Evidensprofiler PICO 2-10: NKR for behandling af patienter med skizofreni og komplekse behandlingsforløb

Evidensprofiler PICO 2: Reduktion af clozapin-dosis ved plasmakoncentration over den øvre grænse i det vejledende terapeutiske interval.

Tabel 1: Depotinjektion af antipsykotiske lægemidler, RCT'er.

Question: PICO 1 Should Long-Acting Injectable antipsychotics versus oral antipsychotics be used for schizophrenia?
Bibliography: Update of Kishomoto 2014

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Long-Acting Injectable antipsychotics versus oral antipsychotics	Control	Relative (95% CI)	Absolute		
Relapse (longest time point, at least 6 months)												
21	randomised trials	serious[1]	serious[2]	serious[3]	serious[4]	none	645/2752 (23.4%)	730/2577 (28.3%)	RR 0.93 (0.79 to 1.1)	20 fewer per 1000 (from 59 fewer to 28 more)	⊕OOO VERY LOW	CRITICAL
Hospitalization (at least 1 hospitalization within study duration, at least 6 months)												
10	randomised trials	serious[1]	no serious inconsistency	serious[3]	no serious imprecision	none	243/1187 (20.5%)	310/1203 (25.8%)	RR 0.87 (0.7 to 1.08)	33 fewer per 1000 (from 77 fewer to 21 more)	⊕⊕OO LOW	IMPORTANT
All-cause discontinuation												
19	randomised trials	serious[1]	no serious inconsistency	serious[3]	no serious imprecision	none	990/2564 (38.6%)	999/2414 (41.4%)	RR 0.97 (0.87 to 1.08)	12 fewer per 1000 (from 54 fewer to 33 more)	⊕⊕OO LOW	IMPORTANT
Mortality												
8	randomised trials	serious[1]	no serious inconsistency	serious[3]	serious[4]	none	10/2297 (0.44%)	18/2005 (0.9%)	RR 0.6 (0.28 to 1.3)	4 fewer per 1000 (from 6 fewer to 3 more)	⊕OOO VERY LOW	IMPORTANT
Quality of life - Heinrichs-Carpenter Quality of Life Scale (QLS) (Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	serious[3]	serious[4]	none	454	452	-	SMD 0.64 lower (1.99 lower to 0.72 higher)	⊕OOO VERY LOW	IMPORTANT
Injection site adverse events												
2	randomised trials	serious[1]	no serious inconsistency	serious[3]	serious[4]	none	37/529 (7%)	6/526 (1.1%)	RR 7.8 (0.68 to 89.73)	78 more per 1000 (from 4 fewer to 1000 more)	⊕OOO VERY LOW	IMPORTANT
Discontinuation due to adverse events												
18	randomised trials	serious[1]	serious[5]	serious[3]	serious[4]	none	91/2456 (3.7%)	75/2293 (3.3%)	RR 1.06 (0.78 to 1.45)	2 more per 1000 (from 7 fewer to 15 more)	⊕OOO VERY LOW	IMPORTANT
Number of violent episodes per month during the study (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[6]	none	26	20	-	MD 1.19 lower (1.84 to 0.54 lower)	⊕⊕OO LOW	IMPORTANT
Criminal behaviour - not reported												
0	-	-	-	-	-	none	-	-	-	-		

[1] Many studies with unclear randomization sequence generation and allocation concealment and/or high risk of performance/detection bias
[2] Studies before 2005 report positive findings compared with studies after 2005, but even in studies after 2005 there is some inconsistency between results
[3] RCTs included in general patients that are more compliant and with less illness severity than the clinical population of patients with schizophrenia. This pose a special problem when investigating LAIs because the patient population that should have been included in the studies, i.e. patients with poor treatment adherence, are not investigated. As such the results have poor generalizability to the clinical population of patients with schizophrenia that is in question for use of LAI antipsychotics
[4] Either end of the CI would yield a different result
[5] Inconsistent results across included studies
[6] Only 1 study

Tabel 2: Depotinjektion af antipsykotiske lægemidler, mirror-image studier

Question: Should antipsychotic LAI be used in schizophrenia?
Settings: PICO 2_mirror-image studies
Bibliography: Data from Kishimoto et al. 2013: Meta-analysis of mirror-image studies

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antipsychotic LAI**	**Control**	**Relative (95% CI)**	**Absolute**		
Risk of hospitalization (follow-up 12 months)												
16	observational studies	very serious[1]	serious[2]	no serious indirectness	no serious imprecision	strong association[3]	-	0%	RR 0.430 (0.35 to 0.527)	-	⊕OOO VERY LOW	IMPORTANT
Number of hospitalizations (Better indicated by lower values)												
15	observational studies	very serious[1]	serious[2]	no serious indirectness	no serious imprecision	strong association[4]	0	-	-	RR 0.381 higher (0.238 to 0.512 higher)	⊕OOO VERY LOW	IMPORTANT

[1] Mirror-image studies are associated with risk of bias, i.e., expectation bias, regression to the mean, all studies investigated switch from oral to LAI, selection bias, change in health policies etc.
[2] Estimates for individual studies differ (not all CIs overlap)
[3] RR = 0.43 for rehospitalization
[4] RR = 0.381 for number of hospitalizations

Tabel 3: Depotinjektion af antipsykotiske lægemidler, kohorte studier

Question: Should Long-Acting Injectable antipsychotics vs oral antipsychotics be used for Schizophrenia?
Settings: PICO 2_cohort studies

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Long-Acting Injectable antipsychotics**	**Oral antipsychotics**	**Relative (95% CI)**	**Absolute**		
All cause discontinuation												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	strong association		0%	HR 0.41 (0.27 to 0.61)[2]		⊕OOO VERY LOW	IMPORTANT
Rehospitalization												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	strong association		0%	HR 0.36 (0.17 to 0.75)[2]		⊕OOO VERY LOW	IMPORTANT

[1] Observational study, no randomisation
[2] adjusted by: age at diagnosis, sex, duration of first hospital episode, and current and previous use of anxiolytics, hypnotics and sedatives, antidepressants, drugs used in addictive disorders, analgesics, antiparkinsonian drugs, blood glucose-lowering drugs, lipid-modifying agents, previous use of antipsychotics, during the follow-up and the choice of initial antipsychotic (serving as a surrogate for the patient's clinical status at baseline and thus reflecting the clinical correlates determining the selection of treatment).

Evidensprofiler PICO 3: Tillægsbehandling med SSRI/SNRI

Tabel 4: Tillægsbehandling med SSRI

Question: PICO 3 Should Antidepressants (SSRI) be used in schizophrenia?
Settings: mostly outpatients without concomitant depression

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antidepressants (SSRI)	Control	Relative (95% CI)	Absolute		
Negative symptoms (PANSS, SANS, BPRS), end of treatment (duration 4 weeks to 6 months) (Better indicated by lower values)												
14	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	281	284	-	SMD 0.31 lower (0.51 to 0.10 lower)	⊕⊕OO LOW	CRITICAL
Positive symptoms (PANSS, SAPS, BPRS), end of treatment (duration 4 weeks to 6 month) (Better indicated by lower values)												
12	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	245	247	-	SMD 0.07 lower (0.25 lower to 0.11 higher)	⊕⊕⊕O MODERATE	IMPORTANT
All-cause discontinuation (study duration: 4 weeks to 6 months)												
11	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[2]	43/235 (18.3%)	29/238 (12.2%)	RR 1.38 (0.88 to 2.16)	46 more per 1000 (from 15 fewer to 141 more)	⊕OOO VERY LOW	IMPORTANT
Neurological side effects, end of treatment (higher=worse) (Better indicated by lower values)												
8	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	168	168	-	SMD 0.02 lower (0.32 lower to 0.28 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Agitation, end of treatment (number of events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	1/13 (7.7%)	4/13 (30.8%)	RR 0.19 (0.02 to 1.98)	249 fewer per 1000 (from 302 fewer to 302 more)	⊕⊕OO LOW	IMPORTANT
QoL (QLS scale), end of intervention (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	23	24	-	SMD 6.3 lower (17.22 lower to 4.62 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Negative symptoms, longest follow-up - not reported[5]												
0[5]	-	-	-	-	-	none	0	-	-	-		IMPORTANT
Suicide/serious attempt - not reported[6]												
0[6]	-	-	-	-	-	none	-	-	-	-		IMPORTANT

[1] Considerable number of risk-of-bias assessment judged 'unclear'
[2] Asymmetric funnel plot
[3] different ends of CI yields different conclusions
[4] small sample size
[5] No studies estimated outcome at longer follow-up than 6 months
[6] Suicide or suicide attempt was not mentioned in any of the studies

Tabel 5: Tillægsbehandling med SNRI

Question: PICO 3 Should Antidepressants (SNRI) be used in schizophrenia?
Settings: mostly outpatients without concomitant depression

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antidepressants (SNRI)	Control	Relative (95% CI)	Absolute		
Negative symptoms (PANSS), end of treatment (duration 4 weeks to 6 months) (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3]	none	20	20	-	SMD 1.38 lower (2.07 to 0.68 lower)	⊕OOO VERY LOW	CRITICAL
Positive symptoms (PANSS), end of treatment (duration 4 weeks to 6 month) (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3,4]	none	20	20	-	SMD 0.00 higher (0.62 lower to 0.62 higher)	⊕OOO VERY LOW	IMPORTANT
All-cause discontinuation (study duration: 4 weeks to 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3,4]	none	3/20 (15%)	4/20 (20%)	RR 0.75 (0.19 to 2.93)	50 fewer per 1000 (from 162 fewer to 386 more)	⊕OOO VERY LOW	IMPORTANT
Neurological side effects, end of treatment (higher=worse) - not reported												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT
Agitation, end of treatment (number of events) - not reported												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT
QoL (QLS scale), end of intervention - not reported												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT
Negative symptoms, longest follow-up - not reported												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT
Suicide/serious attempt - not reported												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT

[1] Risk of performance bias (not sufficient blinding)
[2] small sample size
[3] Only one study
[4] different ends of CI yields different conclusions

Evidensprofil PICO 4: Ophør med antipsykotisk behandling

Tabel 6: Vedligeholdelsesbehandling med antipsykotiske lægemidler, ikke-remitterede patienter

Question: PICO 4 Should Maintenance AP drug treatment be used for non-remitted schizophrenia patients?
Settings: Outpatients

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Maintenance AP drug treatment	Control	Relative (95% CI)	Absolute		
Relapse up to 3 months												
10	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	142/943 (15.1%)	266/794 (33.5%)	RR 0.44 (0.37 to 0.53)	188 fewer per 1000 (from 157 fewer to 211 fewer)	⊕⊕OO LOW	CRITICAL
Relapse from 7 months to 1 year												
18	randomised trials	serious[1,3]	no serious inconsistency	serious[2]	no serious imprecision	none	351/1621 (21.7%)	782/1417 (55.2%)	RR 0.38 (0.32 to 0.46)	342 fewer per 1000 (from 298 fewer to 375 fewer)	⊕⊕OO LOW	CRITICAL
Number of participants hospitalized (> 7 months)												
8	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	103/718 (14.3%)	195/684 (28.5%)	RR 0.51 (0.4 to 0.66)	140 fewer per 1000 (from 97 fewer to 171 fewer)	⊕⊕OO LOW	CRITICAL
Adverse effects: weight gain >= 7% (7 to 12 months)												
4	randomised trials	serious[3]	no serious inconsistency	serious[2]	no serious imprecision	none	47/573 (8.2%)	17/572 (3%)	RR 2.83 (1.29 to 6.2)	54 more per 1000 (from 9 more to 155 more)	⊕⊕OO LOW	IMPORTANT
Adverse effects: at least one adverse event (7 to 12 months)												
6	randomised trials	serious[4]	no serious inconsistency	serious[2]	serious[5]	none	509/1049 (48.5%)	340/777 (43.8%)	RR 0.97 (0.88 to 1.06)	13 fewer per 1000 (from 53 fewer to 26 more)	⊕OOO VERY LOW	IMPORTANT
Leaving the study early due to adverse events (> 7 months)												
11	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[5]	none	39/1031 (3.8%)	27/751 (3.6%)	RR 0.76 (0.46 to 1.26)	9 fewer per 1000 (from 19 fewer to 9 more)	⊕OOO VERY LOW	IMPORTANT
Suicide (7 to 12 months)												
4	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[5]	none	0/600 (0%)	1/455 (0.22%)	RR 0.32 (0.01 to 7.86)	1 fewer per 1000 (from 2 fewer to 15 more)	⊕⊕OO LOW	IMPORTANT
Suicide attempt												
2	randomised trials	serious[6]	no serious inconsistency	serious[2]	serious[5]	none	1/374 (0.27%)	1/236 (0.42%)	RR 0.7 (0.07 to 6.65)	1 fewer per 1000 (from 4 fewer to 24 more)	⊕OOO VERY LOW	IMPORTANT
Quality of life (7 to 12 months) (measured with: Schizophrenia Quality-of-Life Scale; Better indicated by lower values)												
1	randomised trials	serious[7]	no serious inconsistency	serious[8]	serious[3]	none	104	101	-	SMD 0.01 lower (0.29 lower to 0.26 higher)	⊕OOO VERY LOW	IMPORTANT
Functioning (measured with: GAF or PSP; Better indicated by higher values)												
2	randomised trials	serious[9]	no serious inconsistency	serious[2]	serious[5]	none	175	171	-	SMD 0.12 higher (0.46 lower to 0.7 higher)	⊕OOO VERY LOW	IMPORTANT
Criminal behaviour (7 to 12 months) (assessed with: Violent/aggressive behavior)												

2	randomised trials	serious[9]	no serious inconsistency	serious[2]	no serious imprecision	none	8/146 (5.5%)	27/142 (19%)	RR 0.3 (0.15 to 0.6)	133 fewer per 1000 (from 76 fewer to 162 fewer)	⊕⊕OO LOW	IMPORTANT
Coercion												
0	No evidence available					none	-	-	-	-		IMPORTANT

[1] Many studies with unclear randomisation sequence generation and allocation concealment
[2] Only maintenance trials of not remitted patients were included, however, all the trials only recruited patients previously stabilised on antipsychotic drug treatment and many trials required fairly low burden of symptoms to be included in the maintenance versus placebo phase
[3] No explanation was provided
[4] All included studies high risk of attrition bias
[5] Either end of the CI would give a different results
[6] Half of items are either unclear or low risk of attrition bias
[7] High risk of performance bias, attrition bias and other bias (study was stopped after interim analysis and showed clear advantage of AP)
[8] Included patients had a low symptom score
[9] Of few studies available many items with high risk of bias

Evidensprofil PICO 5: Familieintervention

Tabel 7: Familieintervention til patienter med skizofreni og betydelig funktionsnedsættelse

Question: PICO 5 Should family intervention vs TAU be used in Schizophrenia?

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Familyintervention	TAU	Relative (95% CI)	Absolute		
Family burden, end of treatment (measured with: FBIS, SBAS, Family Burden; Better indicated by lower values)												
8	randomised trials	serious[1,2,3]	serious[4]	no serious indirectness	no serious imprecision	none	195	191	-	SMD 0.56 lower (1.13 to 0.01 lower)	⊕⊕OO LOW	CRITICAL
Clinical relapse, end of treatment												
34	randomised trials	very serious[1,2,3,5,6]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[7]	287/1377 (20.8%)	522/1383 (37.7%)	RR 0.55 (0.47 to 0.65)	170 fewer per 1000 (from 132 fewer to 200 fewer)	⊕OOO VERY LOW	CRITICAL
Clinical relapse, longest FU												
11	randomised trials	serious[1,2,3,6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	140/334 (41.9%)	146/300 (48.7%)	RR 0.77 (0.6 to 0.98)	112 fewer per 1000 (from 10 fewer to 195 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
Days at hospital, end of treatment (Better indicated by lower values)												
8	randomised trials	serious[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	269	264	-	MD 3.2 lower (4.54 to 1.86 lower)	⊕⊕⊕O MODERATE	IMPORTANT
Carer satisfaction, end of treatment (measured with: SSQ6, VSSS, modified Patient Satisfaction Questionnaire; Better indicated by higher values)												
4	randomised trials	serious[1,2,6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	139	136	-	SMD 0.34 higher (0.63 to 0.05 higher)	⊕⊕⊕O MODERATE	IMPORTANT
QoL (higher=better), end of treatment (measured with: final scores, change scores; Better indicated by higher values)												
2	randomised trials	serious[1,2,3,6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	129	134	-	SMD 0.5 higher (0.75 to 0.25 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Social functioning, end of treatment (measured with: SFS, SLFS, SOFAS. SDSS, HoNOS; Better indicated by lower values)												
10	randomised trials	serious[1,2,3]	serious[4]	no serious indirectness	no serious imprecision	none	392	380	-	SMD 0.42 lower (0.70 to 0.15 lower)	⊕⊕OO LOW	IMPORTANT
Crime (imprisonment), longest FU												
1	randomised trials	serious[1,2,3,6]	no serious inconsistency	no serious indirectness	serious[8]	none	3/20 (15%)	3/19 (15.8%)	RR 0.95 (0.22 to 4.14)	8 fewer per 1000 (from 123 fewer to 496 more)	⊕⊕OO LOW	IMPORTANT
Family burden, longest FU - not reported												
0	-	-	-	-	-	none	0	-	-	-		IMPORTANT

[1] Risk of selection bias
[2] Risk of performance bias
[3] Risk of detection bias
[4] High heterogeneity among studies
[5] Risk of attrition bias
[6] Risk of reporting bias
[7] Funnel plot suggests risk of publication bias
[8] 95% CI could be in favour of both intervention and control

Evidensprofil PICO 6: Neurokognitiv træning

Tabel 8: Neurokognitiv træning til patienter med skizofreni og betydelig funktionsnedsættelse

Question: PICO 8 Should Cognitive remediation versus TAU be used in schizofrenia?

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Cognitive remediation**		**Relative (95% CI)**	**Absolute**		
Global cognition score (Z score), end of treatment (Better indicated by higher values)												
2	randomised trials	serious[1,2]	no serious inconsistency	no serious indirectness	serious[3]	none	63	55	-	SMD 0.28 higher (0.7 lower to 0.13 higher)	⊕⊕OO LOW	CRITICAL
Social functioning, end of treatment (measured with: SBS, SFS, SSSI, WHODAS, SOFAS; Better indicated by higher values)												
6	randomised trials	serious[1,2]	serious[4]	no serious indirectness	no serious imprecision	none	236	243	-	SMD 0.56 higher (0.16 to 0.96 higher)	⊕⊕OO LOW	IMPORTANT
Social functioning, longest FU (measured with: SBS, SFS, SoFAS; Better indicated by higher values)												
4	randomised trials	serious[1,2,5]	no serious inconsistency	no serious indirectness	serious[3]	none	130	131	-	SMD 0.26 higher (0.01 to 0.51 higher)	⊕⊕OO LOW	IMPORTANT
Working memory, end of treatment (measured with: ANS, ACT, BACS, WAIS, WAIS II, WAIS III, WAIS-R ; Better indicated by higher values)												
9	randomised trials	serious[1,2,5]	serious[4]	no serious indirectness	no serious imprecision	none	302	272	-	SMD 0.66 higher (0.27 to 1.04 higher)	⊕⊕OO LOW	IMPORTANT
Verbal learning and memory, Total, end of treatment (measured with: HVLT, RAVLT; Better indicated by higher values)												
2	randomised trials	serious[2,5,6]	serious[4]	no serious indirectness	no serious imprecision	none	53	44	-	SMD 0.5 higher (1.37 lower to 2.37 higher)	⊕⊕OO LOW	IMPORTANT
Verbal learning, end of treatment (measured with: RAVLT, CVLT, WLM, WMS-ST, HVLT; Better indicated by higher values)												
6	randomised trials	serious[1,2]	serious[4]	no serious indirectness	serious[3]	none	172	158	-	SMD 0.23 higher (0.09 to 0.55 higher)	⊕OOO VERY LOW	IMPORTANT
Verbal memory, end of treatment (measured with: CVLT, HVLT, RAVLT, Cognistat, Groebe DfR16, BACS, WMS-LT, HVLT-R; Better indicated by higher values)												
10	randomised trials	serious[1,2,5]	serious[4]	no serious indirectness	no serious imprecision	none	323	255	-	SMD 0.34 higher (0.04 lower to 0.71 higher)	⊕⊕OO LOW	IMPORTANT
Symptoms, End of treatment (measured with: PANSS, BPRS; Better indicated by lower values)												
6	randomised trials	serious[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	185	182	-	SMD 0.12 lower (0.32 lower to 0.08 higher)	⊕⊕⊕O MODERATE	IMPORTANT
QoL, end of treatment (measured with: QOLI, OLS, SQoL; Better indicated by higher values)												
4	randomised trials	serious[1,2,5]	serious[4]	no serious indirectness	serious[3]	none	139	118	-	SMD 0.85 higher (0.34 lower to 2.03 higher)	⊕OOO VERY LOW	IMPORTANT
Days at hospital - not reported												
0	-	-	-	-	-	none	0	-	-	-		IMPORTANT

[1] Risk of selection bias
[2] Risk of performance bias
[3] 95% CI could be in favour of both intervention and control
[4] Considerable inconsistency between studies
[5] Risk of attrition bias
[6] Risk of reporting bias

Evidensprofil PICO 7: Socialkognitiv træning

Tabel 9: Socialkognitiv træning til patienter med skizofreni og betydelig funktionsnedsættelse

Question: PICO 9 Should Socialcognition vs TAU be used in Schizophrenia?

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Socialcognition	TAU	Relative (95% CI)	Absolute		
Theory of mind, end of treatment (measured with: PST, Hinting task, Attribution of intentions[1]; Better indicated by higher values)												
3	randomised trials	serious[2,3,4,5]	serious[6]	no serious indirectness	no serious imprecision	none	67	59	-	SMD 0.29 higher (0.4 lower to 0.98 higher)	⊕⊕OO LOW	CRITICAL
Theory of mind, Longest FU (min 4-6 mo) (measured with: Eyes task, hinting task; Better indicated by higher values)												
2	randomised trials	serious[2,3,5]	serious[6]	no serious indirectness	no serious imprecision	none	52	47	-	SMD 0.45 higher (0.67 lower to 1.57 higher)	⊕⊕OO LOW	IMPORTANT
Emotion processing/emotion perception (higher=better), end of treatment (measured with: PFA, ERT, POFA, Emotion discrimination task; Better indicated by higher values)												
5	randomised trials	serious[2,3,4,5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	95	83	-	SMD 0.81 higher (0.5 to 1.12 higher)	⊕⊕⊕O MODERATE	CRITICAL
Emotion processing/Emotion perception, longest FU (measured with: FEIT; Better indicated by higher values)												
1	randomised trials	serious[3,5]	no serious inconsistency	no serious indirectness	serious[7]	none	22	17	-	MD 2.65 higher (0.78 to 4.52 higher)	⊕⊕OO LOW	IMPORTANT
Social function, end of treatment (measured with: SFS, VSSS, GSFS, Whodas2[1]; Better indicated by lower values)												
4	randomised trials	serious[2,3,4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	87	91	-	SMD 0.02 higher (0.27 lower to 0.32 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Social function Longest FU (min 4-6 mo) (measured with: SFS, VSSS, GSFS, PSP; Better indicated by higher values)												
4	randomised trials	serious[2,3,4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	100	100	-	SMD 0.54 higher (0.04 to 1.04 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Social perception, End of treatment (measured with: EPS, TASIT; Better indicated by higher values)												
2	randomised trials	serious[2,3,4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	39	38	-	MD 0.4 higher (3.17 lower to 3.96 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Social perception, longest FU (measured with: TASIT; Better indicated by higher values)												
1	randomised trials	serious[2,3,4]	no serious inconsistency	no serious indirectness	serious[7]	none	30	30	-	SMD 0 higher (0.51 lower to 0.5 higher)	⊕⊕OO LOW	IMPORTANT
Symptomatic relapse												
3	randomised trials		no serious inconsistency	no serious indirectness	serious[8]	none	28/130 (21.5%)	28/108 (25.9%)	RR 0.75 (0.45 to 1.24)	65 fewer per 1000 (from 143 fewer to 62 more)	⊕⊕OO LOW	IMPORTANT
Symptoms, end of treatment (measured with: PANNS, BPRS; Better indicated by lower values)												
6	randomised trials	serious[2,3,4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	134	132	-	SMD 0.08 lower (0.39 lower to 0.22 higher)	⊕⊕⊕O MODERATE	IMPORTANT
QoL Mental/Psych, end of treatment (measured with: SF-36, WHOQoL; Better indicated by higher values)												
2	randomised trials	serious[2,3,4]	serious[6]	no serious indirectness	serious[8]	none	33	36	-	SMD 0.89 higher (0.56 lower to 2.33 higher)	⊕OOO VERY LOW	IMPORTANT
QoL (social), end of treatment (measured with: SF-36, WHOQoL; Better indicated by higher values)												
2	randomised trials	serious[2,3,4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	52	49	-	SMD 0.24 higher (0.15 lower to 0.64 higher)	⊕⊕⊕O MODERATE	IMPORTANT
QLS, wellbeing (Better indicated by higher values)												

2	randomised trials		serious[6]	no serious indirectness	serious[8]	none	36	36	-	MD 2.6 higher (5.8 lower to 11 higher)		IMPORTANT
Symptomatic remitted												
0	No evidence available					none	-	0%	not pooled	not pooled		
Days at hospital (Better indicated by lower values)												
0	No evidence available					none	0	-	-	not pooled		

[1] Scales reversed
[2] Risk of selection bias
[3] Risk of performance bias
[4] Risk of detection bias
[5] Risk of reporting bias
[6] Considerable inconsistency between studies
[7] Small sample size
[8] 95% CI could be in favour of both Socialcognition and TAU

Evidensprofil PICO 8: Kognitiv adfærdsterapi

Tabel 10: Kognitiv adfærdsterapi til patienter med skizofreni og betydelig funktionsnedsættelse

Question: PICO 8 Should CBT vs TAU be used in Schizophrenia?

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CBT**	**TAU**	**Relative (95% CI)**	**Absolute**		
Psychotic symptoms, end of treatment (measured with: PANSS positive, SAPS, BPRS positive; Better indicated by lower values)												
14	randomised trials	serious[1,2]	no serious inconsistency[3]	no serious indirectness	no serious imprecision	none	555	506	-	SMD 0.36 lower (0.61 to 0.11 lower)	⊕⊕⊕O MODERATE	CRITICAL
Negative symptoms, end of treatment (measured with: PANSS negative, SANS, BPRS negative, BRIANS; Better indicated by lower values)												
17	randomised trials	serious[1,2,4]	no serious inconsistency[3]	no serious indirectness	no serious imprecision	none	618	568	-	SMD 0.32 lower (0.6 to 0.04 lower)	⊕⊕⊕O MODERATE	CRITICAL
Psychotic symptoms, min. 4-6 month FU (measured with: PANSS positive, SAPS, BPRS positive; Better indicated by lower values)												
8	randomised trials	serious[1,2]	serious[5]	no serious indirectness	no serious imprecision	none	318	361	-	SMD 0.12 higher (0.1 lower to 0.34 higher)	⊕⊕OO LOW	IMPORTANT
Negative symptoms, min. 4-6 month FU (measured with: PANSS negative, SANS, BPRS negative, BRIANS; Better indicated by lower values)												
10	randomised trials	serious[1,2,4]	serious[5]	no serious indirectness	serious[6]	none	377	421	-	SMD 0.10 higher (0.1 lower to 0.3 higher)	⊕OOO VERY LOW	IMPORTANT
Social function, end of treatment (measured with: SOFAS, Social Provision Scale, SFS, GAS, GAF; Better indicated by higher values)												
8	randomised trials	serious[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	266	309	-	SMD 0.07 higher (0.1 lower to 0.23 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Distress, PSYRATS (measured with: hallucinations; Better indicated by lower values)												
5	randomised trials	serious[1,2]	serious[5]	no serious indirectness	no serious imprecision[6]	none	103	99	-	MD 0.22 lower (1.28 lower to 0.84 higher)	⊕⊕OO LOW	IMPORTANT
Relapse, end of treatment												
4	randomised trials	serious[1,2]	no serious inconsistency	no serious indirectness	serious[6]	none	50/185 (27%)	38/178 (21.3%)	RR 0.80 (0.48 to 1.32)	43 fewer per 1000 (from 111 fewer to 68 more)	⊕⊕OO LOW	IMPORTANT
QoL, end of intervention (Better indicated by higher values)												
4	randomised trials	serious[1,2,4]	no serious inconsistency	no serious indirectness	serious[6]	none	141	156	-	SMD 0.29 lower (0.61 lower to 0.03 higher)	⊕⊕OO LOW	IMPORTANT
Days in hospital, end of intervention (Better indicated by lower values)												
4	randomised trials	serious[1,2]	no serious inconsistency	no serious indirectness	serious[6]	none	210	215	-	MD 10.64 lower (32.14 lower to 10.86 higher)	⊕⊕OO LOW	IMPORTANT

1 Risk of performance bias
2 Risk of reporting bias
3 Inconsistency is explained by the study by Grant et al. (Low IÂ² without)
4 Risk of selection bias
5 Considerable Heterogeneity
6 95% CI could be in favour of both TAU and CBT with clinical relevance

Evidensprofil PICO 9: Misbrug og mangelfuld behandlingstilknytning

Tabel 11: Kognitiv adfærdsterapi i kombination med Motivational Interviewing til behandling af samtidigt misbrug

Question: PICO 9 Should Cognitive behaviour therapy + Motivational interviewing vs Standard care be used in Schizophrenia?

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cognitive behaviour therapy + Motivational interviewing	Standard care	Relative (95% CI)	Absolute		
Cannabis use, end of treatment (follow-up 3 months; Better indicated by lower values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	75	52	-	SMD 0.06 lower (0.42 lower to 0.29 higher)	⊕⊕⊕O MODERATE	CRITICAL
Amphetamine, end of treatment (follow-up 3 months; measured with: estimated daily consumption past month; Better indicated by lower values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	11	9	-	MD 0.16 higher (0.73 lower to 1.04 higher)	⊕OOO VERY LOW	CRITICAL
Cannabis use, longest FU (follow-up min. 4-6 months; Better indicated by lower values)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	94	74	-	SMD 0.03 higher (0.34 lower to 0.41 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Amphetamine, estimated daily use, 12 months FU (follow-up min. 4-6 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	9	8	-	MD 0.13 higher (0.11 lower to 0.37 higher)	⊕⊕OO LOW	IMPORTANT
Symptoms, end of treatment (follow-up 3-6 months; measured with: PANSS/SANS; Better indicated by lower values)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	84	74	-	SMD 0.16 higher (0.15 lower to 0.47 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Relapse (mental state), end of treatment (follow-up 9 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	5/18 (27.8%)	10/18 (55.6%)	RR 0.5 (0.21 to 1.17)	278 fewer per 1000 (from 439 fewer to 94 more)	⊕⊕OO LOW	IMPORTANT
Use of alcohol, end of treatment (follow-up 3-6 months; Better indicated by lower values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1,3]	none	31	37	-	SMD 0.32 higher (0.17 lower to 0.81 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Quality of Life, end of treatment (follow-up 6 months; measured with: BQOL, WHOQOL, MANSA; Better indicated by higher values)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[1]	none	106	84	-	SMD 0.17 higher (0.13 lower to 0.48 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Social functioning, end of treatment (follow-up median 3-9 months; measured with: SFS, GAF average score ; Better indicated by higher values)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	114	95	-	SMD 0.08 lower (0.54 lower to 0.37 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Days in hospital (Better indicated by lower values)												
0	No evidence available					none	0	-	-	not pooled		IMPORTANT
Mortality (at follow up) (follow-up 12 months)												
3	randomised trials	no serious risk of bias[4]	no serious inconsistency	no serious indirectness	serious[5]	none	6/247 (2.4%)	3.1%	RR 0.72 (0.22 to 2.41)	9 fewer per 1000 (from 24 fewer to 44 more)	⊕⊕⊕O MODERATE	IMPORTANT
Crimes (follow-up 6 months; assessed with: number of arrests)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	8/61 (13.1%)	13/49 (26.5%)	OR 0.42 (0.16 to 1.11)	134 fewer per 1000 (from 211 fewer to 21 more)	⊕⊕OO LOW	IMPORTANT

[1] only one study
[2] attrition bias (incomplete outcome data)
[3] these were skewed data
[4] Risk of bias: vurderet serious. Alle tre inkluderede studier havde et frafald på over 20%, og der er uklart risk of bias.
[5] Absolute effect contains both evidence for and against treatment

Evidensprofil PICO 10: Assertive Community Treatment

Question: PICO 10 Should Assertive Community Treatment vs Treatment as usual be used for schizophrenia with decreased function?: Assertive community treatment versus standard care for schizophrenia.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Assertive Community Treatment	Treatment as usual	Relative (95% CI)	Absolute		
Loss of contact, longest FU (follow-up max 24 months)												
8	randomised trials	serious[1,2,3,4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	83/774 (10.7%)	201/764 (26.3%)	RR 0.4 (0.27 to 0.61)	158 fewer per 1000 (from 103 fewer to 192 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Days of hospital pr. month. longest FU (follow-up max. 24 months; Better indicated by lower values)												
26	randomised trials	serious[1,2,3,4]	serious[5]	no serious indirectness	no serious imprecision	none	1913	1804	-	MD 0.86 lower (1.38 to 0.35 lower)	⊕⊕OO LOW	IMPORTANT
Other health care costs, longest FU (follow-up max 24 months; assessed with: emergency room visits)												
1	randomised trials	serious[1,2,3,4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	41/117 (35%)	19/61 (31.1%)	RR 1.13 (0.72 to 1.76)	40 more per 1000 (from 87 fewer to 237 more)	⊕⊕⊕O MODERATE	IMPORTANT
Symptoms, longest FU (follow-up max. 24 months; measured with: CSI, BPRS, SCL-90, PSE, CPRS, split-GAF; Better indicated by lower values)												
10	randomised trials	serious[1,2,3,4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	688	601	-	SMD 0.27 lower (0.38 to 0.15 lower)	⊕⊕⊕O MODERATE	IMPORTANT
Quality of life, longest FU (follow-up 6-12 months; measured with: QOLI, LQoLP, MANSA, ; Better indicated by higher values)												
6	randomised trials	serious[1,2,3,4]	serious[5]	no serious indirectness	no serious imprecision	none	234	219	-	MD 0.10 lower (0.36 lower to 0.16 higher)	⊕⊕OO LOW	IMPORTANT
Patient satisfaction, longest FU (follow-up max 12 months; Better indicated by higher values)												
2	randomised trials	serious[2,4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	66	61	-	SMD 0.75 higher (1.11 to 0.38 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Mortalitet (all causes) longest FU (follow-up max 24 months)												
12	randomised trials	serious[1,2,3,4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	28/885 (3.2%)	29/857 (3.4%)	RR 0.89 (0.53 to 1.51)	4 fewer per 1000 (from 16 fewer to 17 more)	⊕⊕⊕O MODERATE	IMPORTANT
Social functioning (follow-up max 24 months; measured with: social role performance (DAS, RFS, Strauss-Carpenter Scale; Better indicated by higher values)												
3	randomised trials	serious[1,2,3,4]	serious[5]	no serious indirectness	no serious imprecision	none	128	132	-	SMD 0.28 higher (0.65 higher to 0.1 lower)	⊕⊕OO LOW	IMPORTANT
Crime, longest FU (follow-up max 24 months; assessed with: police contact (6-12m FU), arrests (7-12+m), imprisoned (7-12+m))												
10	randomised trials	serious[1,2,3,4]	serious[5]	no serious indirectness	no serious imprecision	none	125/758 (16.5%)	102/646 (15.8%)	RR 0.84 (0.52 to 1.33)	25 fewer per 1000 (from 76 fewer to 52 more)	⊕⊕OO LOW	IMPORTANT

[1] Risk of attrition bias (incomplete outcome data)
[2] Risk of reporting bias
[3] Risk of selection bias (insufficient randomisation procedure)
[4] Risk of performance bias
[5] wide variation across studies