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Co-morbid mental and substance use disorders – a  
meta-review of treatment effectiveness

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# CO-MORBID MENTAL AND SUBSTANCE USE DISORDERS – A META-REVIEW OF TREATMENT EFFECTIVENESS

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## EXECUTIVE SUMMARY

**Background:** People with comorbid mental and substance use disorders experience greater combined disease severity than those with non-comorbid conditions. This study provides a comprehensive understanding of the methods and findings of systematic reviews on the effectiveness of different treatments for this population. It also provides a database of available literature on treatments for comorbid mental and substance use disorders that can be used to inform evidence-based health service planning.

**Method:** We conducted a meta-review of systematic reviews published between 2004 and 2016 that evaluated treatments for adults with diagnosed comorbid mental and substance use disorders. Reviews were identified via a systematic search of the PubMed, PsycINFO, CINAHL and Cochrane Library databases. Details of the systematic reviews, such as search strings, interventions examined, and type of mental and substance use disorders examined are presented. A comprehensive database of relevant studies was developed in Endnote. Interventions were considered within four categories: integrated treatments (i.e., the delivery of treatments for mental and substance use disorders by the same service provider), non-integrated psychological treatments, non-integrated pharmacological treatments and other treatments. Outcomes included changes in substance use or abstinence rates, and changes in mental health symptomatology. Gaps and limitations in the literature were identified.

**Results:** Twelve systematic reviews published between 2005 and 2014, which evaluated 131 unique original studies, met inclusion criteria. There was some support for the superiority of integrated treatments for substance use and mental health outcomes compared to non-integrated standard care. Non-integrated psychosocial treatments, such as cognitive behaviour therapy, delivered individually and through group format, also demonstrated positive substance use and mental health outcomes compared to other types of non-integrated standard care. The methodological quality and publication bias of included studies were rarely assessed in existing systematic reviews, which is a limitation.

**Conclusions:** Available evidence supports the provision of psychosocial treatments (either integrated within the same service, or delivered in different services) for improving mental health and substance use outcomes for this population. Researchers, clinicians and policy makers can use the findings and database created in this review to guide decision making for best practice, and future research, related to treating comorbid mental and substance use disorders. Findings should be interpreted with caution, as they are limited by the heterogeneity of study methodologies. More research is warranted to provide a strong level of evidence on effective treatments for different types of mental and substance use disorders comorbidity.

# 1. INTRODUCTION

Comorbidity of mental and substance use disorders is common, debilitating and associated with poor clinical and functional outcomes. Data from the Australian National Survey of Mental Health and Wellbeing (NSMHWB) showed that 25.4% of people with a 12-month mental or substance use disorder had a comorbid diagnosis (Slade, Teesson, & Burgess, 2009). Mental and substance use disorders accounted for 183.9 million disability-adjusted life years (DALYs), or 7.4% of all DALYs worldwide in 2010 (Whiteford et al., 2013). Comorbidity magnifies the already heavy burden experienced by people with either a mental health or substance use disorder in isolation. Experimental trials consistently demonstrate that this population experience greater symptom severity, poly-drug use, increased risk of violence, increased suicidal ideation and a greater number of previous suicide attempts (Barrett, Mills, & Teesson, 2011; Davis et al., 2006; Erfan, Hashim, Shaheen, & Sabry, 2010). Individuals with comorbid mental and substance use disorders are more likely to experience poorer short- and long-term outcomes for their mental health and substance use (Burns, Teesson, & O'Neill, 2005; Teesson et al., 2015b; Torrens, Fonseca, Mateu, & Farré, 2005), more severe levels of impairment (Kessler, Chiu, Demler, & Walters, 2005; Slade et al., 2009), and greater use health of services than those with no comorbidity (Slade et al., 2009).

Treatment models for persons with a comorbid mental health and substance use disorder are typically classified into 'integrated services' whereby treatments for mental health and substance use problems are provided at the same service; and 'non-integrated', whereby treatments are provided in parallel or sequentially at separate services, or treatments are provided to target the more severe disorder initially. In order to plan treatment services for people with comorbid substance use and mental disorders, policy makers need to know which interventions should be delivered for this population based on contemporary evidence of treatment effectiveness.

A number of systematic reviews have summarised the effectiveness of various treatments for people with comorbid mental and substance use disorders. This systematic meta-review aimed to collate and summarise the evidence from these existing reviews on specialised treatments for people with comorbid substance use and mental disorder, by: 1) providing a synthesis of evidence on the effectiveness of different types of specialist treatments in reducing substance use and improving mental health for people with comorbid substance use and mental disorders; 2) evaluating the methods of existing literature to identify limitations in current research and areas in need of future research, and ; 3) creating a database of empirical literature sources stratified by disorder and treatment types, which researchers, clinicians, and policy makers can draw upon to guide clinical practice and service system resource allocation.

## 2. METHODS

This meta-review encompassed systematic searches for systematic reviews on the effectiveness of specialised clinical treatments for people with comorbid mental and substance use disorders, compared to no interventions or standard care in reducing symptoms associated with mental and substance use disorders . The review was conducted in accordance with the PRISMA protocol (Moher, Liberati, Tetzlaff, & Altman, 2009).

### 2.1 Search strategy

Systematic reviews and meta-analyses (hereafter referred to as reviews), peer-reviewed and published between 2004 and 2016, on outcomes of treatment for persons with mental and substance use disorders were identified via searches of the PubMed, PsycINFO, CINAHL and Cochrane Library electronic databases. Search strings were constructed using a combination of Medical Subject Heading (MeSH) terms and keyword terms, varied based on synonyms accepted in each of the databases. Two search strategies were developed to comprehensively capture treatment outcomes for comorbid 1) substance use disorders and 2) mental disorders. The first search strategy comprised terms: substance-related disorders, substance abuse, substance disorder, illicit, drug abuse, alcohol abuse, individual substance types (alcohol, hallucinogen\*, cannabis, opioi\*, heroin, stimulants, cocaine, benzodiazepines, amphetamines, ecstasy, methamphetamines) AND comorbid\*, diagnosis, dual, co-occurring AND treatment, treatment outcome, intervention AND review, systematic review, meta-analysis. The second search focused on mental disorders and comorbidity. This search used the same structure as the first search, replacing the substance keywords with mental disorder

keywords: mental health, mental disorder, mental illness, psychiatric disorder, psychiatric illness, individual mental disorder types (depress\*, dysthymi\*, mood, affective, bipolar, schizophrenia, anxiety, obsessive compulsive, phobia, post-traumatic, posttraumatic, PTSD, panic disorder). Results were limited to English language, human subjects, and reviews as the article type.

## 2.2 Inclusion and exclusion criteria

Reviews were included in this meta-review if: 1) it was a peer-reviewed systematic review that followed a protocol; 2) the review focused on adults aged 18 or older with a co-occurring diagnosed substance use disorder according to the diagnostic criteria of the International Statistical Classification of Diseases (ICD-10) or the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; APA, 2000); (including any of ICD-10 F10-F16 or DSM-IV- 305.00,-305.90; 303.90- 304.90), and an Axis-I ICD-10 or DSM-IV diagnosed mental disorder, 3) the review evaluated treatments for people with comorbid mental and substance use disorders; and 4) the review evaluated treatment outcomes in terms of changes in substance use or increased abstinence rates, and/or changes in mental health outcomes, such as reduced psychiatric symptoms or improved psychological functioning based on validated measures. A review was excluded if focused on complementary and alternative medicine or non-specialised treatments (e.g. acupuncture, general practitioner only). Nicotine focused treatment only and tobacco use disorders were not included.

## 2.3 Quality assessment, data extraction, synthesis and analysis

Screening, data extraction, and quality ratings were conducted independently by two reviewers with discrepancies (n = 7) resolved via discussion to reach consensus. Eligible reviews were critically assessed using AMSTAR, a measurement tool developed to assess the methodological quality of systematic reviews (Shea et al., 2007). The AMSTAR tool comprises 11 criteria, which are:

- 1) Was an 'a priori' design provided?
- 2) Was there duplicate study selection and data extraction?
- 3) Was a comprehensive literature search performed?
- 4) Was the status of publication (i.e. grey literature) used as an inclusion criterion?
- 5) Was a list of studies (included and excluded) provided?
- 6) Were the characteristics of the included studies provided?
- 7) Was the scientific quality of the included studies assessed and documented?
- 8) Was the scientific quality of the included studies used appropriately in formulating conclusions?
- 9) Were the methods used to combine the findings of studies appropriate?
- 10) Was the likelihood of publication bias assessed?
- 11) Was the conflict of interest included?

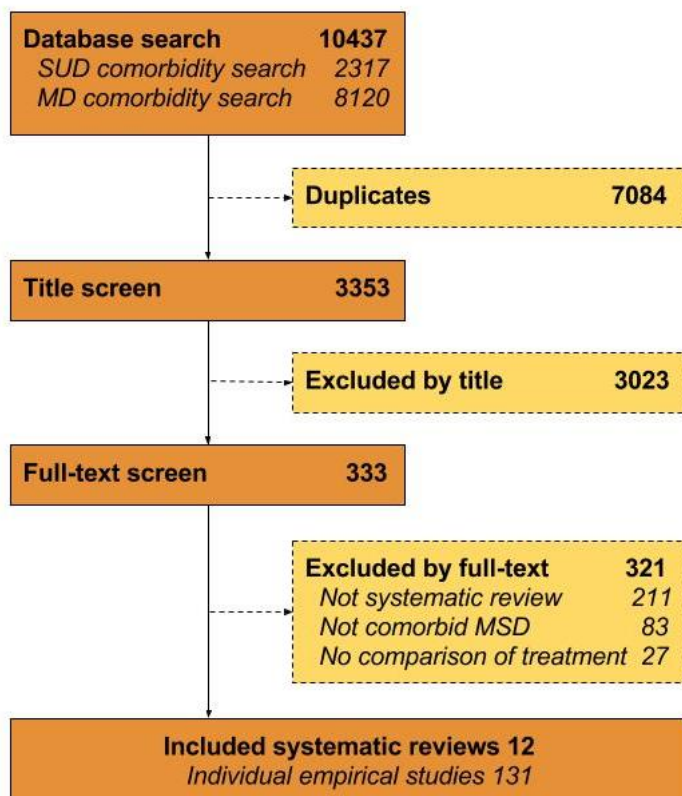
The reviewer assigned a score of one to each criterion fulfilled. Summed scores ranged from 0 to 11 points; with higher scores indicating higher methodological quality. Data extracted included the review's sample characteristics, mental and substance use disorders studied, interventions and comparison treatments delivered, substance use and mental health outcomes, the study design, and the timeframe and/or intensity of treatment.

Reviews were summarised based on their study type (systematic review with/without meta-analysis), substance use disorders included (e.g. alcohol, cannabis, opiates), mental disorders included (e.g. depression, anxiety, schizophrenia), intervention focus (e.g. integrated, psychological, pharmacological), study designs (e.g. randomised controlled trials), and mental health and substance use outcomes. Endnote X7 was used to manage the references.

## 3. RESULTS

### 3.1 Review inclusion

Figure 1 presents the inclusion flowchart. The search yielded a total of 10437 records, including 2317 from the substance use focused search and 8120 from the mental disorder focused search. Of those, 3353 were non-duplicates and went through title and abstract screening, from which 333 were selected for full-text review. A total of 12 reviews (comprising 131 empirical studies; see Appendix) were included in this meta-review.



**Figure 1: Inclusion flowchart of systematic review articles published between 2004 and 2016 on treatment effectiveness for comorbid substance use (SUD) and mental (MD) disorders**

Search details, including search terms used, of the systematic reviews are presented in Table 1. An Endnote database cataloguing the 131 studies evaluated by the 12 systematic reviews, grouped by specific type of mental and substance use disorder comorbidity, is supplied [online available for download](#) (Leung, Wong, Galasyuk, & Stockings, 2017).

**Table 1: Comorbidity focus and search details of systematic reviews on the treatment effects for people with comorbid mental and substance use disorders**

First author (year)	Comorbidity focus	Search year (year range of included studies)	Search Terms
Chow (2013)	Mental illness and SUD	nr (1995-2009)	substance abuse and mental health', 'dual diagnosis', 'Integrated Dual Disorder Treatment', 'integrated treatment or co-occurring disorder', 'integrated treatment or dual disorder'
Donald (2005)	Mental and substance use disorders	nr (1993-2001)	Diagnosis-Dual-Psychiatry, Comorbid*, Comorbidity, randomised controlled trial, random*, double blind and placebo, and "Appropriate synonyms"
Drake (2008)	Severe mental and SUD	nr (1997-2001)	search for dual diagnosis, co-occurring disorders, mental illness and chemical addiction, or substance abuse and mental



illness

Gregory (2011)	SUD with bipolar	2010 (2000-2009)	"bipolar and cognitive and substance and group", "bipolar and substance and cognitive-behavioral", "CBT and bipolar and alcohol", "bipolar and dual diagnosis and treatment and cognitive", "bipolar and comorbidity and treatment and cognitive", "bipolar and addiction and cognitive-behavioral", "bipolar and cognitive therapy and substance abuse"
Hesse (2009)	SUD with depression/anxiety	nr (1996-2008)	mood', 'depression', 'depressive', 'anxiety', 'substance abuse', 'substance dependence', 'cocaine', 'heroin', 'cannabis', 'alcohol', 'MDMA' (no results), 'randomized', 'control group', 'behavioral therapy', 'psychotherapy', 'psychosocial intervention'
Hides (2010)	SUD with depression	2010 (1997-2010)	alcohol abuse, drug abuse, substance abuse, depression, dysthymia, affective disorders, mood disorders, cognitive behaviour therapy, cognitive therapy, behaviour therapy
Hjorthoj (2009)	Cannabis use disorders with schizophrenia	2008 (1998-2008)	cannabis or marijuana or addiction or abuse or substance AND schizophrenia or schizotypal or psychosis AND treatment or reduction or cessation; dual diagnosis or comorbid or comorbidity AND schizophrenia or schizotypal or psychosis
Iovieno (2011)	Alcohol use disorders with depression/dysthymia	2010 (1997-2010)	placebo', amitriptyline, nortriptyline, imipramine, desipramine, clomipramine, trimipramine, protriptyline, dothiepin, doxepin, lofepramine, amoxapine, maprotiline, amineptine, nomifensine, bupropion, phenelzine, tranylcypromine, isocarboxazid, moclobemide, brofaromine, fluoxetine, sertraline, paroxetine, citalopram, escitalopram, fluvoxamine, zimelidine, tianeptine, ritanserin, trazodone, nefazodone, agomelatine, venlafaxine, desvenlafaxine, duloxetine, violoxazine, milnacipran, reboxetine, mirtazapine, mianserin
Pedrelli (2011)	Opioid use disorders with depression/dysthymia	2010 (1990-2004)	"placebo", "methadone", "antidepressants": amitriptyline, nortriptyline, imipramine, desipramine, clomipramine, trimipramine, protriptyline, dothiepin, doxepin, lofepramine, amoxapine, maprotiline, amineptine, nomifensine, bupropion, phenelzine, tranylcypromine, isocarboxazid, moclobemide, brofaromine, fluoxetine, sertraline, paroxetine, citalopram, escitalopram, fluvoxamine, zimelidine,

			tianeptine, ritanserin, trazodone, nefazodone, agomelatine, venlafaxine, desvenlafaxine, duloxetine, viloxazine, milnacipran, reboxetine, mirtazapine, and mianserin
Riper (2014)	Alcohol use disorders and depression	2013 (1997-2013)	psychological treatment and depression terms
Torrens (2005)	Cocaine/Opioid/Alcohol use disorders with depression	2004 (1975-2004)	opioid dependence', 'alcohol dependence', 'nicotine dependence', 'cocaine dependence', 'antidepressants', 'randomised controlled trial'
van Dam (2012)	SUD with post-traumatic stress disorder	2011 (1998-2010)	(PTSD or posttraumatic or post-traumatic) AND (treatment or intervention* or randomized controlled trial or RCT or therap*) AND (addiction or SUD or substance-related disorders or substance abuse or substance dependence or alcohol abuse or alcohol dependence or drug abuse or cocaine abuse or cocaine dependence or opioids abuse or opioids dependence or cannabis abuse or cannabis dependence or sedative abuse or sedative dependence or hypnotic abuse or hypnotic dependence or anxiolytic abuse or anxiolytic dependence or polydrug abuse or polydrug dependence)

SUD: substance use disorders; nr: not reported.

### 3.2 Methods and characteristics of reviews

Disorders and study type included in the 12 systematic reviews are presented in Table 2. Most reviews examined 'any' substance use disorder (66.7%) rather than a specific disorder. Depressive disorders (50%) were the most common mental disorders studied. One third of reviews included only randomised controlled trials (RCTs; 33.3%).

**Table 2: Disorders and study type included in the 12 systematic reviews on treatment effects for comorbid mental and substance use disorders**

Study characteristics <sup>a</sup>	Count	Percentage	AMSTAR <sup>b</sup>
Total	12	100%	4.8
Substance use disorders examined			
Alcohol	2	16.7%	7
Cannabis	1	8.3%	6
Opiates	1	8.3%	6
Any	8	66.7%	4
Mental disorders examined			
Depressive	6	50.0%	5.3
Anxiety	1	8.3%	5
Schizophrenia	1	8.3%	6
Bipolar	1	8.3%	2

Post-Traumatic Stress	1	8.3%	4
Any	3	25.0%	4.7
Study type included			
RCT only	4	33.3%	4.8
RCT and/or other designs <sup>c</sup>	8	66.7%	4.9

<sup>a</sup> Reviews can examine more than one category

<sup>b</sup> Adherence to AMSTAR (Assessing the Methodological Quality of Systematic Reviews), out of 11.

<sup>c</sup> Other design included controlled trials, matched trials, observational studies, retrospective studies.

RCT, Randomised controlled trials.

Table 3 presents the characteristics of the included reviews. Reviews also varied considerably in their intervention focus. Five reviews examined the treatment effects of integrated interventions (Chow, Wieman, Cichocki, Qvicklund, & Hiersteiner, 2013; Donald, Dower, & Kavanagh, 2005; Hesse, 2009; Hides, Samet, & Lubman, 2010; van Dam, Vedel, Ehring, & Emmelkamp, 2012). For reviews that evaluated one specific type of treatment, five reviews examined psychosocial interventions (Drake, O'Neal, & Wallach, 2008b; Gregory, 2011; Hides et al., 2010; Hjorthoj, Fohlmann, & Nordentoft, 2009; Riper, Andersson, Hunter, de Wit, et al., 2014), four reviews examined pharmacological interventions (Hjorthoj et al., 2009; Iovieno, Tedeschini, Bentley, Evins, & Papakostas, 2011; Pedrelli et al., 2011; Torrens et al., 2005), and two reviews examined other interventions (Drake et al., 2008b; Hjorthoj et al., 2009). Three of the reviews covered more than one intervention focus (Drake, O'Neal, & Wallach, 2008a; Hides et al., 2010; Hjorthoj et al., 2009), while others were restricted to a single intervention focus. The comparison groups employed differed by intervention focus. For reviews that focused on pharmacological treatments, the majority (75%) employed placebo as comparison treatment. For reviews that focused on integrated and psychosocial treatments, the comparison groups were variable, including treatment as usual and/or no treatment and/or treatment for a single disorder.

**Table 3: Characteristics of included reviews on treatment effects for comorbid mental and substance use disorders**

Study	Intervention focus included	Comparison groups	Substance use/mental disorder	Number and type of studies	Length of follow-up / sessions
Chow et al. (2013)	Integrated: dual diagnosis treatment	Single-focused care	SUD/MD	13 (RCT/Retrospective)	3 months-3years
Donald et al. (2005)	Integrated: DBT/CBT/MI + substance use interventions, Case management	Parallel treatment; MH treatment only; SUD treatment only; TAU unspecified	SUD/MD	10 (RCT)	18 months
Drake, O'Neal & Wallach (2008)	Psychosocial, Observational: Group: education, peer support; Individual: CBT/ MI	No treatment or TAU unspecified; PE, booklet or TAU unspecified	SUD/MD	45 <sup>a</sup> (CT)	6 months-3 years/ 1-2 times per week
Gregory (2011)	Psychosocial: CBT	No intervention	SUD/Bipolar	4 (RCT/CT)	12-20 sessions

Hesse (2009)	Integrated: psychosocial with SUD treatment	SUD treatment only; RTC and behaviour therapy; TAU, other various treatment as usual, e.g. twelve step facilitation	SUD/ Anxiety, Depression	10 RCT	Not reported
Hides, Samet & Lubman (2010)	Integrated, Psychosocial: CBT, CBT +TSF or MI, SSRIs+ CBT	Single focused CBT, brief intervention or TSF; Placebo + CBT; Standard care (various, e.g. standard pharmacologic al interventions) or RTC	SUD/ Depression	12 (RCT/CT)	12 weeks- 12 months/ 9-22 sessions
Hjorthoj, Fohlmann & Nordentoft (2009)	Psychosocial, Pharmacological, Observational : MI/CBT, CBT, Atypical antipsychotics, Economic contingency management	TAU unspecified, PE or no control; RCT or TAU unspecified;	Cannabis/ Schizophreni a	41 (RCT/CT/CS)	8-25 sessions
Iovieno et al. (2011)	Pharmacological: Antidepressants	Placebo	Alcohol/ Depression	11 (RCT)	Not reported
Pedrelli et al. (2011)	Pharmacological: Antidepressants	Placebo	Opioids/ Depression	4 (RCT)	8-12 weeks
Riper et al. (2014)	Psychosocial: CBT/MI	TAU/TSF (other than psychosocial intervention)	Alcohol/ Depression	12 (RCT/CT)	8-36 sessions
Torrens, Fonseca, Mateu & Farre (2005)	Pharmacological: Antidepressants	Placebo	SUD/ Depression	21 (RCT/CT)	2-24 weeks
van Dam, Vedel, Ehring & Emmelkamp (2012)	Integrated: Non- trauma focused treatments, Trauma- focused treatments	Non-integrated care unspecified; SUD treatment only or no- treatment	SUD/PTSD	17 (RCT, CT, CS)	8-25 sessions

CBT, cognitive behaviour therapy; CS, case studies; CT, controlled trials; DBT, dialectical behaviour therapy; MD, mental disorders; MI, motivational interviewing; PE, psycho-education; PTSD, post-traumatic stress disorder; RCT, randomised controlled trial; SSRIs, selective serotonin reuptake inhibitor; SUD, substance use disorders; TAU, treatment as usual; TSF, Twelve Step Facilitation;

### 3.3 Methodological quality and risk of bias assessment

There was substantial heterogeneity in the methodological quality of the systematic reviews (see Table 4). The overall mean AMSTAR adherence rating was 4.8 out of 11. Only one of the 12 reviews achieved a high AMSTAR adherence rating (9 to 11), with most reviews rated as being of low ( $n = 7$ ; 58.3%) or moderate adherence ( $n = 4$ ; 33.3%). All reviews included an a-priori design and summarised the characteristics of the included studies. Most reviews appropriately combined study findings and stated any conflicts of interest. However, most reviews did not use two independent reviewers for study selection and data extraction ( $n = 11$ ; 91.7%), include grey literature ( $n = 11$ ; 91.7%), or provide a list of excluded studies ( $n = 11$ ; 91.7%). The majority of reviews did not assess the likelihood of publication bias ( $n = 10$ ; 83.3%). Further, few reviews used the scientific quality of the included individual studies in formulating their conclusions and recommendations ( $n = 3$ ; 26.7%).

**Table 4: AMSTAR ratings of the included reviews on treatment effects for people with comorbid mental and substance use disorders, presented in chronological order**

	AMSTAR item number											Total	
	1	2	3	4	5	6	7	8	9	10	11		
Donald et al. (2005)	1	0	0	0	0	1	0	0	1	0	1	4	Low
Torrens, Fonseca, Mateu & Farre (2005)	1	0	0	0	0	1	1	0	0	0	1	4	Low
Drake, O'Neal & Wallach (2008)	0	0	1	0	0	1	0	0	1	0	1	4	Low
Hesse (2009)	1	0	1	0	0	1	0	0	1	0	1	5	Mod
Hjorthoj, Fohlmann & Nordentoft (2009)	1	0	1	0	0	1	1	0	1	0	1	6	Mod
Hides, Samet & Lubman (2010)	1	0	0	0	0	1	0	0	1	0	0	3	Low
Gregory (2011)	1	0	0	0	0	1	0	0	0	0	0	2	Low
Iovieno et al. (2011)	1	0	0	0	0	1	1	0	0	0	1	4	Low
Pedrelli et al. (2011)	1	0	0	0	0	1	1	1	1	0	1	6	Mod
van Dam, Vedel, Ehring & Emmelkamp (2012)	1	0	0	0	1	1	0	0	1	0	0	4	Low
Chow et al. (2013)	1	0	0	0	0	1	1	1	1	1	0	6	Mod
Riper et al.	1	1	1	1	0	1	1	1	1	1	1	10	High

(2014)

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Number of reviews adhered to each item

n	11	1	4	1	1	12	6	3	9	2	8
%	92%	8%	33%	8%	8%	100%	50%	25%	75%	17%	67%

---

Note: AMSTAR item, 1 = yes, 0 = no:

- 1) Was an 'a priori' design provided?
- 2) Was there duplicate study selection and data extraction?
- 3) Was a comprehensive literature search performed?
- 4) Was the status of publication (i.e. grey literature) used as an inclusion criterion?
- 5) Was a list of studies (included and excluded) provided?
- 6) Were the characteristics of the included studies provided?
- 7) Was the scientific quality of the included studies assessed and documented?
- 8) Was the scientific quality of the included studies used appropriately in formulating conclusions?
- 9) Were the methods used to combine the findings of studies appropriate?
- 10) Was the likelihood of publication bias assessed?
- 11) Was the conflict of interest included?

Total level of adherence to AMSTAR: 0-4 = low, 5-8 = moderate, 9-11 = high adherence

### 3.4 Integrated treatments

Five systematic reviews (Chow et al., 2013; Donald et al., 2005; Hesse, 2009; Hides et al., 2010; van Dam et al., 2012) examined the effects of integrated treatments compared to a variety of non-integrated treatments.

A 2005 systematic review by Donald et al. evaluated 10 RCTs, and compared integrated mental health and substance use treatments to non-integrated treatments for any comorbid mental and substance use disorders (Donald et al., 2005). The types of mental health treatments included dialectical behaviour therapy (DBT), cognitive behaviour therapy (CBT) and motivational interviewing (MI). Two studies within the review (Donald et al., 2005) found significantly better substance use outcomes in integrated treatments compared to mental health only treatment, with all other studies finding a non-significant difference by treatment. No significant differences in mental health outcomes by treatment type were found in the studies. It was concluded that there was a lack of evidence to support the superiority of integrated treatments.

Hesse et al. (Hesse, 2009) conducted a systematic review in 2009 of 10 RCTs, and examined the treatment of substance use disorders comorbid with depression or anxiety. The authors also found a lack of empirical evidence to support psychotherapeutic integrated treatments over single-focused treatments, especially for anxiety disorders. They called for more trials to rigorously test the effects of integrated treatments compared with non-integrated treatments.

Hides et al. (Hides et al., 2010) conducted a systematic review in 2010 of 12 RCTs and controlled trials (CTs), and examined treatment outcomes for people with comorbid depression and substance use disorders. They found four studies with results supporting better substance use and mental health outcomes in the CBT integrated treatment groups compared to the non-integrated CBT, brief intervention or Twelve Step Facilitation (TSF) only treatment groups.

Van Dam et al. (van Dam et al., 2012) in 2012 conducted a systematic review of 17 RCTs, CTs and case studies (CS) on comorbid post-traumatic stress disorder and substance use disorders. They compared integrated treatments with non-integrated, substance focused only, or no treatment. They found evidence from eight studies supporting that integrated interventions resulted in significantly better mental and substance use outcomes.

Chow et al.'s (Chow et al., 2013) 2013 systematic review of 13 studies of mixed designs compared any comorbid mental and substance use disorders. They examined the outcomes by any integrated dual diagnosis treatment against single-focused care. They found mixed results, with some significant findings for integrated treatment in reducing psychiatric symptoms and alcohol use, but inadequate evidence to support its effects in reducing drug use.

### 3.5 Psychosocial treatments

Five reviews (Drake et al., 2008b; Gregory, 2011; Hides et al., 2010; Hjorthoj et al., 2009; Riper, Andersson, Hunter, de Wit, et al., 2014) evaluated the effects of non-integrated psychosocial treatment on people with comorbid mental and substance use disorder.

Drake et al. conducted a systematic review of 45 controlled trials (Drake et al., 2008a) in 2008, and they evaluated the effectiveness of group psychosocial treatments, compared to no treatment or non-psychosocial treatments. The review found ten studies reporting better substance use outcomes and four studies reporting better mental health outcomes only. However, the authors highlighted that the studies were limited by heterogeneity of interventions, samples, methods, and outcomes. For example, some studies did not measure mental health outcomes, and among those that did, the type of mental health outcomes measured varied (e.g. suicidal thoughts or general psychological functioning). The authors called for more research to employ consistent methods to enable comparison, before conclusions can be drawn.

Hjorthoj et al. conducted a systematic review of 41 RCTs and non-RCTs in 2009 (Hjorthoj et al., 2009), in which they examined the treatment effects of psychosocial treatments including CBT and MI compared to non-psychosocial interventions for people with comorbid schizophrenia and cannabis use disorder, and found mixed results on both substance use and mental health outcomes. A lack of evidence was available to support the effectiveness of CBT and MI in reducing substance use, when only considering cannabis use as the outcome. When examining studies that combined cannabis with other substance use outcomes, four studies demonstrated that people in the CBT or MI groups showed improvement. Two studies Hjorthoj et al.'s review (Hjorthoj et al., 2009) showed that CBT resulted in significantly better mental health compared to non-psychosocial treatments. It was unclear whether the non-significant effect of psychosocial interventions for reducing cannabis was due to inadequate sample sizes of the small studies that presented specific results for cannabis use, or if the treatment effects differed by the type of substance use disorders. More research comparing treatment effects by the specific type of substance use disorders is needed before conclusions can be drawn.

Hides et al. et al's (Hides et al., 2010) 2010 systematic review compared the effects of CBT psychosocial interventions with other non-CBT interventions including pharmacological interventions or relaxation training control for people with comorbid depression and substance use disorders. For mental health outcomes, Hides et al. (Hides et al., 2010) found two studies that showed greater reductions in depression among participants receiving CBT. For substance use outcomes, they found that CBT was significantly better at reducing substance use among people with alcohol use disorder. However, no significant difference in treatment outcomes were reported for people with opiate, benzodiazepine or cocaine use disorders.

Gregory et al.'s 2011 systematic review (Gregory, 2011) of four controlled trials compared the effects of CBT to no intervention among people with comorbid bipolar and substance use disorders. CBT was found to result in significantly better alcohol and drug use outcomes in three out of four studies, and better mental health outcomes in two studies. Additional trials with consistent methods are needed to allow for data for future meta-analyses, in order to evaluate the effectiveness of CBT for patients with comorbid bipolar and substance use disorders.

Riper et al. (Riper, Andersson, Hunter, de Wit, et al., 2014) conducted a systematic review of 12 RCTs and CTs in 2014, in which they examined the effects of CBT and MI compared to non-psychosocial treatments for people with comorbid depression and alcohol use disorders. Adequate data from 1721 patients were available for meta-analyses, which showed significantly better outcomes for both alcohol consumption and reduced depressive symptoms, however effect sizes were small. The authors noted that further research involving large RCTs could strengthen the evidence, and that future research comparing modes of CBT and MI delivery could provide data on how best to administer the interventions.

### **3.6 Pharmacological treatments**

Four reviews (Hjorthoj et al., 2009; Iovieno et al., 2011; Pedrelli et al., 2011; Torrens et al., 2005) discussed non-integrated pharmacological treatments for people with comorbid mental and substance use disorders, three examined antidepressants (Iovieno et al., 2011; Pedrelli et al., 2011; Torrens et al., 2005), and one examined antipsychotics (Hjorthoj et al., 2009).

Torrens et al. (Torrens et al., 2005) conducted a systematic review in 2005 of 21 RCTs and CTs, in which they examined the effects of antidepressants compared to placebo, and found mixed results for treating people with depression comorbid with alcohol, cocaine, or opioid dependence. The authors called for more evidence on the effects of antidepressants for treating different types of substance use comorbidity in order to draw conclusions on its effectiveness. The authors also suggested that future research needs to examine the effects of different types of specific antidepressant drugs.

Iovieno et al. in 2001 (Iovieno et al., 2011) conducted the second systematic review comparing antidepressants with placebo. Of the 11 included RCTs, they found a significant effect on

treatment efficacy on depression in patients with comorbid alcohol use disorders. However, treatment efficacy was not significant when only including trials with SSRIs (selective serotonin reuptake inhibitor) in the analysis. Iovieno et al.'s (Iovieno et al., 2011) review concluded that there is evidence available to support the efficacy of tricyclics and nefazodone, but more data on SSRIs are needed.

Pedrelli et al. in 2011 (Pedrelli et al., 2011) conducted the third systematic review of four RCTs comparing antidepressants with placebo, on studies involving people with comorbid depression and opioid use disorders on methadone maintenance treatment (MMT). Meta-analysis revealed no significant differences in mental health outcomes between the antidepressant and placebo groups. However, the authors noted that existing studies were limited by the lack of controlling for other treatments the samples could be undergoing, such as psychosocial treatments, and also the type of antidepressants used. The authors concluded that more studies are urgently needed to identify effective treatments in this patient group.

Hjorthoj et al.'s (Hjorthoj et al., 2009) 2009 systematic review of 41 RCTs and non-RCTs evaluated the use of antipsychotics on people with co-occurring schizophrenia and cannabis use disorders (Hjorthoj et al., 2009). Pre/post results from two studies included in this review (neither with a control condition for comparison) indicated that the use of antipsychotics (specifically, quetiapine and clozapine) reduced cannabis use and cravings. Authors concluded that more RCTs are needed, particularly those examining outcomes on mental health symptoms, in order to strengthen the evidence.

### 3.7 Other interventions

Two of the reviews also reported treatment effects from other interventions that do not fit into the above categories (Drake et al., 2008b; Hjorthoj et al., 2009).

Drake et al.'s 2008 (Drake et al., 2008a) systematic review of 45 controlled trials evaluated the effectiveness of case management, defined as intensive, team-based, multi-disciplinary, outreach-oriented, clinically coordinated services, usually involving the assertive community treatment or intensive case management model, for people with severe mental and substance use disorders. Eleven studies of case management treatments (half experimental and half quasi-experimental) produced evidence supporting positive social outcomes, such as community engagement, increased use of services, and improving quality of life, which are traditional outcomes associated with case management. However, inconsistent results were found on substance use and mental health outcomes. The comparison treatment groups varied widely across these studies, and consisted of treatment as usual, different types of case management models, TSF, or a combination of these treatments. There was also large heterogeneity of study samples.

Hjorthoj et al.'s 2009 systematic review of 41 RCTs and non-RCTs (Hjorthoj et al., 2009) evaluated the pre/post treatment effects of economic contingency management on people with comorbid schizophrenia and cannabis use disorders. Two experimental trials, both using the approach of paying participants for urine samples (contingency management) resulted in statistically significant increases in the number of negative urine samples for substance use. These results, however, were not maintained when the contingency management was removed.

## 4. DISCUSSION

### 4.1 Summary of current research findings

This meta-review collated existing evidence of specialised interventions for people with comorbid substance use and mental disorders, to assess the methodological quality of this evidence, to identify areas for future research, and to provide an accessible database of empirical studies of interventions for comorbid mental and substance use disorders. The systematic reviews and meta-analyses on specialised treatments for this population were highly heterogeneous in the interventions evaluated as well as the comparison groups used to evaluate changes in substance use and mental health outcomes. The lack of available evidence to allow for comparable analyses was a recurrent theme highlighted by the reviews, calling for urgent need of trials to test for effective treatments for specific comorbid mental and substance use disorders patient groups. In addition, the majority of reviews were of low or moderate AMSTAR adherence, and most reviews did not consider the potential impact of publication bias and study quality assessments on their conclusions. Integrated treatments and non-integrated psychosocial treatments have the comparatively strongest evidence supporting that they are effective in improving substance use and mental health outcomes for this



comorbid population. Evidence is lacking to draw conclusions on other treatment types, including pharmacological interventions and case management.

Some evidence support that integrated treatments resulted in improvements in substance use and mental health outcomes when compared to standard care. The treatment effects, however, are less clear when compared to single-disorder focused treatment. The inconsistent evidence may be related to the specificity of treatment focus. Studies that focused on specific mental disorders demonstrated superior benefit of integrated treatment over single-focused treatment (Hesse, 2009; Hides et al., 2010; van Dam et al., 2012). In contrast, studies that reviewed mental disorders as a combined condition generated mixed evidence for integrated treatment (Chow et al., 2013; Donald et al., 2005). This finding indicates that integrated treatment may be more effective if targeted at specific mental disorders. It is also possible that the mixed findings indicate integrated treatment may be less effective for specific mental disorders included in the combined reviews, such as schizophrenia and bipolar disorder (Chow et al., 2013; Donald et al., 2005). There is also a lack of studies reviewed that compared integrated versus parallel treatment effects (Mangrum, Spence, & Lopez, 2006).

Non-integrated psychosocial treatments also produced significant treatment gains when compared against standard treatment. The positive findings from the systematic reviews are consistent with a meta-analysis of high AMSTAR adherence that concluded psychosocial treatment to be effective in reducing substance use and psychiatric symptoms (Riper, Andersson, Hunter, Wit, et al., 2014). Positive findings were also reported for psychosocial treatments provided in a group format (Drake et al., 2008a). There are various types of non-integrated treatments. Some non-integrated treatments are designed to treat both mental and substance use disorders, while others are designed only to treat mental disorders. For example, CBT designed to treat depression that are accessed by people with comorbid alcohol dependence are in a different classification treatment type compared to CBT designed to treat both depression and alcohol dependence. Future reviews can provide more detail analysis comparing the effects of different non-integrated treatment designs.

Relatively few reviews focused on, or provided outcomes separately for the effectiveness of pharmacotherapies on co-occurring conditions, and much of this work focused on the effects of antidepressants. While antidepressants produced significant improvements in mental health outcomes, no evidence was available to support their effectiveness in reducing substance use (Iovieno et al., 2011; Pedrelli et al., 2011; Torrens et al., 2005). There is also a lack of evidence to support their effectiveness for people with substance use disorders associated with greater impairment, such as cocaine or opioid use dependence (Torrens et al., 2005). From the available reviews, there was no evidence that SSRIs were effective in improving mental health outcomes for people with comorbid alcohol use and mental disorders (Iovieno et al., 2011; Torrens et al., 2005). Our review focused on reviews examining pharmacological interventions for comorbid mental and substance use disorders, identifying reviews that compared antidepressants versus placebo. Other pharmacological treatments, such as MMT that targets opioid use, have demonstrated to be an effective treatment in reducing substance use (Ferri, Davoli, & Perucci, 2011; Kirchmayer, Davoli, & Verster, 2003; Mattick, Breen, Kimber, & Davoli, 2014; Strang et al., 2012). Future research may consider conducting a targeted search of MMT to review the effectiveness of these treatments on mental health and substance use outcomes in comorbid populations with mental disorders.

## 4.2 Methodological considerations

Of the 12 reviews, only one review received a high adherence score on the AMSTAR checklist (Riper, Andersson, Hunter, de Wit, et al., 2014), while 7 reviews received low adherence scores (Donald et al., 2005; Drake et al., 2008b; Gregory, 2011; Hides et al., 2010; Iovieno et al., 2011; Torrens et al., 2005; van Dam et al., 2012). Therefore, future reviews could be improved via ensuring greater adherence to rigorous and transparent reporting of methodology in accordance to AMSTAR and PRISMA guidelines, such as using two independent reviewers for study selection and data extraction, assessing the likelihood of publication bias, and consideration of methodological qualities of individual studies in formulating conclusions. In preparation of future reviews, authors can follow the PRISMA-P for protocol development (Moher et al., 2015), and register the protocol in for example PROSPERO (National Institute for Health Research (NHS), 2017), an international prospective register of systematic reviews. The existing reviews commonly lack methodological assessment in their results syntheses; under half ( $n = 5$ ; 41.7%) of the reviews undertook such an appraisal. The lack of quality appraisal is of concern as conclusions formulated regarding treatment effectiveness in reviews may be biased by poor-quality studies. Another methodological concern centres on the lack of assessment of publication bias; just under one-fifth (16.7%) of the reviews assessed the likelihood of publication bias. The tendency for articles to be published due to their

significance of findings (i.e. publication bias) has been well documented (Dwan et al., 2008). The lack of assessment of potential publication bias may systematically distort conclusions on treatment effectiveness. Future reviews can address this weakness by including grey literature, such as searching for studies in clinical trials registries. In addition, future reviews with meta-analyses can conduct analyses to detect bias, including creating funnel plots with tests for asymmetry, and applying data augmentation techniques with the trim and fill method to estimate the number of studies missing potentially as sensitivity analyses. For working with two or more independent reviewers in study selection, future reviews can consider using the online tool Covidence (Cochrane Community, 2017). Covidence is a relatively new online tool for conducting systematic reviews, endorsed by Cochrane, that helps streamline the screening and track the process. For example, it has a feature to automatically generate a flowchart reporting on the numbers of studies included and excluded at each of the screening stage, which has not been consistently reported in the reviews evaluated in this report.

### **4.3 Implications for service planning**

Findings from this meta-review found inconsistent evidence regarding integrated treatment over single-focused treatments. There is also lacking empirical evidence to inform the treatment effects of parallel versus sequential treatments for people with comorbid mental and substance use disorders. We do not yet have an adequate amount of empirical evidence to understand whether this discrepancy in findings can be attributable to the specificity of treatment focus. Specific clinical guidelines for different types of comorbid substance use and mental disorders can facilitate assessment and treatment for this population. A recent review of treatment guidelines for people with comorbid affective or anxiety and substance use disorders found that most diagnosis-specific guidelines are silent as to whether the particular treatment recommendation applies to comorbid disorders (Watkins, Hunter, Burnam, Pincus, & Nicholson, 2014). The potential combinations of comorbidities and the corresponding number of treatment approaches require further research to evaluate integration between mental health and substance use services to provide flexible treatment options that can adequately address the treatment needs of this population.

Positive findings for the effectiveness of psychosocial treatments delivered in group format were reported across different disorder groups, suggesting that it may be effective through producing a nonspecific effect based on common elements such as skills building and peer support (Drake et al., 2008a). However, this finding was based on one systematic review, of low AMSTAR adherence, that did not assess the scientific quality and publication bias of the included studies. Given its cost-effectiveness for common mental disorders (Vos et al., 2005) and its potential to improve access to services, the effectiveness of psychosocial treatments delivered in group format for people with comorbid mental health and substance use disorders should be further investigated.

### **4.4 Limitations and future directions**

The findings and implications of this meta-review need to be considered in the context of several limitations. This meta-review was constrained by the methodological rigour of the included reviews, which generally ranged from low to moderate adherence using the AMSTAR rating scale. Future research is needed to improve the methodological and reporting quality of systematic reviews or meta-analyses of the effectiveness of treatments for people with co-occurring substance use and mental disorders, particularly regarding the assessment of component studies' quality and reporting of their publication bias.

A common limitation of meta-review is the potential overlap or "double-counting" of individual studies across the systematic reviews evaluated. After removing the overlapping studies, there was still an adequate amount of available evidence, with 131 unique primary studies on integrated and non-integrated psychosocial treatments. The duplicated studies revealed mixed findings, with approximately half of these studies demonstrating positive substance use and mental health outcomes, distributed across multiple reviews. Therefore, the duplicated studies across different reviews are unlikely to bias the results towards a particular direction. Due to the considerable diversity concerning the definition of integrated treatments (Donald et al., 2005), studies that involve augmenting programs through the addition of either a standard mental health treatment component or a standard substance use treatment component have been included in both non-integrated (Donald et al., 2005) and integrated treatments reviews (Hesse, 2009). Seven studies were represented in reviews that focused on integrated as well as non-integrated psychosocial treatments, five of which

reported positive substance use and mental health outcomes. This overlap is unlikely to bias our main conclusions and recommendations.

The current meta-review only included reviews that provided comparison treatments in terms of control or standard care, and excluded reviews that focused primarily on intragroup comparisons. An accurate control condition may be difficult to establish for some treatment types, such as residential drug rehabilitation for high-risk populations, where undertreating individuals with severe disorders in a control condition may pose a safety risk. As such, research on drug rehabilitation treatments generally consists of pre-post trials, comparison between different intensity levels or sub-types of the same treatment. While these comparisons are outside the scope of the current review, individual studies have demonstrated rehabilitation to be useful in reducing substance use for people with substance use disorders (Drake et al., 2008a; Smith, Gates, & Foxcroft, 2006; Strang et al., 2012), particularly for specific populations, such as people who have severe needs and had not responded to less intensive treatments, or homeless individuals with comorbid mental disorders (Drake et al., 2008a). For example, the Australian Treatment Outcome Study (ATOS) found significantly reduced heroin use and improved general mental health scores at the 11-year follow-up of a heroin dependent cohort with high rates of comorbid mental disorders (22% current major depression; 45% bipolar disorder) who were recruited upon entry to various treatment services (including maintenance therapies, detoxification, and residential rehabilitation) (Teesson et al., 2015a). Studies such as these provide some indication of the merit of exploring substance use and mental health outcomes in non-comparative study designs, particularly for vulnerable populations. These studies highlight that future reviews on treatment outcomes need to clearly define what study designs can be included and compared against each other. For example, if ATOS provided non-integrated substance use treatment for people with comorbid mental and substance use disorders, and measured mental health outcomes as part of the evaluation, can they be classified as a treatment for comorbidity, and what other types of treatment should they be compared against. Related to this, future reviews also need to plan for studies comparing parallel compared to sequential treatments, as discussed above. If not enough studies have compared the same pair of treatment designs, future reviews can consider conducting network meta-analyses, which enables multiple treatment comparison across different studies. Research is urgently needed to systematically evaluate treatment types for people with comorbid substance use and mental disorders for both their substance use and mental health outcomes.

## 4.5 Conclusion

Research on treatments for people with comorbid substance use and mental disorders has grown rapidly over the past 10 years. The most recent systematic review evaluated in this report was from 2014. Given the increased level of original research on treatments for comorbid mental and substance use disorders since then, new systematic reviews on this topic are strongly warranted. Meta-reviews are useful for evaluating and summarising findings of separate reviews to provide evidence of clinical decision makers (Smith, Devane, Begley, & Clarke, 2011). This meta-review provides a summary of evidence base for “what works” for people with mental and substance use disorders. Research shows most empirical support for integrated and non-integrated psychosocial treatments in reducing substance use and psychiatric symptoms. The mixed findings for integrated treatments over single-disorder focused treatments may be due to the specificity of disorders examined. Different treatment approaches might be required for different combinations of disorders, compounding the need for integration between mental health and substance use service providers to deliver flexible treatment options. The positive outcomes for group psychosocial treatment may also have service planning implications in improving the access to services for this population. Further work is needed to systematically review specific and comparable treatment designs and target outcomes. In recent years, there has been an increased emphasis placed on utilising evidence-informed policies within the mental health and alcohol and drug sector. Information gleaned from this meta-review indicates that future reviews with strong methodological and reporting is needed to evaluate emerging evidence in this rapidly growing field. This will support practice and service change when rigorous reviews provide such empirical evidence.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors' contributions**

JL, ES, IW, MH, & AR made substantial contributions to the final conception and design of the work in this publication. JL and IW carried out the acquisition and analysis of data, and together with NG produced the supplementary materials. JL, ES, IW, MH, & AR contributed to the interpretation of data for the work. SD & EL provided input into the original design of the review, and the interpretation and presentation of results, implications, and discussion. MH and HW are the senior authors for the mental health service aspect, and AR and LD are the senior authors for the substance use aspect for the work. All authors contributed to the conception, drafting, revising the work critically for important intellectual content, gave final approval of the version to be published, and are accountable for all aspects of the work.

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## APPENDIX

List of the 131 empirical studies on treatment outcomes for people with comorbid mental and substance use disorders evaluated by the 12 systematic reviews conducted in 2005-2014. The Endnote library with these references grouped by the review they are from, and type of substance use and mental disorders examined, are [online available for download](#) (Leung et al., 2017).

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