BEST in Mental Health

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Best Evidence Summaries of Topics in Mental Healthcare

BEST *in* MH *clinical question-answering service*

Question

"In patients experiencing a first episode of psychosis who misuse substances, what is the most effective intervention for improving patient outcomes?"

Clarification of question using PICO structure

Patients:	Patients experiencing a first episode of psychosis who misuse substances
Intervention:	Any
Comparator:	Any
Outcome:	Any

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Clinical and research implications

No definite clinical implications may be made from the available evidence. Generally, there is a consensus that more randomised controlled trials (RCTs) of psychological interventions for patients with early psychosis and concurrent substance abuse or dependence are required. Some of the included studies also highlighted the difficulties in delivering interventions to this group of participants, so that this needs consideration in the study design.

Regarding pharmaceutical interventions, no RCTs were included in this BEST abstract that exclusively included participants with first-episode psychosis *and* substance use disorder. The authors consistently noted that more RCTs, and new strategies, are needed to treat first-episode participants with substance use disorder. One author suggested that if clinicians are choosing between olanzapine and respiridone, the decision should be based upon factors other than symptom response and short-term substance misuse, as both medications appear to have equal efficacy.

What does the evidence say?

Number of included studies/reviews (number of participants)

Seven RCTs met the inclusion criteria for this BEST summary (Edwards et al. 2006; Green et al. 2004; Kemp et al. 2007; Madigan et al. 2013; Peterson et al. 2007; Sevy et al. 2011; van Nimwegen et al. 2008).

Main Findings

Non-pharmaceutical therapeutic interventions

Four trials evaluated different psychological interventions. One compared an individually delivered cannabis-focused intervention (a cognitive-behavioural-oriented programme) versus psycho-education in 47 young people (15-29 years of age) with first-episode psychosis who were continuing to use cannabis (Edwards et al. 2006). The authors found that both treatments were equally effective, and that in both conditions there was a significant decrease in cannabis use at the end of treatment (approximately 3 months after baseline), and at 6-months follow-up. Both interventions were also associated with comparable changes in psychopathology and psychosocial functioning.

A Danish trial compared integrated treatment (given by OPUS) with standard treatment in 547 participants (18-45 years of age) with first-episode schizophrenia-spectrum disorders (Peterson et al. 2007). The OPUS treatment involved assertive community treatment with family involvement and social skills training. In a subgroup analysis of patients with co-morbid substance abuse (n=82), the authors reported that at 2 years follow-up, OPUS treatment significantly reduced negative and disorganised symptoms ($p<0.001$ and 0.02 respectively), but there was no significant difference between groups for psychotic symptoms, not working – or being in education, or being homeless. Patients with substance abuse who received standard treatment spent significantly more days in hospital during the 2-year period, and had significantly more outpatient visits in the last year than those who received OPUS treatment ($p=0.05$ and $p<0.001$ respectively).

Madigan et al. (2013) compared a group-based psychological intervention that integrated CBT with motivational interviewing, with treatment as usual, in 88 participant (16-65 years of age) in the early course of psychotic illness and who had comorbid cannabis dependence. The authors found no

significant differences between the groups in the frequency of cannabis use, insight, attitude to treatment, positive or negative symptoms, depressive symptoms, or global assessment of functioning at 3 months, or at 1-year follow-up. In terms of quality of life, however, patients who had received the intervention had higher scores than those who received treatment as usual at 3 months ($p=0.01$) and at 1 year ($p=0.05$).

A pilot RCT compared a brief manualised cognitive behavioural therapy (Stop Using Stuff [SUS]) versus treatment as usual for substance abuse in 16 young people (17-25 years of age) with psychosis (Kemp et al. 2007). At 6 months follow-up, the authors reported that those who received active treatment had significantly less frequent alcohol, and drug, consumption ($p<0.05$), but there were no significant differences between groups in the quantity of alcohol or drug consumed.

Pharmaceutical interventions

One RCT compared the effectiveness of with olanzapine with haloperidol in 262 participants (aged 16 to 40 years) with first-episode psychosis (Green et al. 2004). As part of this study, the authors reported 12-week outcome data for patients with a co-occurring substance use disorder (n=97) vs. patients without a co-occurring substance use disorder (n=165). They found that participants with a substance use disorder (whether substance use, alcohol use, or cannabis use) had a poorer response to treatment than those without a substance use disorder, whether treated with olanzapine or haloperidol, but the effect was non-significant.

Another RCT examined compared the efficacy of olanzapine versus risperidone in 128 young adults (18 to 30 years of age) with recent onset schizophrenia or related disorders (van Nimwegen et al. 2008). In a sub-group analysis of patients who used cannabis (n=41), the authors reported that after 6 weeks of treatment, there were no significant differences between treatment groups for craving, drug desire, or the mean number of joints per week.

Another study conducted a secondary analysis of data from a previously published RCT by Robinson et al. (2006) [1] – this analysis by Sevy et al. (2011) also compared the effectiveness of olanzapine with risperidone in a subgroup of 49 participants (aged 16 to 40 years) with first-episode schizophrenia and cannabis use disorders. After 16 weeks of acute treatment, the authors reported no significant differences between the treatment groups for response rates, positive and negative symptoms, or substance abuse.

Authors Conclusions

Of those trials that evaluated psychological interventions, Edwards et al. (2006) concluded that psycho-education and a cannabis-focused intervention were associated with similar reductions in cannabis use in young people with first-episode psychosis. Peterson et al. (2007) concluded that supplementing the OPUS treatment with therapeutic programmes for patients with a comorbid substance abuse would probably further improve outcomes.

[1] This RCT compared risperidone with olanzapine for the treatment of first-episode participants with a diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder.

Madigan et al. (2013) concluded that over the early phase of psychotic illness, group psychological interventions for those with comorbid cannabis dependence improved subjective quality of life. However, this was not associated with reduction in use of cannabis or improvement in clinical outcomes. Based on data from a pilot study, Kemp et al. (2007) concluded that brief manualised CBT intervention can help moderate substance use in young people with psychosis.

Regarding pharmaceutical interventions, Green et al. (2004) concluded that the ability to treat first-episode patients with a lifetime history of substance use disorder with antipsychotic medication (typical or atypical) may not be as good as it is for patients without such a lifetime history. van Nimwegen et al. (2008) concluded that there was no evidence for a differential effect of olanzapine and risperidone on participants well-being or on craving for cannabis, and Sevy et al. (2011) concluded that olanzapine and risperidone had a similar initial efficacy on psychotic symptoms and substance use outcomes in first-episode patients with co-occuring cannabis use disorders.

Reliability of conclusions/Strength of evidence

Although the Edwards et al. (2006) trial was well-reported, it had a very small sample size. Two other trials were considered to have a high risk of bias (Kemp et al. 2007; Peterson et al. 2007), so that the results from this studies are unlikely to be reliable. Indeed, the authors of the Kemp et al. (2007) pilot trial reported that their results should be treated with caution. The Madigan et al. (2013) trial was considered to have a low risk of bias.

The trials that evaluated pharmaceutical interventions had an unclear (Green et al. 2004; van Nimwegen et al. 2008) or high risk of bias (Sevy et al. 2011). All three of these studies, however, were not designed to compare different treatments in participants with first episode psychosis *and* substance abuse *per se*. They reported sub-group analysis for this group of interest, so that any results and the conclusions derived from them, should be treated with caution.

What do guidelines say?

Neither National Institute for Health and Care Excellence (NICE) not Scottish Intercollegiate Guidelines Network (SIGN) guidelines make recommendations regarding the best treatment for individuals with first-episode psychosis and comorbid substance abuse/dependence.

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Date searches conducted: 02/12/2014
Date answer completed: 18/12/2014

References

Edwards, J., Elkins, K., Hinton, M., Harrigan, S. M., Donovan, K., Athanasopoulos, O., & McGorry, P. D. (2006). Randomized controlled trial of a cannabis-focused intervention for young people with first-episode psychosis. *Acta Psychiatrica Scandinavica*, *114*(2), 109-117.

Green, A. I., Tohen, M. F., Hamer, R. M., Strakowski, S. M., Lieberman, J. A., Glick, I., & Scott Clark, W. (2004). First episode schizophrenia-related psychosis and substance use disorders: Acute response to olanzapine and haloperidol. *Schizophrenia Research*, *66*(2), 125-135.

Kemp, R., Harris, A., Vurel, E., & Sitharthan, T. (2007). Stop using stuff: Trial of a drug and alcohol intervention for young people with comorbid mental illness and drug and alcohol problems. *Australasian Psychiatry*, *15*(6), 490-493.

Madigan, K., Brennan, D., Lawlor, E., Turner, N., Kinsella, A., O'Connor, J. J., & O'Callaghan, E. (2013). A multi-center, randomized controlled trial of a group psychological intervention for psychosis with comorbid cannabis dependence over the early course of illness. *Schizophrenia research*, *143*(1), 138-142.

Petersen, L., Jeppesen, P., Thorup, A., Øhlenschlæger, J., Krarup, G., Østergård, T., ... & Nordentoft, M. (2007). Substance abuse and first-episode schizophrenia-spectrum disorders. The Danish OPUS trial. *Early intervention in psychiatry*, *1*(1), 88-96.

Sevy, S., Robinson, D. G., Sunday, S., Napolitano, B., Miller, R., McCormack, J., & Kane, J. (2011). Olanzapine vs. risperidone in patients with first-episode schizophrenia and a lifetime history of cannabis use disorders: 16-week clinical and substance use outcomes. *Psychiatry research*, *188*(3), 310-314.

van Nimwegen, L. J., de Haan, L., Van Beveren, N. J., van der Helm, M., van den Brink, W., & Linszen, D. (2008). Effect of olanzapine and risperidone on subjective well-being and craving for cannabis in patients with schizophrenia or related disorders: A double-blind randomized controlled trial. *Canadian Journal of Psychiatry, 53*(6), 400-405.

Results

RCTs

Author (year)	Inclusion criteria	Number of participants	Summary of results	Risk of bias
Edwards et al. (2006)	*Participants*: Aged 15-29 years, with a DSM-IV diagnosis of a psychotic disorder, first episode (i.e., schizophrenia, schizophreniform, schizoaffective, delusional disorder, bipolar disorder, major depressive disorder with psychotic features, psychosis not otherwise stated, and brief reactive psychosis), and substance use disorder. *Intervention*: Cannabis and Psychosis Therapy (CAP), a cannabis-focused cognitive-behavioural-oriented intervention for individuals who continue to use cannabis despite engagement with early psychosis services. Delivered over 3 months (10 weekly sessions, 20-60 minutes in duration). *Comparator*: Psychoeducation (PE; 10 individual sessions), with a focus upon psychosis without discussion of cannabis. *Outcome*: Diagnosis (Structured Clinical Interview for Diagnosis; SCID), cannabis use (Cannabis and Substance Use	N = 47 (CAP = 23; PE = 24)	There were no significant differences between the treatment groups on the unadjusted mean outcome scores at the end of treatment, or at 6 months follow-up. The outcome scores reported in a table (for end of treatment) were: used cannabis in past 4 weeks (n, %) (13, 56.5%) vs. 13, 54.2%); % days used cannabis past 4 weeks (30.4 vs. 18.8); severity of cannabis use (mean [SD]) 1.4 [1.4] vs. 1.3 [1.4]); BPRS-E (44.1 [13.8] vs. 47.7 [18.2]); BPRS-PS (8.9 [4.8] vs. 9.5 [5.4]); SANS (21.8 [14.9] vs. 23.5 [14.0]); BDI-SF (6.2 [5.9] vs. 7.8 [8.1]); SOFAS (50.5 [17.0] vs. 51.3 [14.9]); KAPQ (22.5 [4.0] vs. 21.7 [5.0]); out-patient attendance (13.4 [8.8] vs. 11.8 [6.8]).	High (well-conducted, but small sample sizes)

	Assessment Schedule, CASUAS; Readiness to Change Questionnaire – Cannabis, RTCQ-C), psychopathology (Brief Psychiatric Rating Scale-Expanded, BPRS-E; Scale for the Assessment of Negative Symptoms, SANS; Beck Depression Inventory-Short Form, BDI-SF), functioning (Social & Occupational Functioning Scale, SOFAS), psychosis knowledge (Knowledge about Psychosis Questionnaire, KAPQ), and out-patient attendance and medication (Service Utilization Rating Scale, SURS). *Study Design*: RCT			
Green et al. (2004)	*Participants*: Aged 16-40 with a DSM-IV diagnosis of first-episode schizophrenia, schizoaffective disorder, or schizophreniform disorder. The psychotic episode must not have lasted longer than 5 years and there could not be evidence of recovery for a period of 6 months or longer. Either with or without a substance-use disorder. *Intervention*: Olanzapine; 12-week acute treatment phase and a 92-week continuation phase. 5-10 mg/day for first 6 weeks, 5-20 mg/day for second 6 weeks. *Comparator*: Haloperidol; 12-week acute treatment phase and a 92-week	N = 263	27% of patients with substance use disorder were responders (23% for olanzapine and 31% for haloperidol) compared to 35% without substance use disorder (38% for olanzapine and 32% for haloperidol). Participants with a substance use disorder (whether substance use, alcohol use, or cannabis use) had a poorer response to treatment than those without a substance use disorder, whether treated with olanzapine or haloperidol, but this effect was non-significant. An ANOVA model demonstrated that neither treatment group nor the substance use disorder by treatment group had an effect on compliance of treatment, but those with substance use disorder had a significantly lower proportion	Unclear (information on methodology not well-reported)

	continuation phase. 2-6 mg/day for first 6 weeks, 2-20 mg/day for second 6 weeks. *Outcome*: Psychopathology (Positive and Negative Syndrome Scale, PANSS; Montgomery-Asperg Depression Rating Scale, MADRS; and Clinical Global Impressions Scale, CGI). *Study Design*: Secondary analysis of RCT, examining differences between individuals with and without substance abuse/dependence (substance abuse, alcohol abuse, and cannabis use).		of compliant days [taking medication] (87.5%) than did those without a substance use history ($p<0.02$). A logistic regression model demonstrated that for participants treated with haloperidol, 71% with no substance abuse disorder completed the study, vs. 51% with a substance use disorder ($p<0.04$). For participants treated with olanzapine, 71% with no substance use disorder completed the study vs. 77% with a substance abuse disorder ($p<0.53$).	
Kemp et al. (2007)	*Participants*: Aged 17-25 years, with a DSM-IV diagnosis of both substance abuse and first-episode psychosis (primary diagnosis being psychosis: e.g., schizophrenia, schizophreniform disorder, substance-induced psychotic disorder, or psychotic mood disorder). *Intervention*: Stop Using Stuff (SUS) intervention - a manualised intervention using motivational interviewing and CBT practices for substance abuse, based upon the Integrated Drug and Alcohol Intervention and oriented towards a harm minimisation approach. *Comparator*: Treatment as usual (TAU). *Outcome*: PANSS, Drug Abuse Screening Test (DAST-10), Alcohol Use Disorders	N = 16 (SUS = 10; TAU = 6	The authors reported that repeated measures ANOVA and two-way ANOVA were used to observe between group differences as a result of the intervention. Significant main effects were observed in the frequency of alcohol [$F(1,14) = 4.718$, $p<0.05$] and drugs consumed [$F(1,14) = 7.0$, $p<0.05$]. There was no significant main effect of quantity of alcohol or drug consumption; there were no significant interactions. The effect size (η^2) of each main effect was 0.162 (33.5% power) and 0.007 (6% power), respectively. Repeated measures ANOVA was conducted on instrument scores. Significant main effects for both groups were observed for DAST [$F(1,14) = 13.67$, $p<0.05$], AUDIT [$F(1,14) = 5.82$, $p<0.05$], WHOQOL [$F(1,14) = 7.79$, $p<0.05$] and SE [$F(1,14) = 4.97$, $p<0.05$]. The effect size (η^2) of each main effect was DAST = 0.167 (34.6% power), AUDIT = 0.294 (61.2% power), WHOQOL = 0.138 (28.7% power) and SE =	High (pilot study with very small sample size)

	Identification test (AUDIT), Depression Anxiety Stress Scale (DASS), Self-Efficacy Scale (SES), and World Health organisation Quality of Life Scale Brief (WHOQoL-BREF). *Study Design*: RCT		0.17 (35.1% power).	
Madigan et al. (2013)	*Participants*: Aged 16-65 years, with a DSM-IV diagnosis of first-episode psychosis with comorbid substance dependence. Exclusions: learning disability, organic brain damage. *Intervention*: Group-based psychological intervention (GPI) that integrates CBT and motivational interviewing. One session per week for 12 weeks, with a booster session 6 weeks later. *Comparator*: TAU (antipsychotic treatment and regular review). *Outcome*: Diagnostic status (SCID), frequency of cannabis use in past 30 days (Addiction Severity Index, ASI), attitude to treatment (Drug Attitude Inventory, DAI), positive psychotic symptoms (Scale for the Assessment of Positive Symptoms, SAPS), negative psychotic symptoms (Scale for the Assessment of Negative Symptoms, SANS), depressive symptoms (Calgary Depression Scale for Schizophrenia, CDSS), psychosocial functioning (Global Assessment of Functioning Scale, GAF),	N = 88 (GPI = 59; TAU = 29)	There were no significant differences between the groups in the frequency of cannabis use, insight (BIS scores), attitude to treatment (DAI scores), positive symptoms (SAPS scores), or negative symptoms (SANS scores), depressive symptoms (CDSS scores), or global assessment of functioning (GAF scores) at 3 months, or at 1-year follow-up. In terms of quality of life, patients who had received the intervention had higher scores (WHOQOL, BREF), than those who received treatment as usual at 3 months (p=0.01) and at 1 year (p=0.05).	Low

	quality of life (WHOQoL-BREF). *Study Design*: RCT			
Petersen et al. (2007)	*Participants*: Aged 18-45 years, with an ICD-10 diagnosis of first-episode schizophrenia, schizotypal disorder, delusional disorder, acute or transient psychosis, schizoaffective disorder, induced psychosis, or non-specific non-organic psychosis. *Intervention*: OPUS treatment – an enriched Assertive Community Treatment model, with a multidisciplinary team to provide the treatment (typically psychoeducation / social skills training). *Comparator*: TAU (e.g., antipsychotic medication). *Outcome*: Substance abuse (Schedules for Clinical Assessment inn neuropsychiatry, SCAN), psychotic symptoms (SAPS; SANS), functioning (GAF). *Study Design*: Secondary analysis of RCT, focusing upon those individuals with substance misuse.	N = 547 overall – of which 146 had a substance abuse; 369 were re-interviewed after 2 years - of which 82 had a substance abuse	At 2-year follow-up, 42 (17.3%) patients who received the intervention and 40 (20.7%) who received standard treatment had a substance abuse (OR 0.5 [95% CI: 0.3 to 1.0]). In this subgroup of patients with substance abuse, the authors reported that OPUS treatment significantly reduced negative and disorganised symptoms compared with standard treatment ($p<0.001$ and 0.02 respectively), but there was no significant difference between groups for psychotic dimension, GAF - symptom or GAF - function, not working or in education, or being homeless. Patients with substance abuse who received standard treatment spent significantly more days in hospital, and had more outpatient visits in the last year, than those who received OPUS treatment ($p=0.05$ and $p<0.001$ respectively).	High (study was not designed to evaluate dual diagnosis patients; high drop-out rate)
Sevy et al. (2011)	*Participants*: Aged 16-40 years, with a current first-episode DSM-IV diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder with less than 12 weeks of lifetime cumulative antipsychotic medication treatment, and	N = 49 (olanzapine = 28; risperidone = 21)	After 16 weeks of acute treatment, there was no significant differences between the treatment groups for response rates, positive and negative symptoms, or substance abuse. Both medications improved positive and negative symptoms.	High (subgroup analysis of data from a previously reported

	DSM-IV criteria for a lifetime history of cannabis abuse or dependence. *Intervention*: Olanzapine (max dose 20mg/day) for 16 weeks. *Comparator*: Risperidone (max dose 6 mg/day) for 16 weeks. *Outcome*: Psychopathology (Schedule for Affective Disorders and Schizophrenia – Change Version with psychosis and disorganised items, SADS-C+PD; CGI; and Hillside Clinical Trials version of the SANS). *Study Design*: Secondary analysis of RCT, only including participants with cannabis abuse/dependence.			RCT)
van Nimwegen et al. (2008)	*Participants*: Aged 18-30 years with a DSM-IV diagnosis of schizophrenia, schizoaffective disorder, or schizophreniform disorder *Intervention*: Olanzapine (5, 10, 15, or 20 mg/day) and psychoeducation about psychoses, substance abuse, and social skills training. *Comparator*: Risperidone (1.25, 2.5, 3.75, or 5 mg/day) and psychoeducation about psychoses, substance abuse, and social skills training. *Outcome*: Subjective wellbeing (Subjective Wellbeing under Neuroleptics Scale, SWN), and craving (Obsessive-Compulsive Drug	N = 128 overall, N = 41 who were using cannabis at baseline (olanzapine = 20; risperidone = 21)	There were no significant differences between the treatment groups for any of the outcomes evaluated. Within the group of patients using cannabis, after adjusting for baseline scores, there were no significant differences between groups for craving (OCDUS), and drug desire (DDQ). In addition, the mean number of joints per week was not significantly different between the treatments.	Unclear

	Use Scale, OCDUS; Drug desire Questionnaire, DDQ). *Study Design*: RCT (only a subsample of participants who use cannabis at baseline is relevant for this summary).			

Risk of Bias:

RCTs

Study	RISK OF BIAS					
	Random allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting
Edwards et al. (2006)	☺	☺	N/A	☺	☺	☺
Green et al. (2003)	?	?	☺	?	?	?
Kemp et al. (2007)	☺	☺	N/A	☹	☹	?
Madigan et al. (2013)	☺	☺	N/A	☺	☺	?
Petersen et al. (2007)	?	?	N/A	☹	☹	?
Sevy et al. (2011)	☺	☺	N/A	☺	☹	?
van Nimwegen et al. (2008)	?	?	☺	Self-rated	☺	?

☺Low Risk ☹High Risk ? Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
NICE	psychosis first episode substance treatment	104	0
DARE	((drug* OR substance* OR alcohol* OR opioid* OR amphetamine* OR opiate* OR cocaine* OR marijuana* OR cannabis or phencyclidine or benzodiaz*) adj3 (misuse OR abuse* OR addict* OR depend*)) IN DARE 526 Delete 2 ((alcohol* or drinker* or drinking*)) IN DARE 724 Delete 3 MeSH DESCRIPTOR Substance-Related Disorders EXPLODE ALL TREES 771 D elete 4 MeSH DESCRIPTOR Substance Abuse, Intravenous EXPLODE ALL TREES 76 Delete 5 MeSH DESCRIPTOR Alcohol Drinking EXPLODE ALL TREES 139 Delete 6 MeSH DESCRIPTOR Alcoholics EXPLODE ALL TREES 0 Delete 7 MeSH DESCRIPTOR Alcoholism EXPLODE ALL TREES 178 Delete 8 MeSH DESCRIPTOR Alcohol-Related Disorders EXPLODE ALL TREES 260 Delete 9 MeSH DESCRIPTOR Drug Users EXPLODE ALL TREES 13 Delete 10 MeSH DESCRIPTOR Cocaine-Related Disorders EXPLODE ALL TREES 24 Delete 11 MeSH DESCRIPTOR Heroin Dependence EXPLODE ALL TREES 29 Delete 12 MeSH DESCRIPTOR Marijuana Abuse EXPLODE ALL TREES 9 Delete 13 MeSH DESCRIPTOR Morphine Dependence EXPLODE ALL TREES 0 Delete 14 MeSH DESCRIPTOR Opioid-Related Disorders EXPLODE ALL TREES 106 Delete 15 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 1459 Delete 16 (psychosis OR psychotic OR schizo* OR schizophrenia) IN DARE 793 Delete 17 MeSH DESCRIPTOR Psychotic Disorders EXPLODE ALL TREES 150 Delete 18 MeSH DESCRIPTOR Schizophrenia and Disorders with Psychotic Features EXPLODE ALL TREES 605 Delete	89	0

	19 MeSH DESCRIPTOR Psychoses, Alcoholic EXPLODE ALL TREES 1 Delete 20 MeSH DESCRIPTOR Psychoses, Substance-Induced EXPLODE ALL TREES 3 Delete 21 #16 OR #17 OR #18 OR #19 OR #20 1069 Delete 22 #15 AND #21		
Primary studies			
CENTRAL	#1 "first episode psychosis" 250 #2 MeSH descriptor: [Psychotic Disorders] explode all trees 1552 #3 "first episode" 1369 #4 #2 and #3 180 #5 "early intervention" 1768 #6 #2 and #5 50 #7 #1 or #4 or #6 340 #8 MeSH descriptor: [Substance-Related Disorders] explode all trees 9533 #9 "drug abuse*" or "substance misuse*" or "substance abuse*" or "drug addict*" 5185 #10 #8 or #9 12303 #11 #7 and #10 43 Central only 20	20	7
PsycINFO	1. PsycINFO; "first episode".ti,ab; 4549 results. 2. PsycINFO; exp PSYCHOSIS/; 93785 results. 3. PsycINFO; 1 AND 2; 3590 results. 4. PsycINFO; ("first episode" adj3 psychosis).ti,ab; 1966 results. 5. PsycINFO; 3 OR 4; 3677 results. 6. PsycINFO; exp DRUG ABUSE/; 89665 results. 7. PsycINFO; ADDICTION/; 6631 results. 8. PsycINFO; "substance abuse".ti,ab; 25303 results. 9. PsycINFO; "substance related disorder".ti,ab; 89 results. 10. PsycINFO; 6 OR 7 OR 8 OR 9; 105009 results. 11. PsycINFO; 5 AND 10; 168 results. 12. PsycINFO; CLINICAL TRIALS/; 8130 results.	50	0

	13. PsycINFO; random*.ti,ab; 135670 results. 14. PsycINFO; groups.ti,ab; 378568 results. 15. PsycINFO; (double adj3 blind).ti,ab; 18296 results. 16. PsycINFO; (single adj3 blind).ti,ab; 1467 results. 17. PsycINFO; EXPERIMENTAL DESIGN/; 9374 results. 18. PsycINFO; controlled.ti,ab; 84042 results. 19. PsycINFO; (clinical adj3 study).ti,ab; 8220 results. 20. PsycINFO; trial.ti,ab; 71322 results. 21. PsycINFO; "treatment outcome clinical trial".md; 28322 results. 22. PsycINFO; 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21; 587254 results. 23. PsycINFO; 11 AND 22; 50 results.		
Embase	12. EMBASE; "first episode".ti,ab; 12215 results. 13. EMBASE; exp PSYCHOSIS/; 209940 results. 14. EMBASE; 12 AND 13; 6003 results. 15. EMBASE; ("first episode" adj3 psychosis).ti,ab; 3082 results. 16. EMBASE; 14 OR 15; 6043 results. 17. EMBASE; exp DRUG ABUSE/; 60783 results. 18. EMBASE; ADDICTION/; 44000 results. 19. EMBASE; "substance abuse".ti,ab; 22855 results. 20. EMBASE; "substance related disorder".ti,ab; 110 results. 21. EMBASE; 17 OR 18 OR 19 OR 20; 119293 results. 22. EMBASE; 16 AND 21; 275 results. 23. EMBASE; random*.ti,ab; 913640 results. 24. EMBASE; factorial*.ti,ab; 23604 results. 25. EMBASE; (crossover* OR cross-over*).ti,ab; 70464 results. 26. EMBASE; placebo*.ti,ab; 204147 results. 27. EMBASE; (doubl* ADJ blind*).ti,ab; 144724 results. 28. EMBASE; (singl* ADJ blind*).ti,ab; 14881 results. 29. EMBASE; assign*.ti,ab; 245285 results.	42	0

	30. EMBASE; allocat*.ti,ab; 86655 results. 31. EMBASE; volunteer*.ti,ab; 179450 results. 32. EMBASE; CROSSOVER PROCEDURE/; 40609 results. 33. EMBASE; DOUBLE BLIND PROCEDURE/; 116034 results. 34. EMBASE; RANDOMIZED CONTROLLED TRIAL/; 353243 results. 35. EMBASE; SINGLE BLIND PROCEDURE/; 19033 results. 36. EMBASE; 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35; 1451064 results. 37. EMBASE; 22 AND 36; 42 results.		
Medline	12. MEDLINE; "first episode".ti,ab; 8566 results. 13. MEDLINE; exp PSYCHOSIS/; 39850 results. 14. MEDLINE; 12 AND 13; 1826 results. 15. MEDLINE; ("first episode" adj3 psychosis).ti,ab; 1995 results. 16. MEDLINE; 14 OR 15; 2368 results. 17. MEDLINE; exp DRUG ABUSE/; 240144 results. 18. MEDLINE; ADDICTION/; 0 results. 19. MEDLINE; "substance abuse".ti,ab; 19419 results. 20. MEDLINE; "substance related disorder".ti,ab; 82 results. 21. MEDLINE; 17 OR 18 OR 19 OR 20; 246790 results. 22. MEDLINE; 16 AND 21; 228 results. 23. MEDLINE; "randomized controlled trial".pt; 400708 results. 24. MEDLINE; "controlled clinical trial".pt; 90738 results. 25. MEDLINE; randomized.ab; 320298 results. 26. MEDLINE; placebo.ab; 164146 results. 27. MEDLINE; "drug therapy".fs; 1786686 results. 28. MEDLINE; randomly.ab; 229419 results. 29. MEDLINE; trial.ab; 334042 results. 30. MEDLINE; groups.ab; 1441910 results. 31. MEDLINE; 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30; 3536224 results. 32. MEDLINE; 22 AND 31; 77 results.	77	0
Summary	**NA**	**NA**	

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