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A systematic review and Bayesian meta-analysis of interventions which target or assess co-use of tobacco and cannabis in single or multi-substance interventions

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Abstract

Background and aims Tobacco and cannabis are commonly co-used, and evidence for the influence of co-use on quit outcomes for either substance is mixed. We sought to determine the efficacy of tobacco and/or cannabis use interventions, delivered to co-users, on cannabis and tobacco use outcomes.

Method Systematic review with meta-analysis and narrative review, using five databases and author requests for co-use data. Controlled and uncontrolled intervention studies focussing on treatment of tobacco and/or cannabis use assessing use of both pre and post intervention were included. Prevention interventions were excluded. Bayesian meta-analysis was used across four outcome measures: risk ratio for tobacco and cannabis cessation post intervention separately; standardised mean change for tobacco and cannabis reduction post intervention separately. Narrative reporting of same outcome measures in non-randomised clinical trials (non-RCTs) and quality assessment of all included studies were conducted.

Results Twenty studies (12 RCTs and 8 uncontrolled) were included. Bayesian meta-analysis with informative priors based on existing data of 11 RCTs (six single substance, five multi-substance interventions) delivered to co-users (n= up to 1117) showed weak evidence for an effect on cannabis cessation (risk ratio [RR]=1.48 [0.92,2.49], studies=8) and no clear effect on tobacco cessation (RR= 1.10 [0.68,1.87], studies=9). Subgroup analysis suggested multi-substance interventions might be more effective than cannabis targeted interventions on cannabis cessation (RR= 2.19 [1.10, 4.36] versus RR=1.39 [0.75,2.74]). A significant intervention effect was observed on cannabis reduction (0.25 [0.03, 0.45], studies =9) but not on tobacco reduction (0.06 [-0.11, 0.23], studies = 9). Quality of evidence was moderate, although measurement of co-use and of cannabis use requires standardisation. Uncontrolled studies targeting both cannabis and tobacco use indicated feasibility and acceptability.

Conclusions Single and multi-substance interventions addressing tobacco and/or cannabis have not shown a clear effect on either tobacco or cannabis cessation and reduction amongst co-users. However, dual substance interventions targeting tobacco and cannabis appear feasible.

Introduction

Tobacco and cannabis are two of the most commonly used psychoactive substances worldwide and are frequently co-used but rarely co-treated in clinical interventions (1).

Tobacco use remains the leading cause of preventable death and disease worldwide, and efforts are required to address the significant use disparity amongst people with co-occurring substance use in particular (2, 3). Cannabis use is also associated with significant harms, although the evidence base is not as established as that for tobacco related harms (4). Each substance poses distinct known harms but also potential aggregated harms (5), and the last few years have seen an increased focus on the relationship between tobacco and cannabis use.

Tobacco is used by over 1.1 billion people worldwide (6), and cannabis by an estimated 188 million (7). Although globally tobacco prevalence is decreasing, use is increasing in some regions such as Africa (6). Cannabis prevalence appears stable in most of Europe and Australasia, though there are early indications it may be increasing in the United Kingdom (UK) and in the United States (US) (8-11) and may change with increasing legalisation. Co-use of tobacco amongst cannabis users is consistently two to three times higher than amongst tobacco only users (12).

Co-use may comprise both substances in the same product, i.e. co-administration, or sequential use in a given time period, i.e. concurrent. Globally, types of co-use vary significantly; broadly speaking tobacco and cannabis are commonly co-administered in Europe and Australia, whereas concurrent use has been more frequent in other parts of the world, although there are indications that co-use and co-administration is increasing in the US (13). Changing regulatory environments and availability of electronic devices used to deliver both tobacco/nicotine and cannabis have created a rapidly evolving landscape for these two substances. It is important to understand how co-use is associated with risk of dependence and amongst which populations, and how co-use variation may influence cessation attempts for all types of combustible and other tobacco and cannabis products.

The relationship between tobacco and cannabis appears synergistic, operating on both a physiological and psychological level (14). Tobacco use seems to be a feature in the development of cannabis use disorder (13, 15), and to negatively influence outcomes of cannabis use treatment interventions (16, 17). Similarly, cannabis use is associated with higher nicotine dependence, though the influence of cannabis use on tobacco cessation is mixed (18-21). Amongst single substance interventions, little is known about the impact of co-use on outcomes, since studies may not measure use of both substances, nor the type of co-use practised. For example it is not known whether co-administration may lead to poorer outcomes for tobacco cessation in comparison to concurrent use (17). Further research into the nature of the relationship between tobacco and cannabis use and its impact on cessation outcomes is warranted.

A significant body of evidence exists on tobacco cessation interventions, as indicated by the 82 Cochrane Reviews on the topic. Combining pharmacotherapy with behavioural support is likely to be the most effective tobacco cessation method (22). By contrast, the evidence base for cannabis use interventions is limited; only two Cochrane Reviews have been published, investigating psychosocial and pharmacotherapy interventions. Evidence for the latter is incomplete and low quality (23). Combining interventions such as Motivational Enhancement Therapy (MET) or Cognitive Behaviour Therapy (CBT) with contingency management (CM)show some positive effects, but, as for other substance use treatments, overall efficacy tends to be low, and abstinence rarely achieved (24).

Systematic reviews of digital interventions for cannabis use have identified a small reduction effect (25-27).

Despite being commonly co-used, tobacco and cannabis use are rarely co-treated. Low rates of tobacco cessation in cannabis users may be partly explained by co-use, hence in addition to addressing co-use within single substance interventions, it is important to investigate what impact dual interventions may have on co-use. For those who co-administer tobacco and cannabis, the shared route of administration and overlapping withdrawal symptoms may act as cues to relapse of either substance indicating that the efficacy of dual or multi-substance interventions in comparison to single substance interventions warrants examination (14, 28-29). Additionally, compensatory use of one substance following cessation of the other is important to consider (30).

Reviews of co-use have considered the potential for pharmacological treatments in dual interventions, for sequential or simultaneous interventions and the most relevant evidence from single substance use interventions (1, 14, 28). Although co-use interventions for African American populations have been reviewed (31), this is the first systematic review to date of interventions targeting or addressing co-use for all populations.

Objectives

This systematic review seeks to investigate the nature and strength of the evidence base for interventions which target both tobacco and cannabis use, or which assess change in use of both; and to estimate the efficacy of included interventions on cessation or reduction of both substances.

Method

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement, PRISMA (32). The protocol was registered prior to commencing the review (33).

Eligibility criteria

Studies were included if they published, or reported measuring, level of use of tobacco and cannabis pre and post treatment intervention. Controlled or uncontrolled, pilot or feasibility studies of single, dual and multi-substance use interventions were included. Prevention interventions were excluded. No limits were placed on age, setting, duration or intervention type.

Identification of studies

Five databases were used: Embase; Web of Science; Medline; PsychINFO; and CINAHL. Reference lists from included studies and cited literature reviews were also searched.

Search strategies were developed for each database using controlled vocabulary and keywords using a combination of terms relating to tobacco and tobacco use treatment and cannabis and cannabis use treatment. Articles published from January 1990 to March 2019 written in English, French and Spanish were included. 1990 was selected as older literature is less consistent in measurement, particularly of cannabis. The Medline search strategy is shown in supplementary materials (S1).

All searches and initial screening of abstracts for review were carried out by HW in July 2017 and repeated in January 2018 and March 2019. HW reviewed full articles, and MD and AM reviewed potentially included articles. Discrepancies were resolved by discussion.

Quality assessment

The Cochrane Risk of Bias assessment tool was used to evaluate the quality of included RCTs (34). Relevant items from the Russell Standard for tobacco studies were used to assess quality of tobacco use reporting (35). Uncontrolled studies were reviewed using Law's Critical Review Form (36). HW carried out the quality reviews, and MD reviewed five of these.

Funnel plots, including trim and fill where indicated, were used to assess publication bias and potential missing studies.

Outcome measures

The primary outcomes were change in use of tobacco and cannabis, measured either by cessation or reduction in use. Each study therefore had potentially four outcome measures of interest: tobacco cessation rate; cannabis cessation rate; tobacco reduction rate; cannabis reduction rate. Some studies also reported a fifth outcome of dual tobacco and cannabis cessation. Each study required a measure of level of tobacco and cannabis use pre and post intervention.

When the article indicated that tobacco and cannabis use measures pre and post intervention were collected but not reported, authors were contacted to provide separate data for this sub-group of participants reporting co-use at baseline.

Contact with authors

A total of 25 authors were contacted up to three times. Of these, seven indicated they did not have the available data or were unable to provide it, four did not reply and one provided data which could not be used as the format was incompatible with other data. Thirteen authors provided data, two of whom provided data on two studies (37-49). Three authors provided the original anonymised dataset for our analysis and the remainder provided analysed outcome data.

Data extraction

Outcome data, characteristics of studies including location, study design, intervention content and whole sample demographics were extracted by HW using a data extraction form which was piloted, then adapted. Data were extracted from each study and dataset by HW and entered into a CSV file. Where authors had provided raw data, the analysis of these data was carried out by HW and both extraction and analysis for each of the studies used in the meta-analysis was checked by MD.

Meta-analysis

Criteria for inclusion in the meta-analysis was a cessation or reduction outcome in an intervention and control condition. In RStudio (50) meta-analyses using Bayesian and traditional frequentist methods were performed on eleven RCTs. Bayesian meta-analysis was selected as it provides complete information about the credible parameter values, and consequently the probability of any given value, and may be more appropriate for a smaller number of studies (51-52). One limiting factor for Bayesian analyses is that they require a prior probability distribution for the parameter of interest. As this is the first review of this type there is no existing empirically based prior distribution. Solutions to this include using broad prior distributions that have minimal effect on the data, or use of data from the studies themselves to provide this (51,53). The latter of these solutions was used in this case to maximise the information, which would be diluted by an uninformative prior distribution.

As this is a relatively novel approach to meta-analysis, traditional frequentist analyses were also carried out to allow for comparison and as a sensitivity analysis for the assumptions made in our models.

Cessation outcomes

The pooled risk ratio for cessation in the intervention group compared to the control group was calculated using the *metafor* package (50), then the *bayesmeta* package (50) for the Bayesian meta-analysis. For informative priors, 1 was used as the minimum risk ratio, and 4 as the standard deviation (51).

Reduction outcomes

The standardised mean change (SMC) in use of each substance in each condition was calculated. The SMC was selected to allow for a variety of pre intervention levels of use and measurement variation (i.e. frequency of use versus amount of use). An effect size was calculated then a Bayesian meta-analysis was carried out again using *bayesmeta*. The median of the effect size and the standard deviation of the median were used as weakly informative priors.

Sub-group analysis by intervention target was carried out as specified in protocol, intention to treat principles were applied across all the meta-analyses using authors' raw data. Heterogeneity was measured using tau (54-55). In all four meta-analyses, a conservative estimate of variance at 0.8 was applied, as variance was not available within original study data. Code used for meta-analyses is presented in supplementary material (S2).

Analysis of uncontrolled studies

Results of uncontrolled studies were extracted and are reported in Figure 2.

Results

Included studies

A total of 6280 study titles were identified through the search process. Duplicates were removed, titles reviewed and 123 articles accessed for full-text review. Following the author data request process, 20 studies were included. The total number of participants within all 20 studies was 1599, on average of 34.5% were female. The selection process is shown in figure 1.

FIGURE 1

Selected characteristics of the included studies are presented in table 1.

TABLE 1

Characteristics of studies

Twelve studies were RCTs (39-45, 47, 48, 56-58); and eight were pilot or feasibility, ("uncontrolled") studies (37, 38, 46, 49, 59-62). Fourteen studies were from the US, two from Switzerland, two from the UK, one from France and one from Australia. Most participants were recruited from non-treatment settings including colleges and community settings. Only five studies were located within substance use treatment settings; notably none of these were cannabis treatment services. Of the total number of participants, 11% were daily tobacco users, and 19% had either cannabis use disorder or frequent cannabis use (>4 times per week).

Intervention content

Six studies were dual interventions targeting tobacco and cannabis (37, 59-62); seven targeted cannabis use (38, 40-43, 45, 49), one targeted tobacco use (47) and six targeted multi-substance use (39, 44, 48, 56, 57), including one which focussed on tobacco and heavy alcohol use (44).

Each dual intervention provided or offered pharmacotherapy in the form of nicotine replacement therapy (NRT) or medication such as varenicline alongside a behavioural component. Most dual interventions created new manuals for the delivery of co-use treatment, which were based on existing resources for both tobacco and cannabis behavioural treatment (58-62), although the extent of integration of these resources to address co-use varied. Two studies (60,62) set the same quit date for both substances, and one compared simultaneous with sequential quit attempts (58). Most studies used contingency management in additional to other behavioural components; some used a computer-delivered and mobile-phone delivered interventions (58-59, 61). With one exception (62), all interventions were individual. Only one dual intervention was an RCT.

Cannabis use interventions consisted mainly of behavioural interventions, with only two using pharmacological treatment, one of which was an inpatient study (42, 49). The single tobacco use intervention employed behavioural components only, delivered via Facebook in both an individual and group format (47). The majority of the multi-substance interventions (MSI) were brief, with two exceptions (44, 46), one of which delivered a lengthy culturally adapted intervention.

Outcome measurement across all studies

Frequency vs amount

Measurement of tobacco use was relatively standard across all studies, most using cigarettes per day (n=14). Measurement of cannabis use was more varied between frequency of use and amount used; frequency of days used in past 30 was the most commonly used measure (n=8).

Type of co-use

None of the dual studies reported any detailed measurement of co-use, i.e. whether participants used both concurrently, or co-administered, although two studies targeting cannabis use did ask about co-use (42, 49).

Biochemical verification

All brief, single session interventions as well as the single tobacco targeted intervention used self-report as measures for tobacco and cannabis use at follow-up.

Of the six dual intervention studies, all used biochemical verification for tobacco cessation, and all except one (62) used biochemical verification for cannabis cessation.

Methods used to verify tobacco abstinence included carbon monoxide testing and saliva and/or urine cotinine analysis. Methods used to verify cannabis abstinence were more varied; most used urinalysis without specifying cut off points for cannabis levels.

Meta-analyses of RCTs

Although intervention format in the twelve RCTs varied, all addressed the same clinical question, i.e. efficacy of intervention on change in use of tobacco and cannabis, therefore meta-analyses were conducted. One RCT was excluded from the meta-analysis and included in the narrative synthesis (58) as the two conditions tested were simultaneous versus sequential dual intervention whereas the other RCTs measured intervention versus no intervention.

Measures used in meta-analyses

Each study measured two, three or four outcomes as indicated in Table 2.

TABLE 2

Cessation outcomes

Meta-analysis of tobacco cessation outcomes shown in Figure 2 (studies = 9) shows a pooled risk ratio of 1.10 [Credibility Interval (CrI) 0.68, 1.87]. There was little evidence of heterogeneity ($Q=8.57$, $df=8$, $p=0.6$; $I^2=0.14$).

FIGURE 2

Meta-analysis of cannabis cessation outcomes shown in Figure 3 (studies=8) shows a pooled risk ratio of 1.48 [CrI 0.92, 2.49] indicating a small effect which may be clinically significant. Heterogeneity across the nine studies was moderate ($Q=11.35$, $df=7$, $p=0.9$, $I^2=0.41$).

FIGURE 3

Frequentist meta-analysis for cessation outcomes was performed. Using a random effects model, tobacco cessation risk ratio was 1.07 [0.76, 1.52], p=0.69. For cannabis cessation, pooled risk ratio was 1.46 [1.03, 2.09], indicating almost no difference to Bayesian analysis outcomes.

Sub-group analysis

For tobacco cessation outcomes, subgroup analysis by intervention target showed very little difference; the pooled risk ratio for cannabis targeted interventions was 1.10 [0.48, 2.85] and for multi-substance interventions 1.25 [0.53, 2.94].

However, for cannabis cessation outcomes, subgroup analyses did indicate a difference by intervention target. Multi-substance interventions showed a significantly positive effect (RR= 2.19 [1.10, 4.36]), whereas the cannabis targeted interventions mean estimate was similar to the all-studies outcome, (RR=1.39 [0.75,2.74]). Heterogeneity of sub-group analysis of each substance indicated that I^2 reduced to 15% and 26% respectively, suggesting it may be explained by differences in intervention target.

Reduction outcomes

Meta-analysis of standardised mean change (SMC) in tobacco use reduction as shown in Figure 4 (studies = 9) showed no intervention effect at 0.06 [-0.11, 0.23]. Heterogeneity was high ($Q=45.55$, $df=8$, $p=0.5$, $I^2=0.88$).

FIGURE 4

Meta-analysis of cannabis reduction outcomes shown in Figure 5 (studies = 9) showed a small significant effect of 0.25 [0.03, 0.45]. Heterogeneity was also high ($Q=59.76$, $df=8$, $p=0.8$, $I^2=0.93$).

FIGURE 5

Frequentist meta-analysis for reduction outcomes was performed. Using a random effects model, tobacco reduction effect size estimate was 0.09, p=0.30 and for cannabis the estimate was 0.32, p=0.001. This indicates no significant difference from Bayesian meta-analysis outcomes.

Subgroup analysis

For tobacco reduction outcomes, subgroup analysis by intervention target made little difference; the estimate for cannabis targeted interventions was 0.09 [-0.16, 0.34] and for multi-substance interventions 0.04 [0.13, 0.169].

Similarly, for cannabis reduction outcomes, subgroup analysis did not show any meaningful differences by intervention target. For cannabis targeted studies the mean estimate was similar to the all studies outcome, at 0.17 [-0.14, 0.45] and by multi-substance interventions at 0.26 [0.03, 0.54].

Sensitivity analysis altering the variance in each analysis to 0.2 made no significant difference to any of the four outcomes

Outcomes of uncontrolled and other studies

Table 3 shows tobacco and cannabis cessation outcomes for all studies not included in meta-analysis in order of sample size.

TABLE 3

The data suggest that a higher proportion of people achieved cannabis cessation than tobacco cessation, and that cessation of both tobacco and cannabis was relatively rare, even within dual studies. Reduction outcomes are not presented as data were incomplete, but all studies indicated a small degree of reduction in both substances.

Quality appraisal

Risk of bias summary

The Risk of Bias summary (supplementary materials S3) indicates that overall the RCT studies are of moderate quality. Appraisal of the uncontrolled studies indicates reasonable quality, including high rates of biochemical verification amongst the uncontrolled studies compared to RCTs.

Russell Standard

Studies targeting tobacco, including the dual interventions showed higher concordance with the Russell standard for tobacco abstinence. In the other studies reporting of tobacco outcomes was inconsistent.

Publication bias

No evidence of asymmetry was seen when trim and fill was used on funnel plot of tobacco cessation meta-analysis (see supplementary material S5). However for cannabis cessation, when trim and fill was used to add three studies, the risk ratio reduced from 1.46 to 1.18 [0.8, 1.77], suggesting some evidence of publication bias.

For reduction meta-analysis, no evidence of publication bias was observed as estimates within funnel plots were very close to original outcomes. Plots are not shown for this reason.

Discussion

This is the first systematic review and meta-analysis to look at interventions for tobacco or cannabis which have been delivered to co-users. The review has reported on a population previously hidden within intervention findings by using unpublished data on co-users provided by authors. Using a novel analysis approach, Bayesian meta-analysis of RCTs delivered to co-users showed a small positive impact on cannabis cessation which approached significance (1.48 [0.92, 2.49]); but a negligible impact on tobacco cessation (1.10 [0.68, 1.87]). Subgroup analysis indicated that multi-substance interventions appeared to have a greater impact than cannabis targeted interventions on cannabis cessation, which may explain heterogeneity found in analysis. A small intervention effect was observed on cannabis reduction (0.25 [0.03, 0.45]) but not tobacco reduction (0.06 [-0.11, 0.23]). Significant heterogeneity within reduction outcomes was not explained by subgroup analysis by intervention target.

Quality of evidence is considered moderate, and although heterogeneity should be taken into consideration, overall the quality of evidence should not influence the validity of the findings.

Our meta-analysis of tobacco cessation outcomes showed no intervention effect, irrespective of intervention target. This contrasts with a recent Cochrane Review of tobacco cessation treatment offered to people with an SUD which found positive outcomes overall (63). Importantly, most of the

interventions in our meta-analysis did not include evidence-based tobacco cessation treatment. This may partly explain the absence of an effect, in addition to the influence of cannabis use on tobacco cessation. An earlier systematic review considering tobacco cessation outcomes within alcohol brief interventions also found no intervention effect for tobacco cessation, although brief interventions may be less effective in targeting cessation (64). In future interventions, greater attention to types of co-use practised is required; for example, co-administration of tobacco and cannabis may increase use of the other substance post cessation in comparison to concurrent use.

Our meta-analysis of cannabis cessation shows an intervention effect lower than that found in the Cochrane Review of psychosocial interventions for CUD (RR=2.55, [1.34, 4.83]), although the evidence in that review was considered low quality (24). The Cochrane Review of pharmacotherapies for cannabis dependence found mixed quality evidence, (RR 0.98, 0.64 to 1.52)(23), comparable to the small effect we found. Evidence of asymmetry in the funnel plot for cannabis cessation may be explained by a non-reporting bias, although there were no obvious indications of such bias in the review process. However, the large number of authors who didn't provide data for co-users, and the potential for interventions to have measured cannabis use but not reported this, especially in tobacco cessation interventions, may indicate a non-reporting bias. Analysis of future studies reporting fully on a range of substance use outcomes can address this potential bias.

Our analysis showed a small effect for cannabis reduction. Cannabis cessation or reduction amongst regular users has been characterised as challenging, requiring multiple attempts (65), and intervention effects appear small (23, 25), in keeping with our findings. An effect on tobacco reduction was not seen in our analysis, although reduction in comparison to cessation is less commonly used within tobacco interventions.

This analysis has used both Bayesian and traditional methods of meta-analysis. Although the results are similar, their interpretation is very different; the Bayesian analysis giving both a point estimate and full distribution of the parameter in the form of a credible interval. One of the obstacles to undertaking Bayesian analysis is the lack of informative prior distributions, here we have demonstrated one solution to this which is to use priors from the data itself. The more logical interpretation of the full posterior distribution may compensate for any limitation relating to the absence of prior information.

The findings from our meta-analysis do not clearly indicate whether single substance use interventions are any more or less effective than multi-substance use interventions. Dual studies addressing both tobacco and cannabis were identified, although not included in the meta-analysis. These demonstrated feasibility and suggest a greater impact on cannabis cessation than tobacco cessation, comparable to our meta-analysis findings. Notably, adherence to tobacco cessation outcome standards was high in the dual studies, e.g. defining abstinence, which may explain some of the differences between tobacco and cannabis outcomes. Feasibility findings indicate that attention must be given to the sampling frame as community settings appear more successful for recruitment than substance misuse settings. Motivation may be a barrier to recruitment; an intervention to address this prior to commencing recruitment for treatment appeared effective (66).

This review has also highlighted methodological issues with the literature. First, a large number of studies were excluded as they did not measure use of both substances pre and post intervention, or reported only presence/absence of cannabis, rather than level of use. Biochemical testing may be

challenging on the basis of cost, but self-report measures are of value, and easily obtainable. The availability of such data would allow for further investigation by secondary analysis of the role of co-use in single and multi-substance intervention studies, and would strengthen the evidence base for addressing these commonly used substances.

Second, measurement of co-use, including whether concurrent and/or co-administered would reduce potential bias and provide detail and context of use behaviours (67-68). Participants in studies may under-report co-use, for example when asked about cannabis may ignore tobacco used in joints. Specific patterns of co-use may be associated with higher levels of dependency on either substance, and with varying success of cessation or reduction of either substance.

Third, no studies within this review reported measuring cannabis type or potency. Literature indicates that potency may play a significant factor in the experience of adverse effects and the development of CUD (69). Differences between frequency and amount of cannabis use presents a further challenge in reviewing studies, and both concepts are subject to recall bias (70-71). Tobacco cessation outcome reporting has been set out in the Russell Standard; cannabis studies which measure tobacco use would benefit from adherence to these guidelines (35), and from a set of cannabis reporting standards. Measurement of cannabis use requires further discussion and consensus development within the field (72); this process has begun (73).

This review contains limitations and has only partially met its objectives. The number of studies in the meta-analysis is small, most studies primarily targeted cannabis, and most participants were male. The lack of tobacco targeted studies is a significant limitation, and should be taken into account when considering the greater impact seen on cannabis targeted studies. Future interventions which target either but measure both can be added to the data to expand on these conclusions. Unfortunately, no RCTs which targeted co-use could be included in the meta-analyses; hopefully these will be developed. Evidence of potential compensatory use of the second substance post intervention of the primary substance was not available, and also limits our ability to draw conclusions about the efficacy of single vs. dual interventions on use of both substances. This data should be made available in future intervention studies, allowing for an investigation of potential compensatory use.

Due to time constraints, only one author conducted the initial screening process, potentially increasing the risk of selection bias. Additionally, we contacted a large number of authors (n=25), of whom only thirteen provided data. Older datasets were less likely to be available, however changes in cannabis potency in the last few decades indicate that more recent data is likely to be most relevant (74).

Although heterogeneity of intervention targets has been explored within the sub-group analysis, other sources include variability of measurement, as discussed previously, differences in duration of intervention and biochemical verification of cessation. Further sensitivity analyses across other domains may indicate the source of the heterogeneity, although were not planned in this review.

Most of the evidence reviewed was from the US, though patterns of both cannabis use and co-use vary significantly worldwide (75). Inadequate measurement of types of co-use limits the transfer of these findings to other countries. One study adapted materials for a specific population (46) but further discussion of how socio-cultural influences pertaining to tobacco and cannabis use may impact on intervention effects is required. Increasing variety in routes of administration for both

tobacco, nicotine, and cannabis in its many forms may elicit changes in co-use practises such as co-administration and future intervention studies need to take these complexities into account. This requires scrutiny across all populations, including those from more deprived populations where more harmful methods of tobacco and cannabis use may prevail.

Future research should consider the theoretical framework required for addressing use of two closely related substances. The theoretical basis of interventions was described by some studies in our review, but most dual interventions adapted existing materials for either substance, delivered concurrently. As the theoretical basis for dual interventions is yet to be fully developed, it is not known whether delivering a tobacco intervention alongside a cannabis intervention results in a different outcome to an intervention which seek to integrate treatment of both. The single study in this review to evaluate simultaneous versus sequential dual treatment was inconclusive. Further research using more intensive tobacco treatment interventions is also warranted.

Conclusions

Dual interventions for tobacco and cannabis co-use have demonstrated feasibility. Meta-analysis of treatment interventions targeting tobacco and/or cannabis use showed a small intervention effect on cannabis reduction but not on tobacco reduction. No significant effect was seen on tobacco cessation or cannabis cessation. Further research is required to extricate potential reasons for poor outcomes amongst co-users.

Outcomes for co-use of tobacco and cannabis need routine measurement to fully account for the potential impact of co-use in both tobacco and cannabis specific interventions. Interventions must collect details of type of co-use practised, as well as fuller details of cannabis use.

RCTs of dual interventions are required to address co-use. Future dual interventions should ensure that tobacco dependence is fully measured and that adequate tobacco cessation treatment is provided.

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Table 1 Characteristics of included studies

Study	Target substance	Location	Study design	Inclusion criteria	Intervention	Comparison/ control	Length of follow-up	Duration of intervention	Sample size of co-users	Attrition rate (whole sample)
Becker 2015 (62)	Tobacco & cannabis	Switzerland	Feasibility	Age 18+; daily T smoker; weekly C smoker	GT, IT, NRT + V	-	6 months	5-6 weeks	77	24%
Beckham 2018 (59)		USA	Pilot study	Age 18-70; has CUD; 40/past 90 day C use; daily T use in past week and smoked for past year	ART, CM, CBT, NRT	-	6 months	6 weeks	5	0%
Adams 2018 (37)		USA	Within subject cross-over; medication	Age 18+; C use 5 days/past 7; +ve urine C test	MAT, SCC, V	MAT, SCC (crossover design)	8 weeks	4+4 weeks	6	0%
Hill 2013 (60)		USA	Pilot	Age 18+; meet DSM criteria for CUD + TUD	IT, CBT, NRT	-	10 weeks	10 weeks	12	42%
Lee 2015 (61)		USA	Single treatment with historical control	Age 18+; C use 45/past 90 days; daily T smoker	CAIT, MET, CBT, CM, NRT	Historical trial data	12 weeks	12 weeks	32	44%
Lee 2019 (58)		USA	RCT	Age 18=, has CUD, T use past 5 days	MET, CBT, CM, NRT	Sequential cessation	24 weeks	12 weeks	67	35%
Buchowski 2011 (38)	Cannabis	USA	Pilot	Age 18+, meet DSM criteria for CUD, non-treatment seeking, less than 10 CPD in past year	AE	-	4 weeks	2 weeks	6	14%

Laporte 2017 (41)		France	Cluster RCT	Age 15-25, C use 1 joint per month over 1 year	BI	Usual care	12 months	Single session	240	55.7%
Kadden 2007 (40)		USA	RCT	Age 18+, meet DSM criteria for CUD	CaseM or MET+CBT or CM or MET + CBT + CM	Each intervention	14 months	9 weeks	114	17%
McCambridge 2008 (43)		UK	RCT	Age 16-19; C use weekly;	MI	DIA	6 months	1 hr	265	19%
McClure 2014 (42)		USA	Parallel double-blind RCT; medication	Age 15-21; C use 3x weekly	NAC, CM, IT	Placebo, CM, IT	8 weeks	8 weeks	68	28%
Peters 2013 (45)		USA	RCT	18+, met criteria for C dependence	CBT or CBT+CM or CM or CM + CBT	Each intervention	13 months	12 weeks	91	13%
Winstock 2009 (49)		Australia	Inpatient medication trial for safety + utility	Age 18+; met criteria for CUD in past year	Li	-	12 weeks	1 week	13	15%
Vogel 2018 (47)	Tobacco	USA	RCT	Age 18-25; 1 CPD, 3 x per wk; current C use	OG, CBT	SC advice website	12 months	12 weeks	254	29.2%
Gmel 2013 (39)	Multi-substance	Switzerland	RCT	Conscripts to military service, interested in receiving intervention	BI	ASU	6 months	20 mins	230	21%
McCambridge 2004 (56)		UK	RCT	Students reporting current drug use	BMI	'Education as usual'	12 weeks	Single session	19	10.5%
Metrik 2011 (44)		USA	RCT	Age 18+; 10+ CPD; heavy drinker	IT incl. alcohol; NRT	IT, NRT	26 weeks	4 weeks	57	15%
Venner 2016 (46)		USA	Pilot	DSM diagnosis of SUD, tribal enrolment, treatment seeking	MICRA (culturally adapted MI + community reinforcement approach	-	24 weeks	16-20 sessions	3	Not given
White 2007 (48)		USA	RCT	18+, students mandated to receive treatment	BMI	Written feedback	15 months	Single session	26	5.5%

White 2008 (57)		USA	RCT	18+, students mandated to receive treatment	Immediate written feedback	Delayed written feedback	7 months	Single session	14	4.8%

Key: AE; Aerobic Exercise; ART: Abstinence Reinforcement Therapy; ASU: Assessment of substance use; BI: Brief Intervention; BMI: Brief Motivational Interviewing; C: cannabis; CAIT: Computer-assisted Individual Therapy; CaseM: Case Management; CBT: Cognitive Behaviour Therapy; CM: Contingency management; CPD: cigarettes per day; CUD: cannabis use disorder;; DIA: Drug information and advice; DSM: Diagnostic and Statistical Manual; OGT: Online group; GT: Group therapy; IT: Individual therapy; Li: Lithium carbonate; MAT: Medication assisted treatment (for opioid use); MET: Motivation Enhancement Therapy; MI: Motivational Interviewing; NAC: N-acetylcysteine; NRT: Nicotine replacement therapy; PPA: point prevalence abstinence; RCT: Randomised controlled trial; SC: Smoking cessation; SCC: Standard clinical care; T: tobacco; V: Varenicline

Table 2 Outcome measures used for each RCT included in meta-analysis. CPD =cigarettes per day, past 30 days = days of use in past 30

	Tobacco cessation *Biochemically verified (BV) or self-reported (SR)*	**Cannabis cessation** *Biochemically verified (BV) or self-reported (SR)*	**Tobacco reduction**	**Cannabis reduction**	**Length of follow up**
Laporte 2017 (41)	-	-	*cigarettes per week*	*joints per month*	*12 months*
Kadden 2007 (40)	*SR*	*BV*	*CPD*	*joints per day*	*14 months*
McCambridge 2008 (43)	*SR*	*SR*	*CPD*	*past 30 days*	*6 months*
McClure 2014 (42)	*BV*	*BV*	*CPD*	-	*8 weeks*
Peters 2013 (45)	-	-	*days used in past 28*	*past 30 days*	*13 months*
Gmel 2013 (39)	*SR*	*SR*	*CPD*	*past 30 days*	*6 months*
McCambridge 2004 (56)	*SR*	*SR*	*cigarettes per week*	*frequency of use per week*	*12 weeks*
Metrik 2011 (44)	*BV*	-	-	*past 30 days*	*26 weeks*
White 2007 (48)	*SR*	*SR*	*CPD*	*frequency of use in past month*	*15 months*
White 2008 (57)	*SR*	*SR*	*CPD*	*frequency of use in past month*	*7 months*
Vogel 2018 (47)	*SR*	*SR*	-	-	*12 weeks*
Total number of participants	1117	1095	1068	1103	

Table 3 Outcomes of tobacco and cannabis cessation within studies excluded from meta-analysis;

T=tobacco, C=cannabis, MSI = multi-substance intervention

Study	Target	Sample size	Length of follow-up	n quit tobacco and cannabis, (%)	n quit tobacco, (%)	n quit cannabis, (%)
Becker 2015 (61)	T&C	77	6 months	4 (7.8)	8 (10.4)	15 (19.5)
Lee 2019 (58)	T&C	67	12 weeks	-	6 (17.6)	7 (20.6)
Lee 2015 (61)	T&C	32	12 weeks	0	4 (12.5)	14 (44)
Winstock 2009 (49)	C	13	12 weeks	0	0	3 (23)
Hill 2013 (60)	T&C	7	10 weeks	0	0	0
Adams 2018 (37)	T&C	6	8 weeks	0	0	1(14)
Buchowski 2011 (38)	C	6	4 weeks	0	0	0
Beckham 2018 (59)	T&C	5	6 months	1 (20)	0	1 (20)
Venner 2016 (46)	MSI	3	8 months	0	3 (100)	0
n		127	-	5	21	31

Figure 1: PRISMA diagram showing search and review process

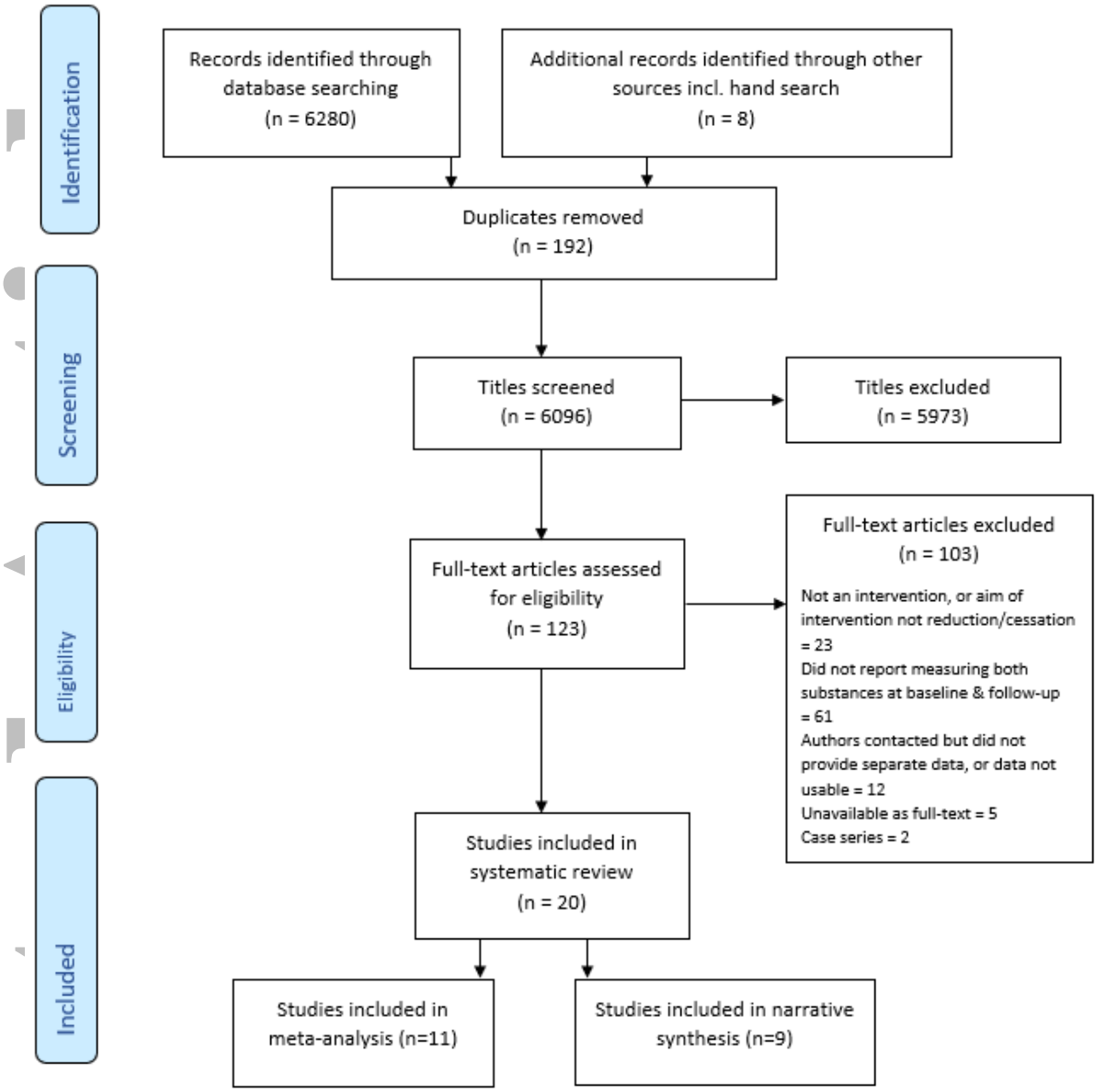
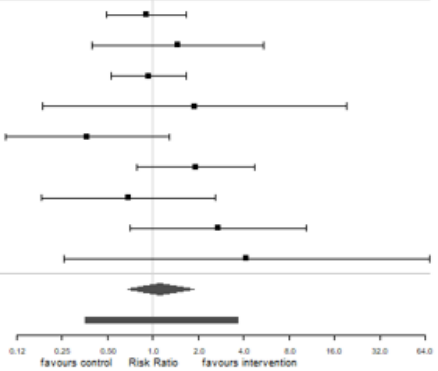


Figure 2 Tobacco cessation

study	int quit	ctrl quit	estimate	95% CrI
Vogel 2018 (tobacco)	16/119	20/135	0.91	[0.49, 1.67]
Kadden 2007 (cannabis)	5/25	3/22	1.47	[0.40, 5.44]
McCambridge 2008 (cannabis)	19/130	21/135	0.94	[0.53, 1.66]
McClure 2014 (cannabis)	2/19	1/18	1.89	[0.19, 19.13]
Gmel 2013 (multi)	3/98	11/132	0.37	[0.11, 1.28]
McCambridge 2004 (multi)	13/64	6/57	1.93	[0.79, 4.74]
Metrik 2011 (multi)	3/26	5/30	0.69	[0.18, 2.62]
White 2007 (multi)	3/7	3/19	2.71	[0.71, 10.42]
White 2008 (multi)	3/9	0/5	4.20	[0.26, 68.04]
mean			**1.10**	**[0.68, 1.87]**
prediction			**1.09**	**[0.36, 3.70]**

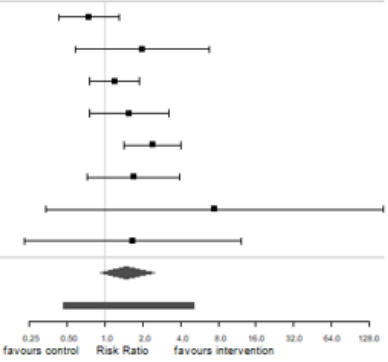


Heterogeneity: Q= 8.57, df=8, p=0.6, I^2=0.14, n=1050

Key: 'Intervention' = number who quit in intervention group/total in group; 'control' = number who quit in control group/total in group; intervention target shown in brackets after study name; CrI = Credibility Interval. NB not all studies targeted both substances

Figure 3 Cannabis cessation

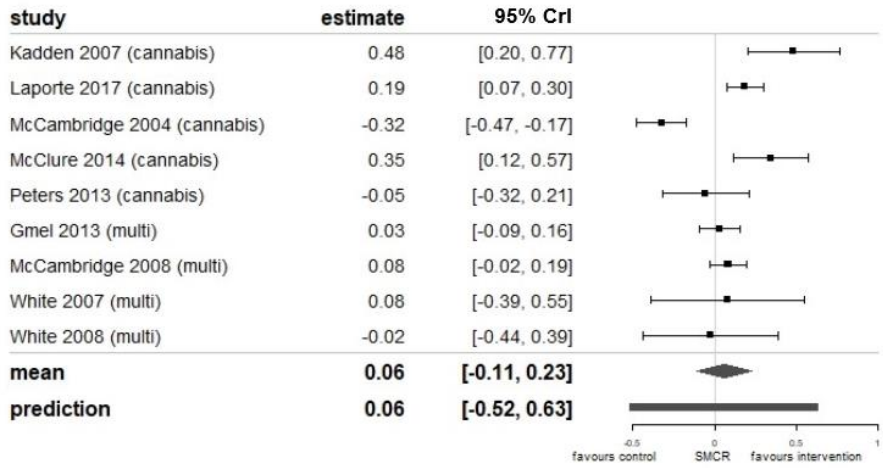
study	int quit	ctrl quit	estimate	95% CrI
Vogel 2018 (tobacco)	17/119	26/135	0.74	[0.42, 1.30]
Kadden 2007 (cannabis)	7/27	3/23	1.99	[0.58, 6.82]
McCambridge 2008 (cannabis)	31/130	27/135	1.19	[0.76, 1.88]
McClure 2014 (cannabis)	13/32	8/31	1.57	[0.76, 3.26]
Gmel 2013 (multi)	32/98	18/132	2.39	[1.43, 4.01]
McCambridge 2004 (multi)	13/66	7/60	1.69	[0.72, 3.95]
White 2007 (multi)	1/7	0/19	7.50	[0.34, 165.46]
White 2008 (multi)	3/9	1/5	1.67	[0.23, 12.09]
mean			**1.48**	**[0.92, 2.49]**
prediction			**1.47**	**[0.46, 5.08]**



Heterogeneity: Q=11.35, df=7, p=0.9, I^2=0.41, n=1028

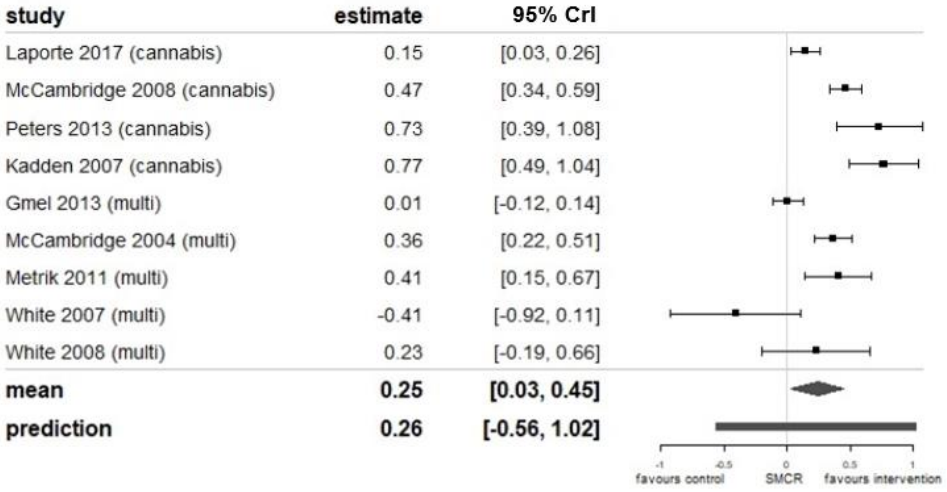
Key: 'Intervention' = number who quit in intervention group/total in group; 'control' = number who quit in control group/total in group; intervention target shown in brackets after study name; CrI = Credibility Interval. NB not all studies targeted both substances

Figure 4 Tobacco reduction



Heterogeneity: Q= 45.55, p value= 0.5, I^2=0.88, n=1068

Figure 5 Cannabis reduction



Heterogeneity: Q=59.76, p value = 0.8, I^2= 0.93, n=1103