	**-**	See comment	See comment

[1] Monotherapy
[2] Patients with index episode of various polarity
[3] One study with enrichment design, two studies with non-enrichment design
[4] Wide CI, crossing decision threshold
[5] Small total sample size
[6] Study non-enriched for study drug
[7] Low event rate
[8] Based on too few events to estimate relative difference