Psychosis with coexisting substance misuse: Evidence Update December 2012

A summary of selected new evidence relevant to NICE clinical guideline 120 'Psychosis with coexisting substance misuse: assessment and management in adults and young people' (2011)

Evidence Update 26

Evidence Updates provide a summary of selected new evidence published since the literature search was last conducted for the accredited guidance they relate to. They reduce the need for individuals, managers and commissioners to search for new evidence. Evidence Updates highlight key points from the new evidence and provide a commentary describing its strengths and weaknesses. They also indicate whether the new evidence may have a potential impact on current guidance. For contextual information, this Evidence Update should be read in conjunction with Psychosis with coexisting substance misuse (NICE clinical guideline 120).

Evidence Updates do not replace current accredited guidance and do not provide formal practice recommendations.

NHS Evidence is a service provided by NICE to improve use of, and access to, evidence-based information about health and social care.

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Introduction

This Evidence Update identifies new evidence that is relevant to, and may have a potential impact on, the following reference guidance:

[1] **Psychosis with coexisting substance misuse. NICE clinical guideline 120 (2011).**

A search was conducted for new evidence from 1 May 2010 to 13 August 2012. A total of 3956 pieces of evidence were identified and assessed, of which 5 were selected for the Evidence Update (see Appendix A for details of the evidence search and selection process). An Evidence Update Advisory Group, comprised of topic experts, reviewed the prioritised evidence and provided a commentary.

Although the process of updating NICE guidance is distinct from the process of an Evidence Update, the relevant NICE guidance development centres have been made aware of the new evidence, which will be considered when guidance is reviewed.

Other relevant NICE guidance

The focus of the Evidence Update is on the guidance stated above. However, overlap with other accredited guidance has been outlined as part of the Evidence Update process. Where relevant, this Evidence Update therefore makes reference to the following guidance:

[1] Schizophrenia. NICE clinical guideline 82 (2009)

[1] Drug misuse: psychosocial interventions. NICE clinical guideline 51 (2007)

- [2] Bipolar disorder. NICE clinical guideline 38 (2006)

Feedback

If you have any comments you would like to make on this Evidence Update, please email contactus@evidence.nhs.uk

[1] NICE-accredited guidance is denoted by the Accreditation Mark
[2] Guidance published prior to NICE accreditation

Key points

The following table summarises what the Evidence Update Advisory Group (EUAG) decided were the key points for this Evidence Update. It also indicates the EUAG's opinion on whether the new evidence may have a potential impact on the current guidance listed in the introduction. For further details of the evidence behind these key points, please see the full commentaries.

The section headings used in the table below are taken from the guidance.

	Potential impact on guidance	
Key point	**Yes**	**No**
Secondary care mental health services		
• Current evidence for choosing between atypical antipsychotic drugs in people who have psychosis with coexisting substance misuse has limitations and shows conflicting results.		✓
• Quetiapine in combination with lithium or valproate semisodium in people with bipolar I disorder with coexisting alcohol dependence does not seem to have any additive effect on manic or depressive symptoms or level of alcohol use.		✓
• Limited evidence suggests that a motivational intervention seems to reduce cannabis use in people with coexisting psychosis and cannabis misuse to a greater extent than usual care, but these differences may not be sustained over 12 months.		✓
Inpatient mental health services		
• Limited evidence suggests a care coordination intervention including assertive outreach and peer support may be effective for increasing engagement with outpatient services after discharge from inpatient mental health services.		✓

1 Commentary on new evidence

These commentaries analyse the key references identified specifically for the Evidence Update. The commentaries focus on the 'key references' (those identified through the search process and prioritised by the EUAG for inclusion in the Evidence Update), which are identified in bold text. Supporting references provide context or additional information to the commentary. Section headings are taken from the guidance.

1.1 Principles of care

No new key evidence was found for this section.

1.2 Recognition of psychosis with coexisting substance misuse

No new key evidence was found for this section.

1.3 Primary care

No new key evidence was found for this section.

1.4 Secondary care mental health services

Treatment – clozapine, olanzapine and risperidone

NICE CG120 recommends that antipsychotic medication is prescribed according to the guideline on schizophrenia (NICE CG82) or bipolar disorder (NICE CG38) because there is no evidence of a differential benefit of one antipsychotic over another for people with psychosis and coexisting substance misuse. A research recommendation in NICE CG120 notes that expert opinion suggests that clozapine has a particular role in this population but that evidence to support this statement is lacking, and clozapine has several side effects, some of which may be life-threatening if not monitored appropriately.

Clozapine is licensed for use in patients with treatment resistant schizophrenia (that is, no satisfactory clinical improvement with two previous antipsychotic drugs, including an atypical antipsychotic) or in patients with schizophrenia who have severe, untreatable neurological adverse reactions to antipsychotics. The research recommendation suggested that a randomised controlled trial of at least 12 months' duration was needed, looking at short-term and longer-term outcomes of clozapine compared with other antipsychotics, in people with psychosis with coexisting substance misuse.

Machielsen et al. (2012) selected a sample of 141 participants from the Genetic Risk and Outcome of Psychosis (GROUP) study in the Netherlands (n=1120). The GROUP study is a cohort study examining the 6-year course of patients with non-affective psychotic disorders and their siblings. The sample studied by Machielsen et al. (2012) were participants taking a single antipsychotic drug (risperidone, olanzapine or clozapine) and who had a diagnosis of cannabis dependence. Data for craving assessed by a cannabis-specific version of the Obsessive Compulsive Drug Use Scale (OCDUS) were available for 123 people.

People with cannabis dependence were more likely than those in a comparator group on risperidone, olanzapine and clozapine who did not have cannabis dependence (n=363) to have used nicotine (89% vs 58% respectively, $p<0.001$), alcohol (85% vs 69% respectively, $p<0.001$) or other illicit drugs (28% vs 8% respectively, $p<0.001$) in the past year. People with cannabis dependence were also significantly more likely to be men (91% vs 78%, $p=0.002$).

In the 123 people for whom OCDUS craving data were available, 48 were taking risperidone, 52 were taking olanzapine and 23 people were taking clozapine. There were no significant differences between these groups in gender, alcohol or other illicit drug use in the past year but the group taking clozapine had significantly lower nicotine use in the previous 12 months (74%) compared with those taking risperidone (94%) or olanzapine (92%, p=0.003).

People taking risperidone had significantly higher scores than those on clozapine for OCDUS total score (1.83 vs 1.33, p=0.001), thoughts subscale (1.83 vs 1.50, p=0.006) and craving subscale (1.83 vs 1.17, p=0.002). People taking risperidone had significantly higher scores than those on olanzapine in OCDUS total score (1.83 vs 1.54, p=0.025), thoughts subscale (1.83 vs 1.67, p=0.036) and craving subscale (1.83 vs 1.50, p=0.047). No significant differences were seen between clozapine and olanzapine.

These results may be limited by the fact that only one measurement of craving was taken, so neither the level of craving before antipsychotic drugs were started, nor how craving may have changed over time on each drug is known. Additionally, the severity of misuse of cannabis was not clear, and the amount of alcohol or other illicit drug use in the past year was not reported. Nicotine use was significantly lower in the clozapine group, which could have been a factor contributing to the lower craving for cannabis in this group. The high proportion of men in the study may limit the applicability of the results to women. However, an additional analysis showed no significant differences between craving in men and women.

Sevy et al. (2011) reported a secondary analysis of a 3-year prospective randomised open-label study (n=120) comparing risperidone and olanzapine in people with first-episode schizophrenia. This new analysis looked at data only for the first 16 weeks of treatment in 49 people meeting Diagnostic and Statistical Manual of Mental Disorders (DSM) - IV criteria for a lifetime history of cannabis misuse or dependence (28 people on risperidone and 21 people on olanzapine).

The aims of the original study were to determine the lowest effective dose of olanzapine or risperidone to treat the initial psychotic episode, assessed via titration over several weeks to a maximum daily dose of 20 mg olanzapine or 6 mg risperidone. People who did not have a minimal improvement after 10 weeks ceased the randomly assigned drug. All participants had psychoeducation about schizophrenia, its treatment and the importance of abstinence from cannabis and other substances that may be misused.

No significant differences were seen between the rates of treatment completion or treatment response for either drug. Rates of cannabis use at the end of the study were also not significantly different between people on olanzapine and people on risperidone. As with Machielsen et al. (2012), most participants were men (86% of those on olanzapine and 76% of those on risperidone).

The authors noted that the main limitation of their study was the small sample size, and the subsequent lack of statistical power. Additional limitations recognised by the authors were the lack of accurate measurement of the amount and frequency of substance misuse, and that craving was not assessed.

The results of Machielsen et al. (2012) and Sevy et al. (2011) show conflicting results for comparisons or olanzapine and risperidone, and the sample size for clozapine (n=23) may prevent any firm conclusions about its effects. Therefore, these studies reinforce the need for an adequately powered randomised controlled trial to determine whether differences in the effects of antipsychotic drugs exist in this population. The current evidence is unlikely to affect NICE CG120.

Key references

Machielsen M, Beduin AS, Dekker N et al. (2012) Differences in craving for cannabis between schizophrenia patients using risperidone, olanzapine or clozapine. Journal of Psychopharmacology 26: 189–95

Sevy S, Robinson DG, Sunday S et al. 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: 310–4 [NIH Public Access author manuscript – full text]

Treatment – quetiapine as adjunct in bipolar I disorder

For people with bipolar disorder and coexisting substance misuse, NICE CG120 recommends using antipsychotics according to the guideline for bipolar disorder (NICE CG38).

Stedman et al. (2010) undertook a randomised controlled trial of quetiapine compared with placebo as an add-on treatment to lithium (n=185) or valproate semisodium (n=177) in people with DSM-IV diagnosed bipolar I disorder and alcohol dependence assessed by the Structured Clinical Interview for DSM. The primary outcome was change from baseline in heavy drinking measured by the timeline followback method. The timeline followback method uses questions to aid recall of substance misuse, which is estimated daily on a calendar.

Additional inclusion criteria included heavy drinking (more than 4 standard drinks a day for women or more than 5 standard drinks a day for men for at least 10 of the previous 28 days) that did not need detoxification treatment for alcohol withdrawal or dependence. People who tested positive for opiates or cocaine were excluded if they tested positive in a second test performed within 3 days, as were women who were pregnant, lactating, or of childbearing potential but not using a reliable method of contraception.

Patients were assigned to lithium or valproate semisodium, which they remained on for the 12-week study period. After a washout period of up to 28 days (performed during the screening phase), people were then randomised on day 1 to placebo, or to quetiapine 50 mg, which was titrated to 400 mg on days 5–7. From day 8, a flexible dose of 300–800 mg was used.

The mean number of standardised drinks per day at baseline was about 7 (equal to approximately 95 g of pure alcohol) in both the quetiapine and placebo groups, which reduced to about 4 in both groups at week 12. The mean proportion of heavy drinking days at 12 weeks (−0.36 for both groups) was about half that at baseline (−0.66 for quetiapine and −0.67 for placebo). No significant differences between quetiapine and placebo were seen at 12 weeks for secondary outcomes including the Young Mania Rating Scale, depressive symptoms, severity of illness or anxiety symptoms.

The proportion of people experiencing any adverse event was higher in the quetiapine group (82% vs 70% in the placebo group), but no statistical analysis of overall or group-specific adverse events was reported. Study completion rates were similar between groups (42% for quetiapine and 43% for placebo). More men were included in the study (63%) than women, which may limit the applicability of the results to women.

The authors' only reported limitations were that combination therapy was used in this trial and also that participants may not have been heavy enough drinkers. However, both of these proposed limitations assume that quetiapine is effective in reducing drinking despite this study showing otherwise. Although quetiapine is licensed in the UK for the treatment of bipolar disorder, it has no license for treating alcohol dependence.

The results of this study provide limited evidence that quetiapine has no effect on alcohol use in people with bipolar I disorder who drink heavily, and may not have additive effects on mania, depression or anxiety in people taking lithium or valproate semisodium. This evidence

is unlikely to affect NICE CG120, which recommends that people should have treatment according to the underlying psychotic disorder.

Key reference

Stedman M, Pettinati HM, Brown ES et al. (2010) A double-blind, placebo-controlled study with quetiapine as adjunct therapy with lithium or divalproex in bipolar I patients with coexisting alcohol dependence. Alcoholism: Clinical and Experimental Research 34: 1822–31

Motivational intervention for cannabis use

NICE CG120 recommends treating substance misuse disorders as described in the relevant clinical guideline. In this case, the guideline on 'Drug misuse: psychosocial interventions' (NICE CG51) states that opportunistic brief interventions focused on motivation should be offered to people not in contact with drug services (for example, in primary or secondary care settings, occupational health or tertiary education) if concerns about drug misuse are identified by the person or staff member. These interventions should normally consist of 2 sessions each lasting 10–45 minutes and explore ambivalence about drug use and possible treatment, with the aim of increasing motivation to change behaviour, and provide non-judgemental feedback.

Bonsack et al. (2011) reported on a Swiss single-centre randomised controlled trial of a motivational intervention to reduce cannabis use compared with treatment as usual over 12 months in 62 people with psychosis and coexisting cannabis use. Participants were aged 18–35 years and smoked at least 3 cannabis joints per week in the month before joining the study. People who additionally had dependence on alcohol or substances other than nicotine and cannabis were excluded. The study was conducted during a 'stable phase' of the person's condition, and the main outcome was change in the number of joints smoked per week measured by the timeline followback method.

People in the treatment as usual group (n=32) received community or hospital care as needed, and antipsychotic drugs and treatment monitoring based on each patient's needs. This group received standard counselling and psychoeducation about substance misuse but did not have any specific motivational intervention.

The motivational intervention (n=30) was administered in addition to usual care and consisted of 4–6 sessions depending on the patient's readiness to attend. The first session lasted for 60 minutes with a follow-up within the next week of 45–60 minutes and then 2–4 booster sessions of 30–45 minutes tailored to participants' needs were given during the first 6 months. Three optional motivational group sessions of 1 hour duration were also available, in which 15 people took part. Participants received an average of 5 sessions; however, 4 people received 7–12 sessions and 2 received only 3 sessions.

87% of participants were men and 82% met criteria for cannabis dependence. Baseline cannabis use was an average of 27 joints per week, which were smoked on 77% of days. Cannabis use decreased over time in both groups. At 3 months, the motivational intervention group had a median reduction of 6.0 joints smoked per week compared with 0.5 joints fewer smoked in the treatment as usual group (p=0.015). This was maintained at 6 months (median reduction of 10.5 joints for the motivational intervention group and 0.5 joints for the usual care group p=0.015). However, at 12 months the changes were reported to be not significant (median of 10 joints fewer smoked in the intervention group compared with 3.5 fewer in the treatment as usual group). No significant differences were seen in secondary outcomes of motivation to change cannabis use, psychopathology, functional level or rate of hospital admissions.

The authors noted that the treatment as usual provided during the study was comprehensive, which may have resulted in a larger decrease in cannabis use in this group than had been expected from the sample size calculation. The authors additionally recognised that

participants may have reported lower cannabis use because it was expected to reduce even if use had not actually reduced. The authors did not mention how reliable an indicator the number of joints was as a true measure of cannabis use, in that participants may have smoked fewer joints containing more cannabis, or that cannabis may have been of differing strengths.

This evidence suggests that a specifically designed motivational intervention may reduce cannabis use in people with psychosis to a greater extent than usual care in the 6 months in which the intervention is delivered, but this difference may not be sustained at 12 months. The intervention is more time-intensive and resource-intensive than the general brief motivational intervention recommended in NICE CG51, so is not likely to affect current recommendations.

Key reference

Bonsack C, Manetti SG, Favrod J et al. (2011) Motivational intervention to reduce cannabis use in young people with psychosis: a randomized controlled trial. Psychotherapy and Psychosomatics 80: 287–97

1.5 Substance misuse services

No new key evidence was found for this section.

1.6 Inpatient mental health services

Promoting treatment engagement when transitioning from inpatient to community care

NICE CG120 recommends that when adults and young people are discharged from an inpatient health service, they should have an identified care coordinator and a care plan considering their needs associated with both their psychosis and their substance misuse.

Smelson et al. (2012) undertook an 8-week study of 102 veterans in the USA comparing a time-limited care coordination intervention (n=55) compared with a matched attention control (n=47) to evaluate the effects on engagement with outpatient treatment following discharge from a psychiatric unit. Participants had a schizophrenia spectrum or bipolar I disorder and a substance misuse or dependence disorder and had used drugs or alcohol within the past 3 months. The study began in an inpatient facility and continued in the community after the patient's discharge from hospital.

All participants received treatment as usual for coexisting disorders including psychoeducation, psychotherapy, skills training, medication management and relapse prevention treatment. Time-limited care coordination was delivered by a case manager allocated to the patient for the transition period and consisted of dual recovery therapy for 5 hours per week. This included assertive community intervention and peer specialists serving as role models (for example, to promote healthy living in the community and using public transport). The matched attention control consisted of health education, including discussion of nutrition, disease prevention, injury prevention and healthy ageing.

Engagement in outpatient treatment was measured by attendance at an outpatient session within 14 days of discharge from hospital and at the end of the 8-week intervention period. The outpatient sessions were with the clinician that the patient was referred to by the inpatient service; it did not include any study appointments (that is, with the case manager or peer specialist).

Analyses included only 66 participants who attended at least one intervention session (n=40) or attention control session (n=26). 97% of participants were men, which may limit the applicability of these results to women. Cocaine was the most common drug of primary

misuse (in 39% of participants), although more people (73%) reported alcohol use in the past 30 days.

More people in the intervention group attended sessions while in inpatient care compared with the control group (4.2 vs 1.4 sessions, $p<0.001$). Engagement with outpatient care was higher in the intervention group, with 69% attending an appointment within 14 days compared with 33% in the control group ($p<0.01$), and 44% attending an appointment after the 8 week intervention compared with 22% of those in the control group ($p<0.01$).

The authors suggested that the intervention may have overcome some problems in coordination of inpatient and outpatient care. Limitations recognised by the authors included that no testing of differences in substance use and mental health outcomes between groups was possible. The applicability of these results to a UK population may be limited by differences in the drugs of primary misuse between the USA (alcohol and cocaine in this study) and the UK, where a randomised study of 327 participants with psychosis and substance misuse recorded overall primary alcohol use of 60% and primary cannabis use of 25%; cocaine was only the sixth most common drug of primary misuse (Barrowclough et al. 2010). Furthermore, the differences in health services between the UK and the USA may limit the applicability of these results to the UK.

The results of this study provide limited evidence that an intervention with a specific focus on promoting engagement across the transition from inpatient to community care that includes assertive outreach and peer support components may increase engagement with outpatient treatment in people with psychosis with coexisting substance misuse who are discharged from inpatient psychiatric care. However, the limitations of the evidence mean it is not likely to affect NICE CG120.

Key reference

Smelson D, Kalman D, Losonczy MF et al. (2012) A brief treatment engagement intervention for individuals with co-occurring mental illness and substance use disorders: results of a randomized clinical trial. Community Mental Health Journal 48: 127–32

Supporting reference

Barrowclough C, Haddock G, Wykes T et al. (2010) Integrated motivational interviewing and cognitive behavioural therapy for people with psychosis and comorbid substance misuse: randomised controlled trial. BMJ 341: c6325

1.7 Staffed accommodation

No new key evidence was found for this section.

1.8 Specific issues for young people with psychosis and coexisting substance misuse

No new key evidence was found for this section.

2 New evidence uncertainties

During the development of the Evidence Update, the following evidence uncertainties were identified for the NHS Evidence UK Database of Uncertainties about the Effects of Treatments (UK DUETs).

Secondary care mental health services

- Olanzapine for cannabis cravings or use in people with psychosis and coexisting substance misuse
- Risperidone for cannabis cravings or use in people with psychosis and coexisting substance misuse

Inpatient mental health services

- Peer support for improving service engagement for people with psychosis and coexisting substance misuse

Further evidence uncertainties for psychosis with coexisting substance misuse can be found in the UK DUETs database and in the NICE research recommendations database.

UK DUETs was established to publish uncertainties about the effects of treatments that cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.

Appendix A: Methodology

Scope

The scope of this Evidence Update is taken from the scope of the reference guidance:

- Psychosis with coexisting substance misuse. NICE clinical guideline 120 (2011).

Searches

The literature was searched to identify studies and reviews relevant to the scope. Searches were conducted of the following databases, covering the dates 1 May 2010 (the end of the search period of NICE clinical guideline 120) to 13 August 2012:

- CDSR (Cochrane Database of Systematic Reviews)
- CENTRAL (Cochrane Central Register of Controlled Trials)
- CINAHL (Cumulative Index to Nursing and Allied Health Literature)
- EMBASE (Excerpta Medica database)
- MEDLINE (Medical Literature Analysis and Retrieval System Online)
- NHS EED (Economic Evaluation Database)
- PreMEDLINE
- PsycINFO

Table 1 provides details of the MEDLINE search strategy used, which was adapted to search the other databases listed above. The search strategy used in the reference guidance was adapted to provide a more focused set of results; this was tested to ensure that the comprehensiveness of the results was not compromised. The search strategy was used in conjunction with validated Scottish Intercollegiate Guidelines Network search filters for RCTs, systematic reviews and observational studies.

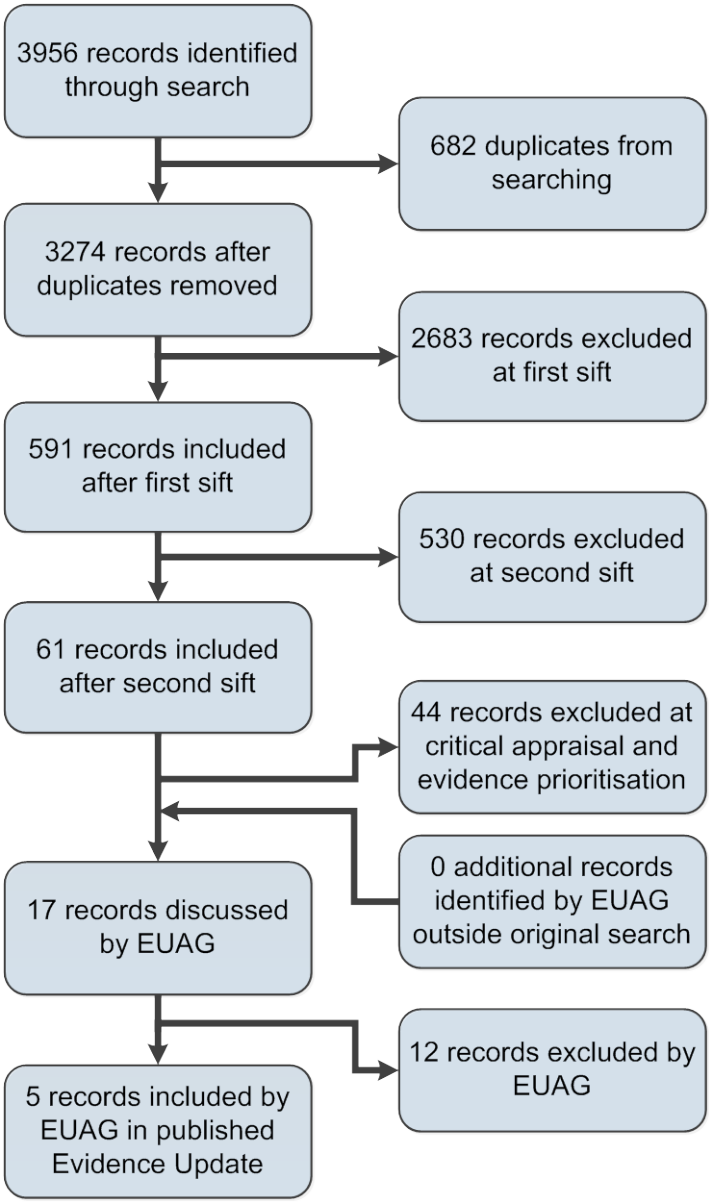
Figure 1 provides details of the evidence selection process. The long list of evidence excluded after review by the Chair of the EUAG, and the full search strategies, are available on request from contactus@evidence.nhs.uk

There is more information about how NICE Evidence Updates are developed on the NHS Evidence website.

Table 1 MEDLINE search strategy (adapted for individual databases)

1	exp psychotic disorders/ or exp affective disorders, psychotic/
2	exp schizophrenia/ or "schizophrenia and disorders with psychotic features"/ or schizophrenic psychology/
3	(((acute or chronic$ or serious$ or sever$) adj3 (mental$ or psych$) adj3 (disease$ or disorder$ or disturbanc$ or ill$)) or smi$1).ti,ab.
4	(bipolar$ or ((cyclothymi$ or rapid or ultradian) adj5 cycl$) or rcbd or hebephreni$ or mania$ or manic$ or oligophreni$ or psychose$ or psychosi$ or psychotic$ or schizo$).ti,ab.
5	"diagnosis, dual (psychiatry)"/
6	(designer drugs or needle exchange programs or needle sharing or overdose or street drugs or substance abuse detection or substance abuse, intravenous or substance abuse treatment centers or substance-related
	disorders or substance withdrawal syndrome).sh.
7	(((drug$1 or polydrug$ or psychotropic$ or substance$) adj3 (abstain$ or abstinen$ or abus$ or addict$ or excessive use$ or criminal or depend$ or habit$ or illegal$ or illicit$ or intoxicat$ or misus$ or nonprescri$ or non prescri$ or over dos$ or overdos$ or recreation$ or unlawful$ or withdraw$)) or ((drug$1 or polydrug$ or recreation$ or substance$) adj use$1) or ((drug$1 or polydrug$ or substance$) adj rehab$) or abusable product$ or (crave$ adj2 inject$) or hard drug$ or needle fixation or soft drug$ or vsa$1).ti,ab.
8	((club or designer or street) adj2 (drug$ or substance$)).ti,ab.
9	1 or 2 or 3 or 4 or 5
10	6 or 7 or 8
11	9 and 10

Figure 1 Flow chart of the evidence selection process



EUAG – Evidence Update Advisory Group

Appendix B: The Evidence Update Advisory Group and Evidence Update project team

Evidence Update Advisory Group

The Evidence Update Advisory Group is a group of topic experts who review the prioritised evidence obtained from the literature search and provide the commentary for the Evidence Update.

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