A meta-analysis of cognitive based techniques as interventions to improve medication adherence

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-002749
Article Type:	Research
Date Submitted by the Author:	18-Feb-2013
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Primary Subject Heading:	Medical management
Secondary Subject Heading:	Medical management
Keywords:	Medication adherence, Meta-analysis, Behaviour change, Motivational Interviewing, Adherence intervention

A meta-analysis of cognitive based techniques as interventions to improve medication adherence

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Keywords: Medication adherence, Motivational Interviewing, Meta-analysis, Behaviour change, Adherence intervention

Word count: 3051

Article summary

Article focus

- Medication non-adherence is widespread and represents a notable barrier to achieving optimal effects from therapeutic intervention.
- Despite the magnitude and consequences of non-adherence, a gold standard intervention to improve it remains elusive.
- Cognitive-based techniques may represent a useful tool in improving medication adherence but their use in this domain had not been established using meta-analytic techniques.

Key messages

- Cognitive-based techniques are effective interventions for improving medication adherence and capable of eliciting improvements in adherence beyond those achieved with educational and behavioural interventions which form the mainstay of current practice
- Cognitive-based techniques can be effectively delivered by routine healthcare providers in standard community based settings. Brief interventions are seemingly effective too.
- Health care providers may wish to consider incorporation of these techniques into their medication adherence consultations

Strengths and limitations of this study

- The studies pooled in this meta-analysis are restricted to RCTs which strengthens their robustness.
- Techniques to account for publication bias have been utilised to provide a conservative effect size estimate offering robustness to our estimate
- Notable heterogeneity was reported when studies were combined which may be a limitation.

Abstract

Objective

To describe and evaluate the use of cognitive-based techniques as interventions to improve medication adherence.

Design

Systematic review and meta-analysis of interventions to improve medication adherence.

Data sources

Search of Medline, Embase, PsycINFO, CINAHL, The Cochrane Library and The National Electronic Library for Medicines (NELM) databases from the earliest year to October 2012 without language restriction. References of included studies were also screened to identify further relevant articles.

Review methods

We used pre-defined criteria to select Randomised Controlled Trials (RCTs) describing a medication adherence intervention that used Motivational Interviewing (MI) or other-cognitive based techniques. Data were extracted and risk of bias was assessed by two independent reviewers. We conducted the meta-analysis using a random effects model and Hedges' *g* as the measure of effect size.

Results

We included 23 studies (4855 participants) in the meta-analysis. Interventions most commonly used MI but many used more generalised techniques such as aiming to increase the patient's confidence and sense of self-efficacy, encouraging support seeking behaviours and challenging negative thoughts. Interventions were most commonly delivered from community based settings by routine healthcare providers such as GPs and nurses. An effect size (95% CI) of 0.36 (0.23 to 0.48), was calculated meaning the overall effect of these interventions is statistically significant (p = <0.001). Adjustment for publication bias generated a more robust estimate of summary effect size of 0.20 (0.07 to 0.33). No statistically significant differences were observed in a range of subgroup analyses.

Conclusion

Cognitive-based techniques are effective interventions eliciting improvements in medication adherence that are likely to be greater than the behavioural and educational interventions largely used in current practice. Results of subgroup analyses indicated that these interventions can be delivered in routine healthcare settings by routine healthcare providers.

Abstract word count: 279

Introduction

Estimates suggest that 30 to 50% of patients prescribed medications for chronic illnesses do not adhere to their prescribed medication regimen.[1] This non-adherence has been demonstrated to diminish treatment effect which can result in prolonged illness, additional investigations and prescribing that may otherwise have been unnecessary.[2] A link between poor adherence and an increased risk of mortality is also well established.[3] Consequently, the World Health Organisation (WHO) has described non-adherence as "a worldwide problem of striking magnitude" and a priority for healthcare researchers and policy makers.[1]

Despite both the magnitude and potential gravity of sub-optimal medication adherence, a gold standard intervention remains elusive; a recent Cochrane review highlighted the paucity of effective interventions in current practice.[4] Evidence suggests that complex, multi-faceted interventions, tailored to meet individual needs are most likely to be efficacious[4 5] which is intuitive given the complex, multi-stage process that is medication taking.

Non-adherent behaviour is traditionally categorised into unintentional and intentional. Unintentional non-adherence includes behaviours arising from forgetfulness, misunderstanding and confusion. Intentional non-adherence describes patient choice to deviate from the prescribed medication regimen. Unintentional and intentional non-adherence are not mutually exclusive thus an amalgam of these behaviours often exists in any one patient. An understanding of patient behaviour and its underpinning psychology plus the wealth of factors, both internal and external that may influence medication taking, is crucial to understanding how to change patient behaviour and thus improve medication adherence.[6]

Historically, adherence interventions have encompassed techniques such as simplifying dosage regimens and providing adherence aids or education. Pooled data for such studies have demonstrated marginal effects[4] yet such interventions continue to form the cornerstone of routine healthcare provision.[2] These interventions may have particularly poor efficacy in cases of intentional non-adherence as the provision of persuasive advice may evoke further resistance to change.[7 8] Through an understanding of the challenges faced in changing behaviours and the motivation necessary to achieve change, novel, cognitive-based techniques have emerged. These 'talking' interventions can vary widely in content such as incorporating techniques to enhance patient sense of self-efficacy, problem solve and increase motivation to adhere.

Motivational interviewing (MI) is one of the most widely recognised cognitive-based techniques and is designed to facilitate behaviour change by resolving patient ambivalence about change.[9] It therefore primarily targets intentional non-adherence but also enables patients to reflect on any unintentional barriers to adherence and seek out solutions. Systematic reviews and meta-analyses have reported MI efficacy in facilitating health related behaviour change such as smoking cessation and alcohol withdrawal[10-16] but have not explored its effects on medication adherence. Adaptations of MI such as Behaviour Change Counselling (BCC)[17] additionally allow the facilitator to educate and advise thus application to both intentional and unintentional non-adherence may be effective.

Best practice guidelines state that evidence of intervention efficacy should ideally be pooled from literature in a systematic review or meta-analysis wherever possible to offer a robust and cohesive evidence base.[18] This study provides a systematic review and meta-analysis of MI and other cognitive-based techniques as interventions to improve medication adherence.

Methods

We used standard systematic review methods[18 19] and registered the study protocol (PROSPERO register reference CRD42011001721). Randomised Controlled Trials (RCTs) reporting an adherence intervention using MI and/or other cognitive-based techniques with medication adherence as an outcome measure were eligible for inclusion. All definitions of adherence such as percentage of doses taken over a given time period and percentage of patients achieving a specified adherence level were considered. All adherence measures were also considered including self-report and electronic monitoring. Where multiple measures were reported, the percentage of patients achieving a specified adherence level was selected as this was common to more studies.

Any intervention using some form of psychological technique to change a patient's adherence behaviour and their thoughts, feelings, confidence, or motivation towards adhering was defined as a cognitive-based technique. Studies examining adherence to medications for the treatment of addiction and/or mental health conditions were excluded as these interventions tend to be specific to these domains.

Search strategies

We developed a search strategy to avoid restriction to pre-determined terms such as 'motivational interviewing' as many of the techniques of interest are not classified using specific or consistent terms. MeSH terms were also used to enhance retrieval of relevant studies. Truncations (*), wild cards ($), hyphens and other relevant Boolean operators were

used where permitted. Scoping searches were conducted prior to finalising the search strategy to ensure suitably of terms in generating a good coverage of relevant material.

We applied the search strategy (as shown in appendix one) to the MEDLINE, EMBASE, PsychINFO, CINAHL, and The National Electronic Library for Medicines (NELM) databases in October 2012 without date or language restrictions. The reference lists of all screened full text articles were also used to identify further relevant articles.

Study selection and data extraction

Two researchers (CE and EP) independently screened titles and abstracts against the inclusion and exclusion criteria using a piloted abstract screening tool. Inter-reviewer agreement using Cohen's weighted Kappa (K) was assessed for the abstract screening stage and the level of agreement was characterised using a qualitative scale.[20] Discrepancies were resolved by discussion between the two reviewers, and if necessary referral to a third independent reviewer (DB) until consensus was reached.

Data extraction was also undertaken by CE and EP, independently using piloted forms. Data extracted included study details (such as year and journal of publication, country and study design); study characteristics (including setting, population, delivery methods and personnel); intervention details (including intervention type, duration and principal components) and outcome details (including adherence assessment measure, data and definition).

Accuracy of data collected was verified by comparison of the forms completed by the two independent reviewers. In cases of discrepancy, consensus was agreed through discussion and where necessary, referral to a third independent reviewer (DB). For studies with missing data or ambiguities, the corresponding author was contacted for clarification.

Quality assessment

A quality assessment of all included studies was made using the Cochrane risk of bias tool.[18] The risk of bias was assessed in five domains deemed relevant to the included studies: random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data and selective reporting. Performance bias (blinding of participants and personnel) was not included as the nature of the interventions meant that blinding of participants and personnel was impossible in almost all studies. None of the included studies were found to contain additional sources of potential bias not represented by the five included domains. The risk of bias for each study, in each of the five domains was classified

as low, uncertain or high, as recommended in the guidelines.[18] The quality assessment process was undertaken independently by two reviewers, with consensus on the final risk classifications reached through discussion.

Data analysis

The meta-analysis was conducted using STATA® (version 12.1). Given the broad inclusion criteria, we anticipated including studies from different populations, with different diseases and which used different cognitive-based techniques. We therefore explored heterogeneity via calculation of the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance.[21 22] A random effects model was employed to calculate a pooled effect size (Hedges' *g*) and 95% confidence interval for the included studies.[23] Calculation of the effect size as Hedges' *g* (standardised difference in means) enabled continuous adherence outcome measures of differing definition and measure, to be combined, transforming this data into a common metric.

Funnel plots were produced where appropriate to explore potential publication biases. STATA® (version 12.1) was used to conduct Egger's test[24] to test funnel plot asymmetry, and trim and fill methods[25 26] to estimate a summary effect size after adjusting for asymmetric funnel plots. These techniques enabled calculation of a pooled effect size that accounted for biases.

Variables of interest in influencing the effect size and informing intervention design were determined a priori and the following subgroup analyses undertaken using a random effects meta-regression: intervention type, location, provider, delivery method and exposure, disease state and methodological quality.

Results

Study selection, characteristics and quality

Figure 1 shows the number of papers excluded at each stage of the review. Of the 402 abstracts screened, 58 studies passed the abstract screening stage with moderate agreement between the two reviewers (k = 0·515). Conflict in classifying an intervention as a cognitive-based technique accounted for 55·1% of discrepancies and was heavily influenced by a paucity of information in the abstracts. After examining 58 full-text articles, we included 23 (39.7%) in the meta-analysis.

The main characteristics of the 23 included studies are summarised in Table 1. The studies provided a total sample size of 4855 participants. Just over half of the included studies

(52.2%) described an intervention with a clearly defined cognitive-based technique; Motivational Interviewing (MI) was most commonly used and this was the case for 10 (43.5%) studies. For 11 (47.8%) studies, a clearly defined cognitive-based technique such as MI could not be identified. Instead, this group comprised of non-specific, multiple components such as 'providing education' or 'increasing patient knowledge' which was reported in 10 (90.9%) studies in this group. Other components included 'increasing self-efficacy' and 'developing or improving problem solving skills' each reported in six (54.5%) studies and 'identifying and resolving adherence barriers' and 'increasing social support' each reported in five (45.5%) studies. Detailed information regarding the identified intervention components extracted from each study are provided as a supplementary table. The majority of interventions had multiple components.

Interventions were most commonly delivered in person, from community based settings and by routine healthcare providers such as nurses, pharmacists and general medical practitioners. The intervention period ranged from four (15·4%) studies reporting singular sessions, to six (23·1%) studies reporting multiple sessions over 12 months. The median (IQ) number of sessions over which interventions were delivered was 4·0 (3.0 to 7.0). The majority of interventions were delivered over a period of six months or less which was the case for 14 studies (63.6%). The comparison group was 'standard care' for all studies; for 12 studies (52.2%) standard care involved some form of technique to improve adherence such as education, encouragement or provision of adherence aids and in these studies, recipients of the intervention received further techniques such as MI.

Table 1: Characteristics of included studies in meta-analysis

Study	Study setting	Disease area	Intervention description*	Identified intervention components	Components received by control group	Sample size	Intervention delivery style (& personnel)	Intervention length (average)
Bailey et al 1990[27]	Hospital clinic, USA	Asthma	Comprehensive programme integrating a skills-orientated self-help workbook with one-to-one counselling & adherence-enhancing strategies.	Multiple components; non-specific techniques	Standard care; education via standardised set of pamphlets and routine physician encouragement	225	Telephone calls and in person (specialist)	240 minutes (4 x 60min sessions) over unknown period
Berger et al 2005[28]	Telephone calls to patients at home, USA	Multiple Sclerosis	Software supported intervention based on Transtheoretical model of change and MI	Motivational Interviewing (MI)	Standard care plus could telephone help line	367	Telephone calls (researcher)	9 sessions of unknown duration delivered over 3 months
Brown et al 2009[29]	Hospital clinic, UK	Epilepsy	Formation of III via completion of a self-administered questionnaire	Implementation Intention Interventions (III)	Standard care plus self-report questionnaires	69	Questionnaire completion (not in person)	One-off intervention of unknown duration
Dilorio et al 2003[30]	Community clinic, USA	HIV	One-to-one counselling sessions based on MI	Motivational Interviewing (MI)	Standard care; usual adherence education provided in the clinic	17	In person (routine HCP)	5 x 35 minutes sessions delivered over 12 months
Dilorio et al 2008[31]	Hospital clinic, USA	HIV	MI as individual counselling sessions	Motivational Interviewing (MI)	Standard care; usual (extensive) education provided at the clinic	213	Mostly in person with some telephone calls (routine HCP)	5 sessions of 35 minutes over 12 months
George et al 2010[32]	Community pharmacies, Australia and Tasmania	Hypertension	Community pharmacy intervention of one-to-one sessions, monitoring & medication review	Motivational Interviewing (MI)	Standard care	343	In person (routine HCP)	3 sessions of unknown duration over 6 months
Golin et al 2006[33]	Community clinic, USA	HIV	Multi-component MI based intervention.	Motivational Interviewing (MI)	General HIV information provided via audio tape, two one-to-one sessions	117	In person (specialist)	2 sessions of unknown duration over 2 months

					and two mail shots.			
Hovell et al 2003[34]	Hospital clinic, USA	Tuberculosis	Adherence coaching involving interviewing, contingency contracting and shaping procedures	Multiple components; non-specific techniques	Standard care; routine advice at appointments	188	Telephone calls & in person (researcher)	12 sessions of 15-30 minutes over 6 months
Maneesriwongul et al 2012[35]	Hospital outpatients clinic & telephone calls to patients at home, Thailand	HIV	Motivational interviewing with counselling	Motivational Interviewing (MI)	Standard care; education and provision of leaflets at point of prescribing	60	Telephone calls & in person (researcher)	3 sessions approximately 30 minutes over a four week period
Murphy et al 2002[36]	Community based clinic, USA	HIV	Multi-component and multi-disciplinary intervention including behavioural strategies and cognitive behavioural therapy	Multiple components; non-specific techniques	Standard care; regular appointments with enquiries about adherence and an additional 30 minute appointment for those with problems where medication schedule is written down for them	33	In person (specialist)	5 sessions of unknown duration over 7 weeks
Ogedegbe et al 2008[37]	Community clinic, USA	Hypertension	Practice-based MI counselling	Motivational Interviewing (MI)	Standard care; usual appointments plus additional visits for MEMS downloads	160	In person (researcher)	4 sessions lasting 30-40 minutes delivered over 12 months
Pradier et al 2003[38]	Hospital clinic, France	HIV	Educational & counselling intervention founded in the principles of motivational psychology and client-centred therapy	Multiple components; non-specific techniques	Standard care; routine follow up appointments	202	In person (routine HCP)	3 sessions of 45-60 minutes over 3 months
Put et al 2003[39]	Hospital clinic, Belgium	Asthma	Behavioural change intervention involving psycho-education with behavioural and cognitive techniques	Multiple components; non-specific techniques	Standard (no details provided)	23	In person (researcher)	360 hours (6 x 60 minutes sessions) over 3 months
Remien et al[40] 2005	Community based clinic,	HIV	Couples-based intervention grounded in	Multiple components;	Standard care; education at point of	196	In person (routine HCP)	4 sessions of 45-60 minutes

	USA		Social action theory	non-specific techniques	prescribing & follow up to check adherence & investigate/address underlying causes of any non-adherence			over 5 weeks
Safren et al 2001[41]	Community clinic, USA	HIV	Single session minimal treatment intervention using cognitive behavioural, motivational interviewing and problem solving techniques	Motivational Interviewing (MI)	Minimal contact intervention; daily diary used to record no. of pills prescribed & taken each day	53	In person (routine HCP)	One-off intervention of unknown duration
Sheeran et al 1999[42]	Visits to patients own home, UK	Vitamin Supplements	Formation of III via completion of a self-administered questionnaire	Implementation Intention Intervention (III)	Completion of same questionnaire but without formation of implementation intention	78	Questionnaire completion (not in person)	One-off intervention of unknown duration
Smith et al 2003[43]	Community based research office, USA	HIV	Self-management intervention based on feedback of adherence performance & principles of social cognitive theory	Multiple components; non-specific techniques	Standard care; usual medication counselling, educational leaflets, scheduling support reminder lists & discussion of adherence strategies	17	In person (routine HCP)	Four sessions of unknown duration over 12 weeks
Solomon et al 2012[44]	Telephone calls to patients own home, USA	Osteoporosis	Telephone based counselling programme rooted in motivational interviewing	Motivational Interviewing (MI)	Standard care plus seven information mailings on osteoarthritis care	2087	Telephones calls (health educator)	8 sessions of 14 minutes over 12 months
Tuldra et al 2000[45]	Hospital clinic, Spain	HIV	Psycheducative intervention based on Self-efficacy theory	Multiple components; non-specific techniques	Standard care; normal clinical follow-up	77	Unknown (routine HCP)	No details provided
Van Es et al 2001[46]	Hospital clinic, Netherlands	Asthma	Intervention programme to stimulate a positive attitude, increase social support and enhance self-efficacy.	Multiple components; non-specific techniques	Standard care; routine check-ups	67	In person (routine HCP)	7 sessions of 30-90 minutes over 12 months

Wagner et al 2006[47]	Community clinic, USA	HIV	Cognitive behavioural intervention with motivational components, based on the information-motivation-behavioural skills (IMB) model	Multiple components; non-specific techniques	Standard care practices for improving adherence; education, tailoring regimen, offering a pillbox, adherence checks & enquiries about side effects	135	In person (routine HCP)	5 sessions of 30-45 minutes over 48 weeks
Weber et al 2004[48]	Community, psychotherapy clinic, Netherlands	HIV	Cognitive behavioural intervention delivered by a psychotherapist.	Multiple components; non-specific techniques	Standard care (no details provided)	53	In person (specialist)	11 sessions of 45 minutes over 12 months
Williams et al. 2012[49]	Telephone calls and visits to patients own home, Australia	Diabetes	Multifactorial intervention consisting of self-monitoring of blood pressure, medicine review, educational DVDs and MI to support blood pressure control and optimal medication adherence	Motivational Interviewing (MI)	Standard care (no details provided)	75	In person and phone calls (specialist)	5 sessions, one of 89 minutes and 4 of an average of 11.75 minutes, over 3 months

* See supplementary table A for detailed breakdown of intervention components

Supplementary figures 1 and 2 show the results of the risk of bias assessment. Only three (13.0%) studies scored 'low risk' in all five bias categories. 18 (78.2%) were described as moderate overall risk, scoring 'low risk' in two to four of the categories and two (8.7%) were described as 'high risk' scoring a low risk of bias in only one category. The most common source of bias was a lack of blinding of the outcome assessment; this is because the measure of adherence was frequently self-report. Self-report measures of adherence are commonly used but subject to patient bias. In the majority of cases the patients were not blind to their treatment group allocation and thus use of self-report measures leaves scope for bias.

Meta-analysis

23 RCTs were pooled to assess the effect of cognitive-based techniques on medication adherence. Three studies showed non-significant negative effects on medication adherence but the remaining 20 studies all showed improvements in medication adherence with receipt of intervention. The effect size calculated for each study is summarised in table 2.

Random effects meta-analysis showed evidence that cognitive-based techniques are associated with improved medication adherence. Figure 2 shows the forest plot for the 23 studies and exemplifies the tendency towards positive adherence effects with intervention. A pooled estimate of effect size (95% CI) (reported as Hedges' *g)* of 0·36 (0·23 to 0·48) was calculated when all studies were combined, although heterogeneity was high (I^2 = 70.2%).

The funnel plot produced was indicative of publication bias (as shown in figure 3) and so further explored using Egger's test which confirmed statistically significant funnel plot asymmetry (p= 0.004). The trim-and-fill technique was used to re-compute an effect size which accounted for this asymmetry, yielding a more conservative effect size estimate of 0.20 (0.07 to 0.33). This effect size suggests that cognitive-based techniques elicit small but statistically significant improvements in medication adherence (p = 0.003) relative to standard care.

Table 2: Study outcomes for studies included in meta-analysis

Study	Sample size (intervention, control)	Adherence definition (assessment measure)	Extracted data			Effect size (Hedges' g) (95% CI)
			Intervention group	Control group	P-value	
Bailey et al 1990	225 (124, 101)	% of patients scored as adherent on all 6 items of a self-report scale (based on Morisky's self-reported scale)	Mean = 91.9	Mean = 61.7	0.001	0.44 (0.18 to 0.71)
Berger et al 2005	367 (172, 195)	% of patients discontinuing treatment by study endpoint (patient interview)	Mean = 98.8	Mean = 91.3	0.001	0.35 (0.14 to 0.55)
Brown et al 2009	69 (36, 33)	% of prescribed doses taken over a month (electronic monitoring)	Mean (SD) = 93.4 (12.3)	Mean (SD) = 79.1 (28.1)		0.66 (0.18 to 1.14)
Dilorio et al 2003	17 (8, 9)	Mean number of missed medicines in the last 30 days (self-report questionnaire)	Mean (SD) = 0.13 (0.35)	Mean (SD) = 0.98 (1.48)		0.73 (-0.21 to 1.67)
Dilorio et al 2008	213 (107, 106)	% of doses taken during intervention period (electronic monitoring)	Mean = 64	Mean = 55	0.09	0.23 (-0.04 to 0.50)
George et al 2010	343 (170, 173)	% of participants classed as adherent (Morisky self-report scale)	Mean = 72.2	Mean = 63.8	0.09	0.18 (-0.03 to 0.39)
Golin et al 2006	117 (59, 58)	% of prescribed doses taken take in month prior to study endpoint (CAS)	Mean (SD) = 76 (27)	Mean (SD) = 71 (27)		0.18 (-0.18 to 0.54)
Hovell et al 2003	188 (92, 96)	Cumulative number of doses taken over 9 months (patient interview)	Mean (SD) = 179.93 (57.01)	Mean (SD) = 150.98 (73.75)		0.44 (0.15 to 0.72)
Maneesriwongul et al 2012	60 (30, 30)	Mean % of doses taken over last 4 weeks (self-report using visual analogue scale)	Mean (SD) = 97.1 (3.3)	Mean (SD) = 89.8 (5.6)		1.55 (0.98 to 2.12)
Murphy et al 2002	33 (17, 16)	% of doses taken during intervention period (self-report questionnaire)	Mean (SD) = 0.86 (0.33)	Mean (SD) = 0.83 (0.36)		0.09 (-0.58 to 0.75)
Ogedegbe et al 2008	160 (79, 81)	% of days during a two month period in which medication was taken correctly (electronic monitoring)	Mean = 56.9	Mean = 42.9	0.027	0.35 (0.04 to 0.66)
Pradier et al 2003	202 (123, 121)	% of patients deemed to be adherent (taking 100% of doses) (self-report questionnaire)	Mean = 75	Mean = 61	0.04	0.34 (0.02 to 0.65)
Put et al 2003	23 (12, 11)	Frequency of non-adherent behaviour over the last 3 months (self-report questionnaire)	Mean (SD) = 6.9 (1.2)	Mean (SD) = 8.1 (3.1)		0.50 (-0.30 to 1.30)
Remien et al 2005	196 (106, 109)	% of doses taken during previous 2 weeks (electronic monitoring)	Mean (SD) = 76 (27)	Mean (SD) = 60 (34)		0.52 (0.25 to 0.79)

Safren et al 2001	53 (28, 25)	% of prescribed doses taken over the last 2 weeks (self-report questionnaire)	Mean (SD) = 93 (22)	Mean (SD) = 94 (10)		-0.06 (-0.59 to 0.47)
Sheeran et al 1999	78 (38, 40)	Number of once daily doses missed over a 3 week period (self-report questionnaire)	Mean = 2.68	Mean = 4.85	0.05	0.45 (0.00 to 0.89)
Smith et al 2003	17 (8, 9)	% of participants taking ≥ 80% of their weekly doses (electronic monitoring)	Odds ratio = 7.8 (2.2 to 28.1)			1.08 (0.41 to 1.74)
Solomon et al 2012	2087 (1046, 1041)	Median % medication possession ratio (prescription refill data)	Median = 49 IQR = 7 to 88	Median = 41 IQR = 2 to 86	0.07	0.08 (-0.01 to 0.17)
Tuldra et al 2000	77 (36, 41)	% of patients with monthly adherence ≥ 95% (self-reported number of pills taken)	Mean = 94	Mean = 69	0.008	0.62 (0.16 to 1.07)
Van Es et al 2001	67 (58, 54)	Adherence score on self-report scale based on how often medication was taken (never-always)	Mean = 7.7	Mean = 6.7	0.05	0.48 (0.00 to 0.96)
Wagner et al 2006	135 (154, 76)	% of doses taken during intervention period (electronic monitoring)	Mean = 83.5	Mean = 86.4	0.57	-0.08 (-0.35 to 0.20)
Weber et al 2004	53 (29, 24)	% of patients with monthly adherence ≥ 95% (electronic monitoring)	Mean = 70.8	Mean = 50	0.014	0.69 (0.14 to 1.24)
Williams et al 2012	75 (36, 39)	% of doses taken during intervention period (pill counts	Mean = 58.4	Mean = 66	0.162	-0.32 (-0.77 to 0.13)

Sub-group analyses via meta-regression

Table 3 summarises the results of the subgroup analyses to explore variation in effect size for the pre-determined variables. Differences in effect size between subgroups were statistically non-significant in all cases. Differences in sub-groups were not found to account for any notable degree of the observed heterogeneity.

Table 3: Summary of sub-group analyses

Variable	Sub-groups	No. of studies (no. of participants) in each sub-group	Co-efficient (95% CI)	P-value
Intervention setting	Hospital Vs. community	9 (1124) Vs. 14 (3731)	0.275 (-0.014 to 0.565)	0.061
Disease area	HIV Vs. other conditions	12 (1173) Vs. 11 (3682)	0.116 (-0.195 to 0.428)	0.447
Intervention components	MI Vs. no MI component	10 (3502) Vs. 13 (1353)	-0.186 (-0.485 to 0.113)	0.210
Intervention delivery method	Entirely in person Vs. other methods	13 (1416) Vs. 10 (3439)	0.006 (-0.354 to 0.366)	0.973
	Entirely over the telephone Vs. other methods	3 (2679) Vs. 20 (2176)	0.005 (-0.317 to 0.327)	0.976
	In person and/or telephone Vs. other	20 (4631) Vs. 3 (224)	0.985 (-0.279 to 0.476)	0.593
Intervention delivery personnel	Routine HCP Vs. others	10 (1320) Vs. 13 (3535)	-0.042 (-0.360 to 0.277)	0.789
	Specialist Vs. others	5 (503) Vs. 18 (4352)	-0.173 (-0.557 to 0.212)	0.360
Intervention exposure	Four sessions or fewer Vs. five sessions or more	11 (1520) Vs. 12 (3335)	-0.912 (-0.492 to 0.106)	0.193
Control group type	Explicit active controls Vs. usual care (no adherence enhancing strategies)	12 (3472) Vs. 11 (1383)	0.548 (-2.609 to 3.706)	0.722
Risk of bias	Outcome assessment blinding Vs. no outcome assessment blinding	12 (3194) Vs. 11 (1661)	0.828 (-0.232 to 0.397)	0.151

Note to Table 3: Differences between subgroups were tested using STATA 'metareg' command for random-effects meta-regression analysis. Co-efficient refers to the difference in effect size between the two sub-groups.

Discussion

Principle findings

We found that receipt of a cognitive-based adherence intervention was associated with small but statistically significant improvements in medication adherence. Heterogeneity was high and notable publication bias was identified. However, techniques have been used to account for these biases resulting in a summary effect size (95% CI) of 0.20 (0.07 to 0.33).

In over half of the included studies, the standard care received by the study control group involved some form of 'adherence enhancing strategy' such as provision of education, monitoring or review. Such strategies form the mainstay of current medication adherence interventions and so our research suggests that cognitive based techniques may be able to elicit adherence benefits beyond the techniques used in current practice.

Sub-group analyses revealed that the effect size achieved is not influenced by variables such as the type of cognitive-based intervention, delivery method and personnel or duration. This suggests that the interventions studied in this meta-analysis may be generalizable across a diverse range of settings.

Comparison with other studies

In 2003, Peterson *et al.* conducted a meta-analysis of educational and behavioural interventions to improve medication adherence in a range of illnesses.[50] The included studies were all RCTs delivered over similar time periods to those included in our study. The educational and behavioural components examined by Peterson *et al.* closely mirror those utilised in the studies from our meta-analysis which used control groups with 'active standard care'. Peterson *et al.* reported a correlation coefficient (*r*) equivalent to a Cohen's *d* effect size of 0·16 (0·08, 0·24). For our study, the effect size for all studies, when adjusting for publication bias and reported as Hedges' *g* was 0.20 (0.07, 0.33). This suggests that inclusion of cognitive based techniques, strengthens the adherence improvements gained, if only marginally. Moreover, Peterson *et al.* report publication bias observed from a funnel plot of their included studies, but have not made allowances for this bias via re-computed effect sizes. With this mind, their Cohen's *d* value of 0.16 is likely exaggerated by the noted publication bias and thus infers that the true difference in effect size between the two meta-analyses may be greater.

For studies using MI, an effect size (Hedges' *g*) of 0.26 (0.08, 0.44) was calculated, which closely matches the effect size calculated when MI is used as a behavioural intervention in other healthcare domains[14] and thus represents novel evidence for the wider application of MI techniques beyond the treatment of substance abuse and gambling.

Strengths and weaknesses of our work

This study represents the first meta-analysis of MI and other cognitive-based techniques as medication adherence interventions and has been undertaken with methodological rigour and in accordance with published guidance.[18] A notable strength of this work is the robust methodological techniques that have been applied to provide an estimate of effect size

which accounts for publication biases and thus greater confidence can be placed in the estimate. The work is also strengthened by restriction to RCTs.

Whilst moderate agreement in abstract screening may be lower than ideal, this is largely attributable to paucity of detail reported in studies and complexities in intervention definitions which are known to be problematic in this domain.[11-13] Heterogeneity between the included studies was high with an I^2 value of 70.2% and thus raises the question as to whether the studies were sufficiently comparable to warrant pooling in a meta-analysis. Whilst we defined our inclusion criteria to ensure studies were as similar as possible (i.e. all using a cognitive-based technique), heterogeneity was expected as other factors such as the populations and disease states studied were more difficult to control for. Interestingly, the inclusion of one particular study which was vastly larger in sample size than all other studies greatly increased the heterogeneity.[44] Aside from these between study differences, the actual interventions themselves were variable, as were the definitions of adherence and assessment tools used. Despite these numerous between study differences, the core of each intervention was the use of a cognitive-based technique to improve medication adherence which was comparable across all studies and thus we would argue that data pooling irrespective of heterogeneity was both intuitive and meaningful.

We have established that receipt of a cognitive-based medication adherence intervention is likely to elicit small improvements in medication adherence, but the clinical relevance and impact of this improvement remains unknown. Based on mean adherence rates in the control groups, mean standard deviations and the effect size calculated, it has been possible to estimate the increase in percentage of doses taken for the intervention groups. Based on the adjusted Hedges' *g* value of 0.20 (0.07 to 0.33), receipt of a cognitive-based technique improved adherence (% of doses taken) by 5.46% (1.83% to 9.12%). For some medications, a 5% increase in the percentage of doses taken may not be of clinical relevance. However, for many medications such as antiretroviral therapy for HIV which requires very high levels of adherence or anti-epileptic therapies with narrow therapeutic windows, a 5% increase in adherence may have notable clinical relevance. Whilst many included studies included data on clinical outcomes, pooling of this data from a diverse range of studies was not possible.

Implications

Motivational and cognitive-based techniques can seemingly be delivered effectively by routine healthcare professionals, in both primary and secondary care settings, with efficacy applicable to a range of diseases. Efficacy was not related to intervention duration or follow-

up period. Interestingly, the results also suggest that these interventions can be delivered via telephone or face-to-face with comparable efficacy. These are valuable traits for an adherence intervention which could be adaptable to a wide range of settings and amenable to tailoring to meet individual need.

The flexibility and adaptability of these techniques coupled with their frequent simplicity means that practitioners may wish to consider incorporation of some of these techniques into their consultations when faced with the need to facilitate medication related behaviour changes.

Recommendations and conclusions

Further investigation of these techniques as medication adherence interventions is warranted in order to further elucidate the characteristics most strongly associated with efficacy. Studies to determine both patient and healthcare practitioner acceptability of these techniques is also necessary to establish their role in routine healthcare.

Declaration of competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgements

CE would like to acknowledge Estelle Payerne for her invaluable contributions as the second reviewer for abstract screening and data extraction. CE would also like to acknowledge David Wright and John Wood for their comments on the protocol design, data analysis and methods of dissemination, and Steven Watson for his on going technical support in using the meta-analysis software and comments regarding data interpretation

Funding

This research has been supported by a PhD studentship awarded by the Dean of Science at the University of East Anglia.

Contributorship

DB and CE were responsible for the overall study co-ordination. CE was responsible for the study conception and protocol design, under the supervision of DB with contributions from FS. All literature searching, abstract screening, study selection and data extraction was undertaken independently by CE and EP with referral to DB as a third reviewer as necessary. Assessment of methodological quality was also undertaken by CE and EP. CE was responsible for all data analysis with guidance from DB and FS. Statistical tests, asymmetry tests and trim, and fill methods were undertaken by FS. CE wrote the first draft of the paper with guidance from DB and advice from FS

Data sharing

No additional unpublished data are available.

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Figure 1: Flow diagram for selection of studies

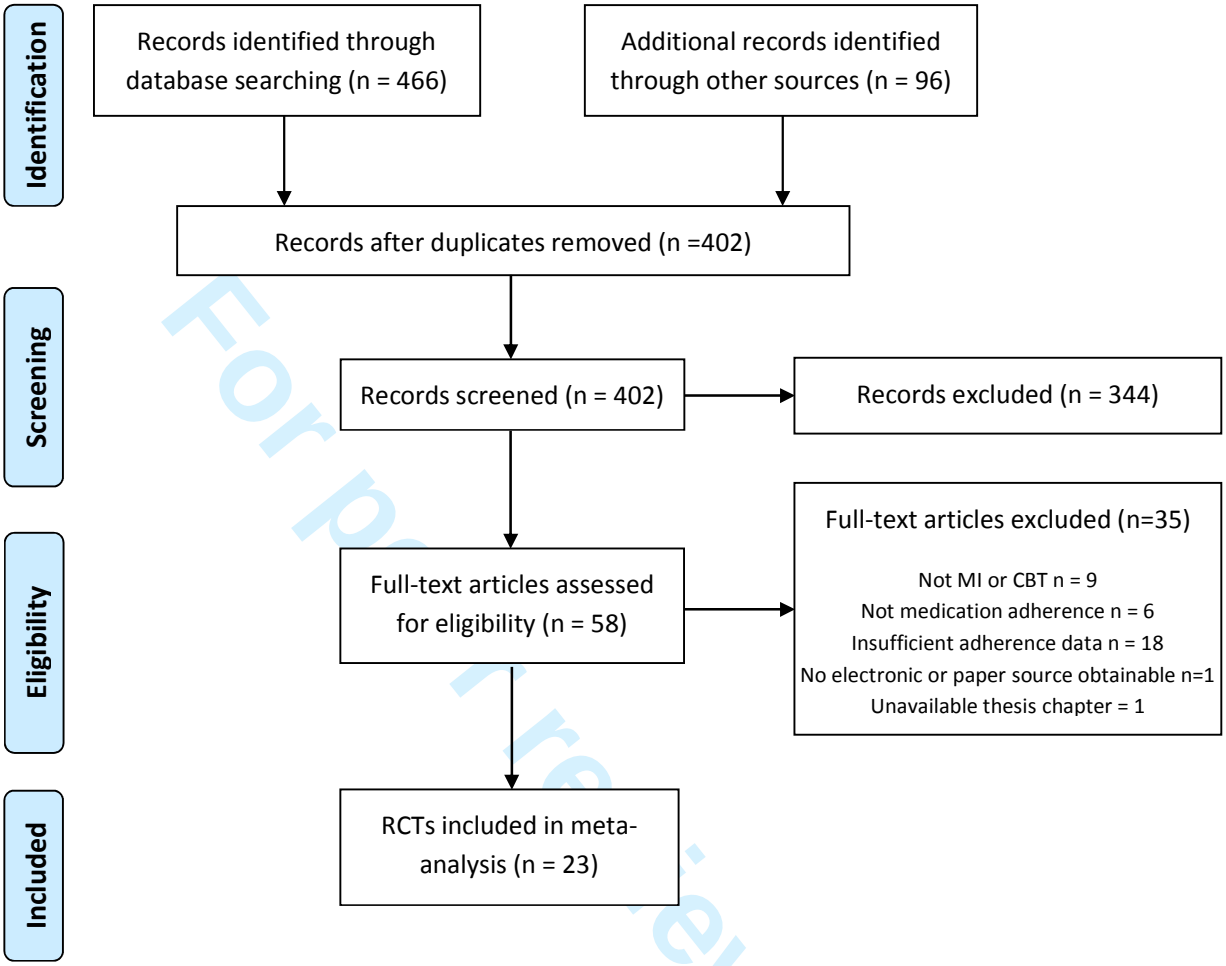


Figure 2: Forrest plot for studies included in meta-analysis

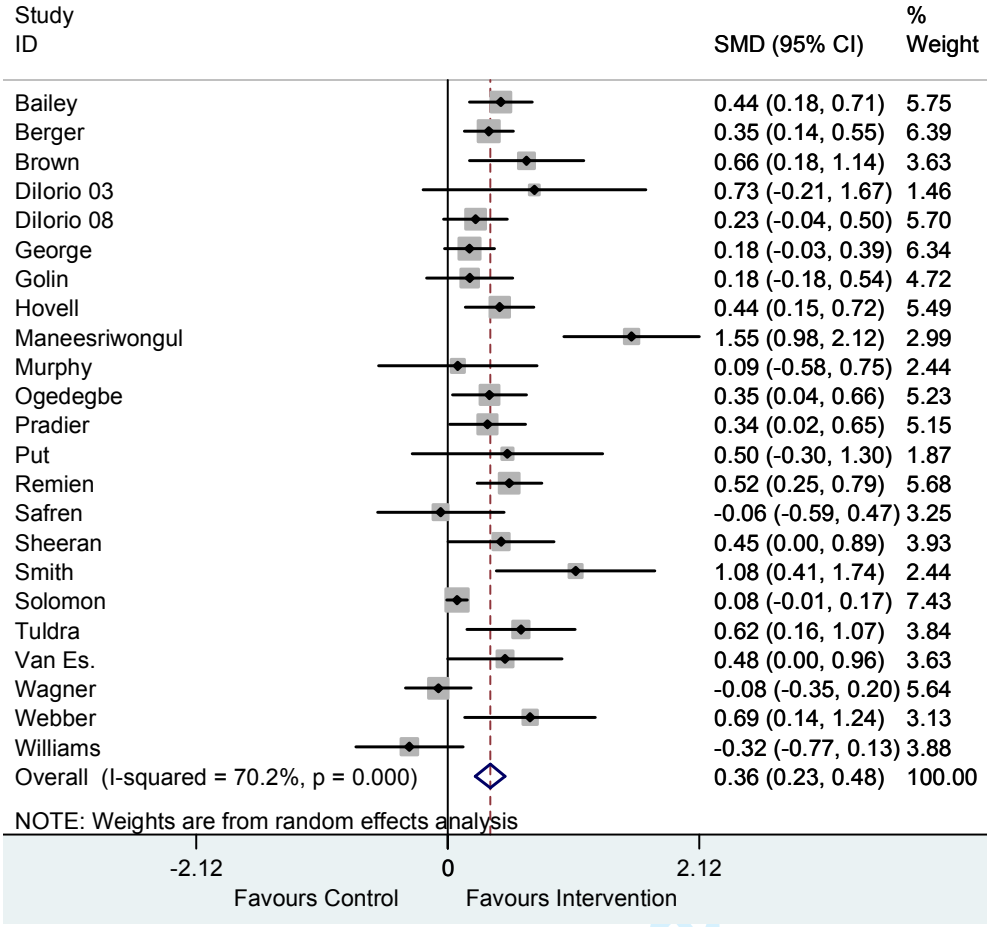
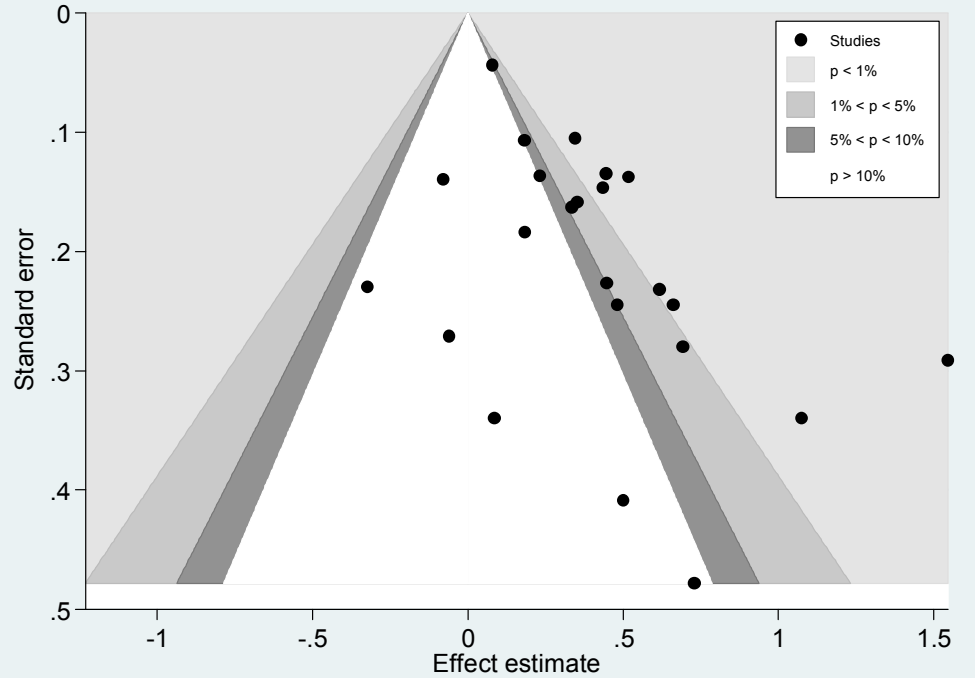
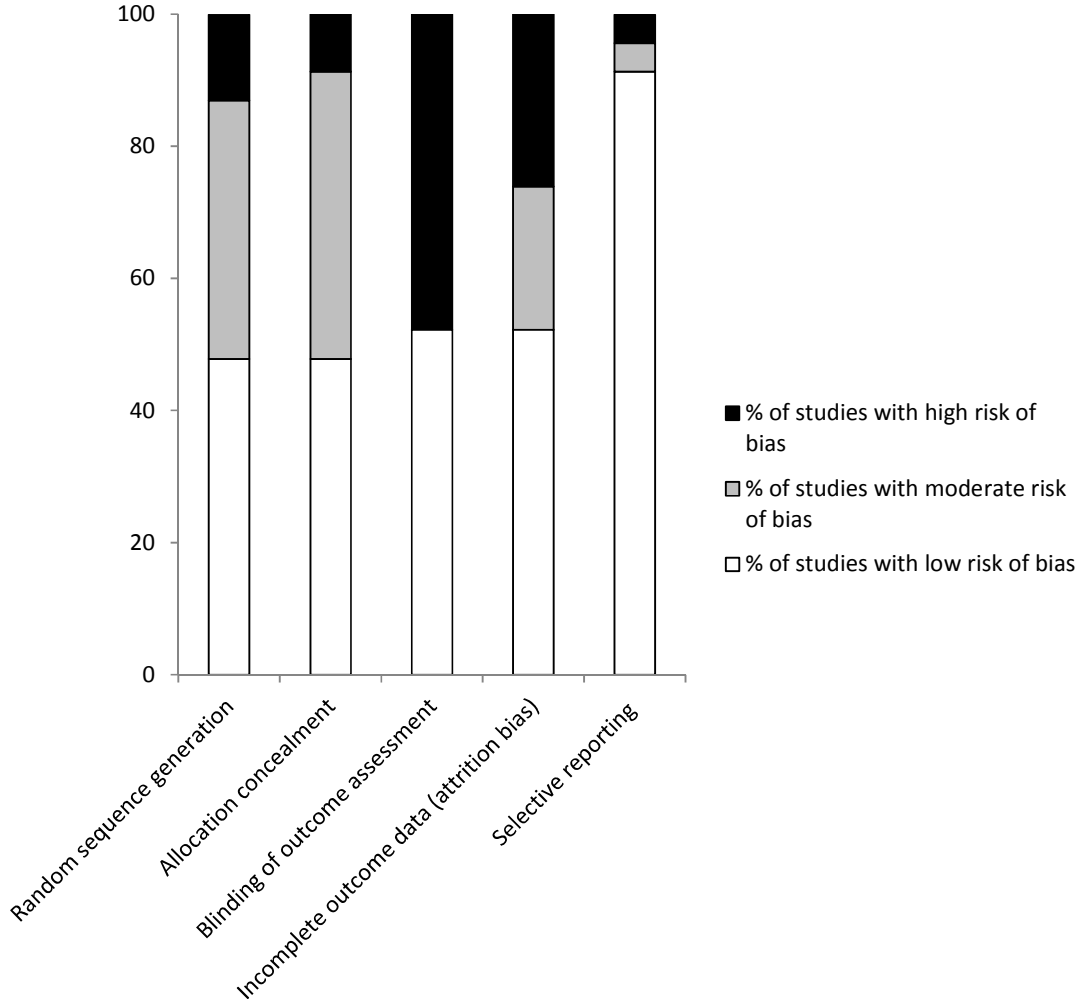


Figure 3: Funnel plot for studies included in meta-analysis



Supplementary figure 1 Outcome of risk of bias assessment by paper

Supplementary figure 2 Outcome of risk of bias assessment by type of bias



Supplementary table 1: Detailed information of intervention components

Study	Education/ Increasing patient knowledge	Motivational interviewing (MI)	Identifying and resolving adherence barriers	Developing/improving problem solving skills	Diary keeping/ self-monitoring	Increasingly sense of self-efficacy	Improving social support/ promoting support seeking	Goal setting/ action planning	Challenging negative thoughts/ changing attitudes	Improving communication with healthcare providers	Increasing confidence	Medication review	Identifying and addressing concerns	Rehearsing the behaviour	Simplifying/ tailoring medication regimen	Pill reminders/ dosing aids/ adherence cues	Formation of Implementation Intentions	Improving self-management/self-care skills	Improving adherence skills	Praising and encouraging	Increasing sense of control over own health	Increasing cognitive skills	Increasing self-awareness	Increasing motivation (not specifically MI)	Eliciting illness representations	Psychotherapy
Bailey 1990	✓		✓				✓		✓	✓								✓				✓				
Berger 2005	✓	✓																								
Brown 2009																	✓									
Dilorio 2003	✓	✓			✓																					
Dilorio 2008	✓	✓	✓					✓			✓															
George 2010	✓	✓			✓							✓				✓										
Golin 2006		✓											✓					✓								
Hovell 2003	✓			✓			✓	✓			✓					✓				✓						

Study	Education/ Increasing patient knowledge	Motivational interviewing (MI)	Identifying and resolving adherence barriers	Developing/improving problem solving skills	Diary keeping/ self-monitoring	Increasingly sense of self-efficacy	Improving social support/ promoting support seeking	Goal setting/ action planning	Challenging negative thoughts/ changing attitudes	Improving communication with healthcare providers	Increasing confidence	Medication review	Identifying and addressing concerns	Rehearsing the behaviour	Simplifying/ tailoring medication regimen	Pill reminders/ dosing aids/ adherence cues	Formation of Implementation Intentions	Improving self-management/self-care skills	Improving adherence skills	Praising and encouraging	Increasing sense of control over own health	Increasing cognitive skills	Increasing self-awareness	Increasing motivation (not specifically MI)	Eliciting illness representations	Psychotherapy
Maneesriwongul 2012		✓	✓					✓												✓						
Murphy 2002	✓		✓					✓													✓					
Ogedegbe 2008		✓	✓																							
Pradier 2003			✓	✓		✓	✓						✓										✓			
Put 2003	✓				✓				✓																✓	
Remien 2005	✓		✓	✓		✓			✓	✓	✓															
Safren 2001	✓	✓		✓	✓					✓				✓												
Sheeran 1999																	✓									
Smith 2003	✓				✓	✓			✓			✓							✓							

Study	Education/ Increasing patient knowledge	Motivational interviewing (MI)	Identifying and resolving adherence barriers	Developing/improving problem solving/coping skills	Diary keeping/ self-monitoring	Increasingly sense of self-efficacy	Improving social support/ promoting support seeking	Goal setting/ action planning	Challenging negative thoughts/ changing attitudes	Improving communication with healthcare providers	Increasing confidence	Medication review	Identifying and addressing concerns	Rehearsing the behaviour	Simplifying/ tailoring medication regimen	Pill reminders/ dosing aids/ adherence cues	Formation of Implementation Intentions	Improving self-management/self-care skills	Improving adherence skills	Praising and encouraging	Increasing sense of control over own health	Increasing cognitive skills	Increasing self-awareness	Increasing motivation (not specifically MI)	Eliciting illness representations	Psychotherapy
Solomon 2012	✓	✓	✓																							
Tuldra 2000	✓			✓		✓							✓		✓				✓							
Van Es 2001	✓			✓		✓	✓		✓	✓																
Wagner 2006	✓		✓	✓		✓	✓		✓					✓	✓									✓		
Weber 2004								✓																		✓
Williams 2012	✓	✓			✓							✓														

Appendix one: Search terms to be applied to databases

	Search terms
1	medication* adheren*.ti,ab
2	medication* complian*.ti,ab
3	medication* concordan*.ti,ab
4	medication* non-adheren*.ti,ab
5	medication* non adheren*.ti,ab.
6	medication* non-complian*.ti,ab
7	medication* non complian*.ti,ab.
8	medication* persist*.ti,ab.
9	drug* adheren*.ti,ab.
10	drug* complian*.ti,ab.
11	drug* concordan*.ti,ab
12	drug non-adheren*.ti,ab.
13	drug* non adheren*.ti,ab.
14	drug* non-complian*.ti,ab.
15	drug* non complian*.ti,ab.
16	drug* persist*.ti,ab
17	medicine adheren*.ti,ab.
18	medicine complian*.ti,ab.
19	medicine concordan*.ti,ab.
20	medicine non-adheren*.ti,ab.
21	medicine non adheren*.ti,ab
22	medicine non-complian*.ti,ab.
23	medicine non complian*.ti,ab
24	medicine persist*.ti,ab
25	patient adheren*.ti,ab.
26	patient complian*.ti,ab.
27	patient concordan*.ti,ab.
28	patient non-adheren*.ti,ab.
29	patient non adheren*.ti,ab.
30	patient non-complian*.ti,ab.
31	patient non complian*.ti,ab
32	patient persist*.ti,ab.
33	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34	motivation* interview*.ti,ab
35	motivation* enhancement therap*.ti,ab.
36	behavio?r change counsel?ing.ti,ab
37	implementation* intention*.ti,ab.
38	if-then plan*.ti,ab
39	if then plan*.ti,ab.
40	motivation* counsel?ing.ti,ab.
41	motivation* behavio?r.ti,ab.
42	motivation* change.ti,ab.
43	motivation* intervention*.ti,ab.
44	health behavio?r change*.ti,ab.
45	brief intervention*.ti,ab.
46	cognitive intervention*.ti,ab.
47	cognitive technique*.ti,ab
48	health behavio?r counsel?ing.ti,ab.
49	problem solving treatment*.ti,ab.
50	problem solving therap*.ti,ab
51	34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50
52	33 and 51
53	Remove duplicates from 52

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix one
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7-8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ open

A meta-analysis of cognitive-based behaviour change techniques as interventions to improve medication adherence

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-002749.R1
Article Type:	Research
Date Submitted by the Author:	17-May-2013
Complete List of Authors:	Easthall, Claire; University of East Anglia, School of Pharmacy Song, Fujian; University of East Anglia, School of Pharmacy Bhattacharya, Debi; University of East Anglia, School of Pharmacy
Primary Subject Heading:	Medical management
Secondary Subject Heading:	Medical management, Health services research, Patient-centred medicine
Keywords:	Medication adherence, Meta-analysis, Behaviour change, Motivational Interviewing, Adherence intervention

A meta-analysis of cognitive-based behaviour change techniques as interventions to improve medication adherence

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Abstract

Objective

To describe and evaluate the use of cognitive-based behaviour change techniques as interventions to improve medication adherence.

Design

Systematic review and meta-analysis of interventions to improve medication adherence.

Data sources

Search of Medline, Embase, PsycINFO, CINAHL and The Cochrane Library databases from the earliest year to April 2013 without language restriction. References of included studies were also screened to identify further relevant articles.

Review methods

We used pre-defined criteria to select Randomised Controlled Trials (RCTs) describing a medication adherence intervention that used Motivational Interviewing (MI) or other-cognitive based techniques. Data were extracted and risk of bias was assessed by two independent reviewers. We conducted the meta-analysis using a random effects model and Hedges' *g* as the measure of effect size.

Results

We included 26 studies (5216 participants) in the meta-analysis. Interventions most commonly used MI but many used techniques such as aiming to increase the patient's confidence and sense of self-efficacy, encouraging support seeking behaviours and challenging negative thoughts, which were not specifically categorised. Interventions were most commonly delivered from community based settings by routine healthcare providers such as GPs and nurses. An effect size (95% CI) of 0.34 (0.23 to 0.46) was calculated and the overall effect of these interventions was statistically significant (p = <0.001). Adjustment for publication bias generated a more conservative estimate of summary effect size of 0.21 (0.08 to 0.33).No statistically significant differences were observed in a range of subgroup analyses.

Conclusion

Cognitive-based behaviour change techniques are effective interventions eliciting improvements in medication adherence that are likely to be greater than the behavioural and educational interventions largely used in current practice. Results of subgroup analyses indicated that these interventions can be delivered in routine healthcare settings by non-specialist healthcare providers.

Introduction

Estimates suggest that 30 to 50% of patients prescribed medications for chronic illnesses do not adhere to their prescribed medication regimen.[1] This non-adherence has been demonstrated to diminish treatment effect which can result in prolonged illness, additional investigations and prescribing that may otherwise have been unnecessary.[2] A link between poor adherence and an increased risk of mortality is also well established.[3] Consequently, the World Health Organisation (WHO) has described non-adherence as "a worldwide problem of striking magnitude" and a priority for healthcare researchers and policy makers.[1]

Despite both the magnitude and potential gravity of sub-optimal medication adherence, a gold standard intervention remains elusive; a recent Cochrane review highlighted the paucity of effective interventions in current practice.[4] Evidence suggests that complex, multi-faceted interventions, tailored to meet individual needs are most likely to be efficacious[4 5] which is intuitive given the complex, multi-stage process that is medication taking.

Non-adherent behaviour is traditionally categorised into unintentional and intentional. Unintentional non-adherence includes behaviours arising from forgetfulness, misunderstanding and confusion. Intentional non-adherence describes patient choice to deviate from the prescribed medication regimen. Unintentional and intentional non-adherence are not mutually exclusive thus an amalgam of these behaviours often exists in any one patient. An understanding of patient behaviour and its underpinning psychology plus the wealth of factors, both internal and external that may influence medication taking, is crucial to understanding how to change patient behaviour and thus improve medication adherence.[6]

Historically, adherence interventions have encompassed behaviour change techniques such as simplifying dosage regimens and providing adherence aids or education to address the practical issues of adherence in terms of knowing how and being able to take the medication as prescribed. Pooled data for such studies have demonstrated marginal effects[4] yet such interventions continue to form the cornerstone of routine healthcare provision.[2] These interventions may have particularly poor efficacy in cases of intentional non-adherence as the provision of persuasive advice may evoke further resistance to change.[7 8] Through an understanding of the challenges faced in changing behaviours and the motivation necessary to achieve change, novel, Cognitive-based Behaviour Change Techniques (CBCT) have emerged. These interventions aim to change a patient's behaviour by altering their thoughts, feelings, confidence or motivation to adhere. CBCT interventions can vary widely

in content such as incorporating techniques to enhance patient sense of self-efficacy, problem solve and increase motivation to adhere.

Motivational interviewing (MI) is one of the most widely recognised CBCT and is designed to facilitate behaviour change by resolving patient ambivalence about change.[9] It therefore primarily targets intentional non-adherence but also enables patients to reflect on any unintentional barriers to adherence and seek out solutions. Systematic reviews and meta-analyses have reported MI efficacy in facilitating health related behaviour change such as smoking cessation and alcohol withdrawal[10-16] but have not explored its effects on medication adherence. Adaptations of MI such as Behaviour Change Counselling (BCC)[17]additionally allow the facilitator to educate and advise thus application to both intentional and unintentional non-adherence may be effective.

Best practice guidelines state that evidence of intervention efficacy should ideally be pooled from literature in a systematic review or meta-analysis wherever possible to offer a robust and cohesive evidence base.[18] This study provides a systematic review and meta-analysis of MI and other cognitive-based techniques as interventions to improve medication adherence.

Methods

We used standard systematic review methods[18 19] and registered the study protocol (PROSPERO register reference CRD42011001721). Randomised Controlled Trials (RCTs) reporting an adherence intervention using MI and/or other cognitive-based techniques with medication adherence as an outcome measure were eligible for inclusion. All definitions of adherence such as percentage of doses taken over a given time period and percentage of patients achieving a specified adherence level were considered. All adherence measures were also considered including self-report and electronic monitoring. Where multiple measures were reported, the percentage of patients achieving a specified adherence level was selected as this was common to more studies.

Any intervention using some form of psychological technique to change a patient's adherence behaviour and their thoughts, feelings, confidence, or motivation towards adhering was defined as a cognitive-based technique. Studies examining adherence to medications for the treatment of addiction and/or mental health conditions were excluded as these interventions tend to be specific to these domains.

Search strategies

We developed a search strategy to avoid restriction to pre-determined terms such as 'motivational interviewing' as many of the techniques of interest are not classified using specific or consistent terms. MeSH terms were also used to enhance retrieval of relevant studies. Truncations (*), wild cards ($), hyphens and other relevant Boolean operators were used where permitted. Scoping searches were conducted prior to finalising the search strategy to ensure suitability of terms in generating a good coverage of relevant material.

We applied the search strategy (as shown in appendix one) to the MEDLINE, EMBASE, PsychINFO, and CINAHL, and databases in April 2013 without date or language restrictions. The reference lists of all screened full text articles were also used to identify further relevant articles.

Study selection and data extraction

Two researchers (CE and EP) independently screened titles and abstracts against the inclusion and exclusion criteria using a piloted abstract screening tool. Inter-reviewer agreement using Cohen's Kappa (K) was assessed for both the abstract and full text screening stage. The level of agreement was characterised using a qualitative scale.[20] Discrepancies were resolved by discussion between the two reviewers, and if necessary referral to a third independent reviewer (DB) until consensus was reached.

Data extraction was also undertaken by CE and EP, independently using piloted forms. Data extracted included study details (such as year and journal of publication, country and study design); study characteristics (including setting, population, delivery methods and personnel); intervention details (including intervention type, duration and principal components) and outcome details (including adherence assessment measure, data and definition). A list of intervention components was independently extracted from the articles verbatim by two reviewers. Grouping of similar components was undertaken by one reviewer and verified by a second reviewer."

Accuracy of data collected was verified by comparison of the forms completed by the two independent reviewers. In cases of discrepancy, consensus was agreed through discussion and where necessary, referral to a third independent reviewer (DB). For studies with missing data or ambiguities, the corresponding author was contacted for clarification.

Quality assessment

A quality assessment of all included studies was made using the Cochrane risk of bias tool.[18] The risk of bias was assessed in five domains deemed relevant to the included

studies: random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data and selective reporting. Performance bias (blinding of participants and personnel) was not included as the nature of the interventions meant that blinding of participants and personnel was impossible in almost all studies. None of the included studies were found to contain additional sources of potential bias not represented by the five included domains. The risk of bias for each study, in each of the five domains was classified as low, uncertain or high, as recommended in the guidelines.[18] The quality assessment process was undertaken independently by two reviewers, with consensus on the final risk classifications reached through discussion.

Data analysis

The meta-analysis was conducted using STATA® (version 12.1). Given the broad inclusion criteria, we anticipated including studies from different populations, with different diseases and which used different CBCT. We therefore explored heterogeneity via calculation of the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance.[21 22] A random effects model (DerSimonian-Laird method) was employed to calculate a pooled effect size (Hedges' *g*) and 95% confidence interval for the included studies.[23] Calculation of the effect size as Hedges' *g* (standardised difference in means) enabled adherence outcome measures of differing definition and measure, to be combined, transforming this data into a common metric. When standard deviation was missing, we estimated standard error of mean difference based on reported P values, means and the number of patients. Odds ratios were converted to standardised mean differences by using the formula SMD=lnOR*√3/π).[23]

Funnel plots were produced where appropriate to explore potential publication biases. STATA® (version 12.1) was used to conduct Egger's test[24] to test funnel plot asymmetry. We used the trim and fill method[25 26] to estimate a summary effect size after adjusting for asymmetric funnel plots.

Variables of interest in influencing the effect size and informing intervention design were determined a priori and the following subgroup analyses undertaken using a random effects meta-regression: intervention components, setting , delivery personnel, delivery method and exposure, disease area and risk of bias and outcome measure (objective compared to subjective)Objective outcome measures included electronic monitoring and pill counts, subject measures included all forms of self-report. Differences between subgroups were tested using STATA 'metareg' command for random-effects univariate meta-regression analysis.

Results

Study selection, characteristics and quality

Figure 1 shows the number of papers excluded at each stage of the review. Of the 442 abstracts screened, 84 studies passed the abstract screening stage with moderate agreement between the two reviewers (k = 0·57). Conflict in classifying an intervention as a CBCT accounted for 31.0% of discrepancies and was heavily influenced by a paucity of information in the abstracts .At the full text screening stage, agreement between the two independent reviewers was much higher, with a kappa value of 0.91, indicating almost perfect agreement. After examining 84 full-text articles, we included 26(31.0%) in the meta-analysis.

The main characteristics of the 26 included studies are summarised in Table 1. The studies provided a total sample size of 5216 participants Studies were primarily undertaken in the United States of America (USA) followed by the United Kingdom (UK),[27-29] Australia[30 31]and the Netherlands[32 33]. Dates of publication ranged from 1990 to 2012 with only two studies (7.7%) pre-dating 2000[28 34]. Ten (38.5%) were published within the last five years (2008-2013).

The most common condition for which medications were prescribed was HIV, accounting for 14 (53.8%) studies. Other studies concerned treatments for a range of conditions including asthma[32 34 35] diabetes[27 31] and hypertension[30 36] Just over half of the included studies(53.8%) described an intervention with a clearly defined CBCT; Motivational Interviewing (MI) was most commonly used and this was the case for 11 (42.3%) studies[30 31 36-44]. For 12 (46.2%) studies, a clearly defined CBCT such as MI could not be identified[32-35 45-52]. Instead, this group comprised of, multiple components such as 'providing education' or 'increasing patient knowledge' which was reported in nine (75.0%) (studies in this group. Other components included 'increasing self-efficacy' and 'developing or improving problem solving skills' each reported in six (50.0) studies and 'identifying and resolving adherence barriers' and 'increasing social support' also each reported in six (50.0%). Detailed information regarding the identified intervention components extracted from each study are provided as a supplementary table. The majority of interventions had multiple components.

Interventions were most commonly delivered in person, from community based settings and by routine healthcare providers such as nurses, pharmacists and general medical practitioners. 'Non-routine' healthcare providers were considered to be those such as

psychologists or psychotherapists, who would not ordinarily be involved in the patient's care in the absence of mental illness. The intervention period ranged from four (15·4%) studies reporting singular sessions, to six (23·1%) studies reporting multiple sessions over 12 months. The median (IQ) number of sessions over which interventions were delivered was5.0 (3.0 to 7.3) . The majority of interventions were delivered over a period of six months or less which was the case for 17 studies (65.4%). The comparison group was 'standard care' for all studies; for 13 studies (50.0%) standard care involved some form of technique to improve adherence such as education, encouragement or provision of adherence aids and in these studies, recipients of the intervention received further techniques such as MI.

Table 1: Characteristics of included studies in meta-analysis

Study	Study setting	Disease area	Intervention description*	Identified intervention components	Components received by control group	Sample size	Intervention delivery style (& personnel)	Intervention length (average)
Bailey et al 1990[34]	Hospital clinic, USA	Asthma	Comprehensive programme integrating a skills-orientated self-help workbook with one-to-one counselling & adherence-enhancing strategies.	Multiple components; non-specific techniques	Standard care; education via standardised set of pamphlets and routine physician encouragement	225	Telephone calls and in person (specialist)	240 minutes (4 x 60min sessions) over unknown period
Berger et al 2005[40]	Telephone calls to patients at home, USA	Multiple Sclerosis	Software supported intervention based on Transtheoretical model of change and MI	Motivational Interviewing (MI)	Standard care plus could telephone help line	367	Telephone calls (researcher)	9 sessions of unknown duration delivered over 3 months
Brown et al 2009[29]	Hospital clinic, UK	Epilepsy	Formation of III via completion of a self-administered questionnaire	Implementation Intention Interventions (III)	Standard care plus self-report questionnaires	69	Questionnaire completion (not in person)	One-off intervention of unknown duration
DiIorio et al 2003[41]	Community clinic, USA	HIV	One-to-one counselling sessions based on MI	Motivational Interviewing (MI)	Standard care; usual adherence education provided in the clinic	17	In person (routine HCP)	5 x 35 minutes sessions delivered over 12 months
DiIorio et al 2008[42]	Hospital clinic, USA	HIV	MI as individual counselling sessions	Motivational Interviewing (MI)	Standard care; usual (extensive) education provided at the clinic	213	Mostly in person with some telephone calls (routine HCP)	5 sessions of 35 minutes over 12 months
Farmer et al. 2012[27]	Community based clinic, UK	Type 2 diabetes	Brief intervention to elicit beliefs, resolve barriers and form 'if-then' plans.	If-then Planning (III)	Standard care plus additional clinic visits for blood tests	211	In person (clinic nurse)	One-off session lasting 30 minutes.
George et al 2010[30]	Community pharmacies, Australia and Tasmania	Hypertension	Community pharmacy intervention of one-to-one sessions, monitoring & medication review	Motivational Interviewing (MI)	Standard care	343	In person (routine HCP)	3 sessions of unknown duration over 6 months

Study	Study setting	Disease area	Intervention description*	Identified intervention components	Components received by control group	Sample size	Intervention delivery style (& personnel)	Intervention length (average)
Golin et al 2006[39]	Community clinic, USA	HIV	Multi-component MI based intervention.	Motivational Interviewing (MI)	General HIV information provided via audio tape, two one-to-one sessions and two mail shots.	117	In person (specialist)	2 sessions of unknown duration over 2 months
Hovell et al 2003[51]	Hospital clinic, USA	Tuberculosis	Adherence coaching involving interviewing, contingency contracting and shaping procedures	Multiple components; non-specific techniques	Standard care; routine advice at appointments	188	Telephone calls & in person (researcher)	12 sessions of 15-30 minutes over 6 months
Konkle-Parker et al. 2012[38]	Community based clinics and patients own homes, USA	HIV	Adherence intervention guided by the Information-Motivation-Behavioural Skills (IMB) model	Motivational Interviewing (MI)	Standard care; usual clinic appointments	36	Telephone calls and in person (nurse practitioner)	8 sessions over 24 weeks. Average overall duration 1h 30 minutes
Maneesriwongul et al 2012[37]	Hospital outpatients clinic & telephone calls to patients at home, Thailand	HIV	Motivational interviewing with counselling	Motivational Interviewing (MI)	Standard care; education and provision of leaflets at point of prescribing	60	Telephone calls & in person (researcher)	3 sessions approximately 30 minutes over a four week period
Murphy et al 2002[52]	Community based clinic, USA	HIV	Multi-component and multi-disciplinary intervention including behavioural strategies and cognitive behavioural therapy	Multiple components; non-specific techniques	Standard care; regular appointments with enquiries about adherence and an additional 30 minute appointment for those with problems where medication schedule is written down for them	33	In person (specialist)	5 sessions of unknown duration over 7 weeks
Ogedegbe et al 2008[36]	Community clinic, USA	Hypertension	Practice-based MI counselling	Motivational Interviewing (MI)	Standard care; usual appointments plus additional visits for MEMS downloads	160	In person (researcher)	4 sessions lasting 30-40 mins delivered over 12 months

Study	Study setting	Disease area	Intervention description*	Identified intervention components	Components received by control group	Sample size	Intervention delivery style (& personnel)	Intervention length (average)
Pradier et al 2003[50]	Hospital clinic, France	HIV	Educational & counselling intervention founded in the principles of motivational psychology and client-centred therapy	Multiple components; non-specific techniques	Standard care; routine follow up appointments	202	In person (routine HCP)	3 sessions of 45-60 minutes over 3 months
Put et al 2003[35]	Hospital clinic, Belgium	Asthma	Behavioural change intervention involving psycho-education with behavioural and cognitive techniques	Multiple components; non-specific techniques	Standard (no details provided)	23	In person (researcher)	360 hours (6 x 60 minutes sessions) over 3 months
Remien et al[49] 2005	Community based clinic, USA	HIV	Couples-based intervention grounded in Social action theory	Multiple components; non-specific techniques	Standard care; education at point of prescribing & follow up to check adherence & investigate/address underlying causes of any non-adherence	196	In person (routine HCP)	4 sessions of 45-60 minutes over 5 weeks
Safren et al 2001[44]	Community clinic, USA	HIV	Single session minimal treatment intervention using cognitive behavioural, motivational interviewing and problem solving techniques	Motivational Interviewing (MI)	Minimal contact intervention; daily diary used to record no. of pills prescribed & taken each day	53	In person (routine HCP)	One-off intervention of unknown duration
Sheeran et al 1999[28]	Visits to patients own home, UK	Vitamin Supplements	Formation of III via completion of a self-administered questionnaire	Implementation Intention Intervention (III)	Completion of same questionnaire but without formation of implementation intention	78	Questionnaire completion (not in person)	One-off intervention of unknown duration
Simoni et al. 2009[48]	Community based clinic & telephone calls to patient's at home, USA	HIV	Peer-led medication-related social support intervention.	Multiple-components; non-specific techniques	Standard care; education programme and social and health referrals as necessary	114	Group sessions and individualtelephone calls (peers)	18 sessions of unknown duration over 3 months

Study	Study setting	Disease area	Intervention description*	Identified intervention components	Components received by control group	Sample size	Intervention delivery style (& personnel)	Intervention length (average)
Smith et al 2003[47]	Community based research office, USA	HIV	Self-management intervention based on feedback of adherence performance & principles of social cognitive theory	Multiple components; non-specific techniques	Standard care; usual medication counselling, educational leaflets, scheduling support reminder lists & discussion of adherence strategies	17	In person (routine HCP)	Four sessions of unknown duration over 12 weeks
Solomon et al 2012[43]	Telephone calls to patients own home, USA	Osteoporosis	Telephone based counselling programme rooted in motivational interviewing	Motivational Interviewing (MI)	Standard care plus seven information mailings on osteoarthritis care	2087	Telephones calls (health educator)	8 sessions of 14 minutes over 12 months
Tuldra et al 2000[46]	Hospital clinic, Spain	HIV	Psycheducative intervention based on Self-efficacy theory	Multiple components; non-specific techniques	Standard care; normal clinical follow-up	77	Unknown (routine HCP)	7 sessions of unknown duration
Van Es et al 2001[32]	Hospital clinic, Netherlands	Asthma	Intervention programme to stimulate a positive attitude, increase social support and enhance self-efficacy.	Multiple components; non-specific techniques	Standard care; routine check-ups	67	In person (routine HCP)	7 sessions of 30-90 minutes over 12 months
Wagner et al 2006[45]	Community clinic, USA	HIV	Cognitive behavioural intervention with motivational components, based on the information-motivation-behavioural skills (IMB) model	Multiple components; non-specific techniques	Standard care practices for improving adherence; education, tailoring regimen, offering a pillbox, adherence checks & enquiries about side effects	135	In person (routine HCP)	5 sessions of 30-45 minutes over 48 weeks
Weber et al 2004[33]	Community, psychotherapy clinic, Netherlands	HIV	Cognitive behavioural intervention delivered by a psychotherapist.	Multiple components; non-specific techniques	Standard care (no details provided)	53	In person (specialist)	11 sessions of 45 minutes over 12 months

Study	Study setting	Disease area	Intervention description*	Identified intervention components	Components received by control group	Sample size	Intervention delivery style (& personnel)	Intervention length (average)
Williams et al. 2012[31]	Telephone calls and visits to patients own home, Australia	Diabetes	Multifactorial intervention consisting of self-monitoring of blood pressure, medicine review, educational DVDs and MI to support blood pressure control and optimal medication adherence	Motivational Interviewing (MI)	Standard care (no details provided)	75	In person and phone calls (specialist)	5 sessions, one of 89 minutes and 4 of an average of 11.75 minutes, over 3 months

* See supplementary table A for detailed breakdown of intervention components

Supplementary figures 1 and 2 show the results of the risk of bias assessment. Only Five (19.2%)studies[27 36 41 48 49] scored 'low risk' in all five bias categories. 19 (73.1%) were described as moderate overall risk, scoring 'low risk' in two to four of the categories and two (7.7%)[40 44] were described as 'high risk' scoring a low risk of bias in only one category. The most common source of bias was a lack of blinding of the outcome assessment; this is because the measure of adherence was frequently self-report. Self-report measures of adherence are commonly used but subject to patient bias. In the majority of cases the patients were not blind to their treatment group allocation and thus use of self-report measures leaves scope for bias.

Meta-analysis

26 RCTs were pooled to assess the effect of CBCT on medication adherence. Three studies showed non-significant negative effects on medication adherence but the remaining 23 studies all showed improvements in medication adherence with receipt of intervention. The effect size calculated for each study is summarised in table 2.

Random effects meta-analysis showed evidence that CBCTare associated with improved medication adherence. Figure 2 shows the forest plot for the 26 studies and exemplifies the tendency towards positive adherence effects with intervention. A pooled estimate of effect size (95% CI) (reported as Hedges' *g)* of 0·34 (0·23 to 0·46) was calculated when all studies were combined, although heterogeneity was high (I^2 = 68%, 95% CI: 52% to 79%).

The funnel plot produced was indicative of publication bias (as shown in figure 3) and so further explored using Egger's test which confirmed statistically significant funnel plot asymmetry (p= 0.005). The trim-and-fill technique was used to re-compute an effect size which accounted for this asymmetry, yielding a more conservative effect size estimate of 0.21 (0.08 to 0.33) (as shown in supplementary figure 3). This effect size suggests that CBCT elicit small but statistically significant improvements in medication adherence (p = 0.001)relative to standard care. According to data from six studies that used the percentage of prescribed dose taken, the pooled standard deviation of this outcome was 30.7%. Then a standardised mean difference of 0.205 (0.084 to 0.326) is corresponding to a difference of 6.3% (2.6% to 10.0%) between the intervention and the control group in the percentage of dose taken.

Table 2: Study outcomes for studies included in meta-analysis

Study	Sample size (intervention, control)	Adherence definition (assessment measure)	Extracted data			Effect size (Hedges's g) (95% CI)
			Intervention group	Control group	P-value	
Bailey et al 1990	225 (124, 101)	% of patients scored as adherent on all 6 items of a self-report scale (based on Morisky's self-reported scale)	Mean = 91.9	Mean = 61.7	0.001	0.44 (0.18 to 0.71)
Berger et al 2005	367 (172, 195)	% of patients discontinuing treatment by study endpoint (patient interview)	Mean = 98.8	Mean = 91.3	0.001	0.35 (0.14 to 0.55)
Brown et al 2009	69 (36, 33)	% of prescribed doses taken over a month (electronic monitoring)	Mean (SD) = 93.4 (12.3)	Mean (SD) = 79.1 (28.1)		0.66 (0.18 to 1.14)
Dilorio et al 2003	17 (8, 9)	Mean number of missed medicines in the last 30 days (self-report questionnaire)	Mean (SD) = 0.13 (0.35)	Mean (SD) = 0.98 (1.48)		0.73 (-0.21 to 1.67)
Dilorio et al 2008	213 (107, 106)	% of doses taken during intervention period (electronic monitoring)	Mean = 64	Mean = 55	0.09	0.23 (-0.04 to 0.50)
Farmer et al. 2012	211 (126, 85)	% of days during a 12 week period in which medication was taken correctly (electronic monitoring)	Mean (SD) = 77.4 (26.3)	Mean (SD) = 64.0 (30.8)	0.04	0.47 (0.20 to 0.75)
George et al 2010	343 (170, 173)	% of participants classed as adherent (Morisky self-report scale)	Mean = 72.2	Mean = 63.8	0.09	0.18 (-0.03 to 0.39)
Golin et al 2006	117 (59, 58)	% of prescribed doses taken take in month prior to study endpoint (CAS)	Mean (SD) = 76 (27)	Mean (SD) = 71 (27)		0.18 (-0.18 to 0.54)
Hovell et al 2003	188 (92, 96)	Cumulative number of doses taken over 9 months (patient interview)	Mean (SD) = 179.93 (57.01)	Mean (SD) = 150.98 (73.75)		0.44 (0.15 to 0.72)
Konkle-Parker et al. 2012	36 (21,15)	% of patients taking >90% of their medications in the last 3-4 weeks (prescription refill data)	Mean (SD) = 0.93 (0.23)	Mean (SD) = 0.92 (0.27)		0.04 (-0.61 to 0.69)
Maneesriwongul et al 2012	60 (30, 30)	Mean % of doses taken over last 4 weeks (self-report using visual analogue scale)	Mean (SD) = 97.1 (3.3)	Mean (SD) = 89.8 (5.6)		1.55 (0.98 to 2.12)
Murphy et al 2002	33 (17, 16)	% of doses taken during intervention period (self-report questionnaire)	Mean (SD) = 0.86 (0.33)	Mean (SD) = 0.83 (0.36)		0.09 (-0.58 to 0.75)
Ogedegbe et al 2008	160 (79, 81)	% of days during a two month period in which medication was taken correctly (electronic monitoring)	Mean = 56.9	Mean = 42.9	0.027	0.35 (0.04 to 0.66)
Pradier et al 2003	202 (123, 121)	% of patients deemed to be adherent (taking 100% of doses) (self-report questionnaire)	Mean = 75	Mean = 61	0.04	0.34 (0.02 to 0.65)

Put et al 2003	23 (12, 11)	Frequency of non-adherent behaviour over the last 3 months (self-report questionnaire)	Mean (SD) = 6.9 (1.2)	Mean (SD) = 8.1 (3.1)		0.50 (-0.30 to 1.30)
Remien et al 2005	196 (106, 109)	% of doses taken during previous 2 weeks (electronic monitoring)	Mean (SD) = 76 (27)	Mean (SD) = 60 (34)		0.52 (0.25 to 0.79)
Safren et al 2001	53 (28, 25)	% of prescribed doses taken over the last 2 weeks (self-report questionnaire)	Mean (SD) = 93 (22)	Mean (SD) = 94 (10)		-0.06 (-0.59 to 0.47)
Sheeran et al 1999	78 (38, 40)	Number of once daily doses missed over a 3 week period (self-report questionnaire)	Mean = 2.68	Mean = 4.85	0.05	0.45 (0.00 to 0.89)
Simoni et al. 2009	114 (57, 57)	% of doses taken over last seven days (electronic monitoring)	Mean (SD) = 32.3 (42.5)	Mean (SD) = 29.1 (39.7)		0.08 (-0.29 to 0.44)
Smith et al 2003	17 (8, 9)	% of participants taking ≥ 80% of their weekly doses (electronic monitoring)	Odds ratio = 7.8 (2.2 to 28.1)			1.08 (0.41 to 1.74)
Solomon et al 2012	2087 (1046, 1041)	Median % medication possession ratio (prescription refill data)	Median = 49 IQR = 7 to 88	Median = 41 IQR = 2 to 86	0.07	0.08 (-0.01 to 0.17)
Tuldra et al 2000	77 (36, 41)	% of patients with monthly adherence ≥ 95% (self-reported number of pills taken)	Mean = 94	Mean = 69	0.008	0.62 (0.16 to 1.07)
Van Es et al 2001	67 (58, 54)	Adherence score on self-report scale based on how often medication was taken (never-always)	Mean = 7.7	Mean = 6.7	0.05	0.48 (0.00 to 0.96)
Wagner et al 2006	135 (154, 76)	% of doses taken during intervention period (electronic monitoring)	Mean = 83.5	Mean = 86.4	0.57	-0.08 (-0.35 to 0.20)
Weber et al 2004	53 (29, 24)	% of patients with monthly adherence ≥ 95% (electronic monitoring)	Mean = 70.8	Mean = 50	0.014	0.69 (0.14 to 1.24)
Williams et al 2012	75 (36, 39)	% of doses taken during intervention period (pill counts	Mean = 58.4	Mean = 66	0.162	-0.32 (-0.77 to 0.13)

Sub-group analyses via meta-regression

Table 3 summarises the results of the subgroup analyses to explore variation in effect size for the pre-determined variables. The regression co-efficient is the difference in pooled Hedges' g between the two subgroups compared. A co-efficient >0 indicates that studies in subgroup-A reported greater treatment effects that those in subgroup-B. Interventions delivered from hospital settings were associated with greater treatment effect compared with interventions in community or other settings (difference 0.27, 95% CI 0.01 to 0.54, P=0.043). Differences in effect size between subgroups were statistically non-significant in all other cases. However, the subgroup analyses may have failed to detect important differences between subgroups because of the small number of studies included.

Table 3: Summary of sub-group analyses

Variable	Sub-group-A vs. subgroup-B	No. of studies (no. of participants) in each sub-group	Co-efficient (95% CI)	P-value
Intervention setting	Hospital vs. community	9 (1124) Vs. 17 (4092)	0.27 (0.01 to 0.54)	0.043
Disease area	HIV vs. other conditions	14 (1323) Vs. 12 (3893)	0.05 (-0.23 to 0.33)	0.72
Intervention components	MI vs. no MI component	11 (3538) Vs. 15 (1678)	-0.17 (-0.44 to 0.09)	0.193
Intervention delivery method	Entirely in person vs. other methods	15 (1663) Vs. 11 (3553)	-0.03 (-0.31 to 0.25)	0.841
	Entirely over the telephone vs. other methods	3 (2679) Vs. 23 (2537)	-0.16 (-0.59 to 0.26)	0.442
	Both in person and telephone vs. other	7 (775) Vs. 19 (4441)	-0.05 (-0.27 to 0.37)	0.744
Intervention delivery personnel	Routine HCP vs. others	12 (1567) Vs. 14 (3649)	-0.02 (-0.30 to 0.26)	0.888
	Specialist vs. others	5 (503) Vs. 21 (4713)	-0.14 (-0.51 to 0.22)	0.419
Intervention exposure	Four sessions or fewer vs. five sessions or more	12 (1731) Vs. 14 (3485)	0.22 (-0.04 to 0.48)	0.095
Control group type	Explicit active controls vs. usual care (no adherence enhancing strategies)	13 (3683) Vs. 13 (1533)	0.09 (-0.18 to 0.37)	0.493
Risk of bias	Outcome assessment blinding vs. no outcome assessment blinding	15 (3555) Vs. 11 (1661)	0.05 (-0.24 to 0.33)	0.736
Outcome measures	Objective vs. subjective measured outcomes	14 (3850) Vs. 12 (1366)	-0.16 (-0.44 to 0.11)	0.225

Discussion

Principal findings

Receipt of a cognitive-based behavioural adherence intervention was associated with small but statistically significant improvements in medication adherence. Heterogeneity was high and notable publication bias was identified. However, techniques have been used to account for these biases resulting in a more conservative summary effect size of 0.21 (95% CI: 0.08 to 0.33; P=0.001).

In half of the included studies, the standard care received by the control group explicitly involved some form of 'adherence enhancing strategy' such as provision of education, monitoring or review. Such strategies form the mainstay of current medication adherence interventions and so our research suggests that CBCT may be able to elicit adherence benefits beyond the techniques used in current practice.

The majority of interventions were complex and multifaceted, thus subgroup analysis to explore whether this is associated with greater effect could not be undertaken. The sub-group analyses performed revealed that the effect size is greater when interventions were delivered in the hospital setting compared with community, but not influenced by other variables such as the type of CBCT, delivery method and personnel or duration. Further work is necessary to explore the effect of setting on effect size.

Comparison with other studies

In 2003, Peterson *et al.* conducted a meta-analysis of educational and behavioural interventions to improve medication adherence in a range of illnesses.[53] The included studies were all RCTs delivered over similar time periods to those included in our study. The educational components and behavioural components such as changes in dosing schedule and reminders examined by Peterson *et al.* closely mirror those utilised in the studies from our meta-analysis which used control groups with 'active standard care'. Peterson *et al.* reported a correlation coefficient (*r*) equivalent to a Cohen's *d* effect size of 0·16 (0·08, 0·24). For our study, the effect size for all studies, when adjusting for publication bias and reported as Hedges' *g* was 0.20 (0.08, 0.33). This suggests that inclusion of CBCT, strengthens the adherence improvements gained, if only marginally. Moreover, Peterson *et al.* report publication bias observed from a funnel plot of their included studies, but have not made allowances for this bias via re-computed effect sizes. Their Cohen's *d* value of 0.16 is likely exaggerated by the noted publication bias and thus infers that the true difference in effect size between the two meta-analyses may be greater.

An effect size (Hedges' *g*) of 0.25 (95% CI 0.07, 0.42) for studies using MI was calculated, compared with an effect size of 0.41 (95% CI 0.278 to 0.541) for non-MI interventions. After adjusting for bias, the estimated Hedges' g was 0.137 (95% CI -0.067 to 0.341) for studies

using MI and 0.356 (95% CI 0.223 to 0.489) for studies using non-MI interventions. These estimated effect sizes closely match the effect size calculated when MI is used as a behavioural intervention in other healthcare domains[14] and thus represents novel evidence for the wider application of MI techniques beyond the treatment of substance abuse and gambling.

Strengths and weaknesses of our work

This study represents the first meta-analysis of MI and other CBCT as medication adherence interventions and has been undertaken with methodological rigour and in accordance with published guidance.[18] A notable strength of this work is the robust methodological techniques that have been applied to provide an estimate of effect size which accounts for publication biases and thus greater confidence can be placed in the estimate. The work is also strengthened by restriction to RCTs.

Whilst moderate agreement in abstract screening may be lower than ideal, this is largely attributable to paucity of detail reported in abstracts and complexities in intervention definitions which are known to be problematic in this domain.[11-13] The conservative approach to abstract screening prevented study exclusion if disagreement was associated with insufficient information and thus prevented exclusion in error. Heterogeneity between the included studies was high with an I^2 value of 68% (95% CI: 52% to 79%) and thus raises the question as to whether the studies were sufficiently comparable to warrant pooling in a meta-analysis. Whilst we defined our inclusion criteria to ensure studies were as similar as possible (i.e. all using a CBCT), heterogeneity was expected as other factors such as the populations and disease states studied were more difficult to control for. Interestingly, the largest study had a small standardized group difference compared to most of the other studies which contributed substantially to the heterogeneity.[43] Furthermore, results from all but three of the studies indicate positive effects of the intervention. Aside from these between study differences, the actual interventions were variable, as were the definitions of adherence and assessment tools used. The differences between subgroups were statistically non-significant in terms of disease area, intervention components, delivery methods, delivery personnel, intensity, usual care and risk of bias. However, the statistical power was limited by the small number of studies included in the subgroup analyses. The analyses may therefore have failed to detect some important subgroup differences.

Despite these numerous between study differences, the core of each intervention was the use of a CBCT to improve medication adherence which was comparable across all studies

and thus we would argue that data pooling irrespective of heterogeneity was both intuitive and meaningful.

We have established that receipt of a cognitive-based behavioural medication adherence intervention is likely to elicit small improvements in medication adherence, but the clinical relevance and impact of this improvement remains unknown. Based on mean adherence rates in the control groups, mean standard deviations and the effect size calculated, it has been possible to estimate the increase in percentage of doses taken for the intervention groups. Based on the adjusted Hedges' *g* value of 0.205 (0.084 to 0.326), receipt of a CBCT improved adherence (% of doses taken) by 6.29% (2.58% to 10.0%). For some medications, a 6% increase in the percentage of doses taken may not be of clinical relevance. However, for other medications such as antiretroviral therapy for HIV which requires very high levels of adherence or anti-epileptic therapies with narrow therapeutic windows, a 6% increase in adherence may have notable clinical relevance. Whilst many included studies included data on clinical outcomes, pooling of this data from a diverse range of studies was not possible.

Implications

Motivational and CBCT can seemingly be delivered effectively by routine healthcare professionals, in both primary and secondary care settings, with efficacy applicable to a range of diseases. Efficacy was not related to intervention duration or follow-up period. Interestingly, the results also suggest that these interventions can be delivered via telephone or face-to-face with comparable efficacy. These are valuable traits for an adherence intervention which could be adaptable to a wide range of settings and amenable to tailoring to meet individual need.

The flexibility and adaptability of these techniques coupled with their frequent simplicity means that practitioners may wish to consider incorporation of these techniques into their consultations when faced with the need to facilitate medication related behaviour changes.

Recommendations and conclusions

Further investigation of these techniques as medication adherence interventions is warranted in order to further elucidate the characteristics most strongly associated with efficacy. Studies to determine both patient and healthcare practitioner acceptability of these techniques is also necessary to establish their role in routine healthcare.

Article summary

Article focus

- Medication non-adherence is widespread and represents a notable barrier to achieving optimal effects from therapeutic intervention.
- Despite the magnitude and consequences of non-adherence, a gold standard intervention to improve it remains elusive.
- Cognitive-based behaviour change techniques may represent a useful tool in improving medication adherence but their use in this domain had not been established using meta-analytic techniques.

Key messages

- Cognitive-based behaviour change techniques are effective interventions for improving medication adherence and capable of eliciting improvements in adherence beyond those achieved with educational and behavioural interventions which form the mainstay of current practice
- Cognitive-based behaviour change techniques can be effectively delivered by routine healthcare providers. Brief interventions are seemingly effective too.
- Health care providers may wish to consider incorporation of these techniques into their medication adherence consultations

Strengths and limitations of this study

- The studies pooled in this meta-analysis are restricted to RCTs which strengthens their robustness.
- Techniques to account for publication bias have been utilised to provide a conservative effect size estimate offering robustness to our estimate
- Notable heterogeneity was reported when studies were combined which may be a limitation.

Declaration of competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgements

CE would like to acknowledge Estelle Payerne for her invaluable contributions as the second reviewer for abstract screening and data extraction. CE would also like to acknowledge David Wright and John Wood for their comments on the protocol design, data analysis and methods of dissemination, and Steven Watson for his on-going technical support in using the meta-analysis software and comments regarding data interpretation

Funding

This research has been supported by a PhD studentship awarded by the Dean of Science at the University of East Anglia.

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A meta-analysis of cognitive-based behaviour change ~~based~~ techniques as interventions to improve medication adherence

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Keywords: Medication adherence, Motivational Interviewing, Meta-analysis, Behaviour change, Adherence intervention

~~Word count: 3051~~

Abstract

Objective

To describe and evaluate the use of cognitive-based behaviour change techniques as interventions to improve medication adherence.

Design

Systematic review and meta-analysis of interventions to improve medication adherence.

Data sources

Search of Medline, Embase, PsycINFO, CINAHL and The Cochrane Library ~~and The National Electronic Library for Medicines (NELM)~~ databases from the earliest year to ~~October 2012~~April 2013 without language restriction. References of included studies were also screened to identify further relevant articles.

Review methods

We used pre-defined criteria to select Randomised Controlled Trials (RCTs) describing a medication adherence intervention that used Motivational Interviewing (MI) or other-cognitive based techniques. Data were extracted and risk of bias was assessed by two independent reviewers. We conducted the meta-analysis using a random effects model and Hedges' *g* as the measure of effect size.

Results

We included 2~~6~~3 studies (5216 ~~4855~~participants) in the meta-analysis. Interventions most commonly used MI but many used ~~more generalised~~ techniques such as aiming to increase the patient's confidence and sense of self-efficacy, encouraging support seeking behaviours and challenging negative thoughts, which were not specifically categorised. Interventions were most commonly delivered from community based settings by routine healthcare providers such as GPs and nurses. An effect size (95% CI) of 0.3~~4~~6 (0.23 to 0.4~~6~~8)~~,~~ was calculated ~~meaning~~ and the overall effect of these interventions wa~~i~~s statistically significant (p = <0.001). Adjustment for publication bias generated a more conservative~~robust~~ estimate of summary effect size of 0.21~~20~~ (0.0~~8~~7 to 0.33).No statistically significant differences were observed in a range of subgroup analyses.

Conclusion

Cognitive-based behaviour change techniques are effective interventions eliciting improvements in medication adherence that are likely to be greater than the behavioural and educational interventions largely used in current practice. Results of subgroup analyses indicated that these interventions can be delivered in routine healthcare settings by ~~routine~~ non-specialist healthcare providers.

~~Abstract word count: 279~~

Introduction

Estimates suggest that 30 to 50% of patients prescribed medications for chronic illnesses do not adhere to their prescribed medication regimen.[1] This non-adherence has been demonstrated to diminish treatment effect which can result in prolonged illness, additional investigations and prescribing that may otherwise have been unnecessary.[2] A link between poor adherence and an increased risk of mortality is also well established.[3] Consequently, the World Health Organisation (WHO) has described non-adherence as "a worldwide problem of striking magnitude" and a priority for healthcare researchers and policy makers.[1]

Despite both the magnitude and potential gravity of sub-optimal medication adherence, a gold standard intervention remains elusive; a recent Cochrane review highlighted the paucity of effective interventions in current practice.[4] Evidence suggests that complex, multi-faceted interventions, tailored to meet individual needs are most likely to be efficacious[4 5] which is intuitive given the complex, multi-stage process that is medication taking.

Non-adherent behaviour is traditionally categorised into unintentional and intentional. Unintentional non-adherence includes behaviours arising from forgetfulness, misunderstanding and confusion. Intentional non-adherence describes patient choice to deviate from the prescribed medication regimen. Unintentional and intentional non-adherence are not mutually exclusive thus an amalgam of these behaviours often exists in any one patient. An understanding of patient behaviour and its underpinning psychology plus the wealth of factors, both internal and external that may influence medication taking, is crucial to understanding how to change patient behaviour and thus improve medication adherence.[6]

Historically, adherence interventions have encompassed behaviour change techniques such as simplifying dosage regimens and providing adherence aids or education to address the practical issues of adherence in terms of knowing how and being able to take the medication as prescribed. Pooled data for such studies have demonstrated marginal effects[4] yet such interventions continue to form the cornerstone of routine healthcare provision.[2] These interventions may have particularly poor efficacy in cases of intentional non-adherence as the provision of persuasive advice may evoke further resistance to change.[7 8] Through an understanding of the challenges faced in changing behaviours and the motivation necessary

to achieve change, novel, Cognitive-based Behaviour Change Techniques (CBCT) have emerged. These interventions aim to change a patient's behaviour by altering their thoughts, feelings, confidence or motivation to adhere. CBCT interventions can vary widely in content such as incorporating techniques to enhance patient sense of self-efficacy, problem solve and increase motivation to adhere.

Motivational interviewing (MI) is one of the most widely recognised ~~cognitive-based techniques~~CBCT and is designed to facilitate behaviour change by resolving patient ambivalence about change.[9] It therefore primarily targets intentional non-adherence but also enables patients to reflect on any unintentional barriers to adherence and seek out solutions. Systematic reviews and meta-analyses have reported MI efficacy in facilitating health related behaviour change such as smoking cessation and alcohol withdrawal[10-16] but have not explored its effects on medication adherence. Adaptations of MI such as Behaviour Change Counselling (BCC)[17]additionally allow the facilitator to educate and advise thus application to both intentional and unintentional non-adherence may be effective.

Best practice guidelines state that evidence of intervention efficacy should ideally be pooled from literature in a systematic review or meta-analysis wherever possible to offer a robust and cohesive evidence base.[18] This study provides a systematic review and meta-analysis of MI and other cognitive-based techniques as interventions to improve medication adherence.

Methods

We used standard systematic review methods[18 19] and registered the study protocol (PROSPERO register reference CRD42011001721). Randomised Controlled Trials (RCTs) reporting an adherence intervention using MI and/or other cognitive-based techniques with medication adherence as an outcome measure were eligible for inclusion. All definitions of adherence such as percentage of doses taken over a given time period and percentage of patients achieving a specified adherence level were considered. All adherence measures were also considered including self-report and electronic monitoring. Where multiple measures were reported, the percentage of patients achieving a specified adherence level was selected as this was common to more studies.

Any intervention using some form of psychological technique to change a patient's adherence behaviour and their thoughts, feelings, confidence, or motivation towards adhering was defined as a cognitive-based technique. Studies examining adherence to

medications for the treatment of addiction and/or mental health conditions were excluded as these interventions tend to be specific to these domains.

Search strategies

We developed a search strategy to avoid restriction to pre-determined terms such as 'motivational interviewing' as many of the techniques of interest are not classified using specific or consistent terms. MeSH terms were also used to enhance retrieval of relevant studies. Truncations (*), wild cards ($), hyphens and other relevant Boolean operators were used where permitted. Scoping searches were conducted prior to finalising the search strategy to ensure suitability~~suitably~~ of terms in generating a good coverage of relevant material.

We applied the search strategy (as shown in appendix one) to the MEDLINE, EMBASE, PsychINFO, and CINAHL, and ~~The National Electronic Library for Medicines (NELM)~~ databases in April 2013 ~~October 2012~~ without date or language restrictions. The reference lists of all screened full text articles were also used to identify further relevant articles.

Study selection and data extraction

Two researchers (CE and EP) independently screened titles and abstracts against the inclusion and exclusion criteria using a piloted abstract screening tool. Inter-reviewer agreement using Cohen's ~~weighted~~ Kappa (K) was assessed for both the abstract ~~screening stage~~and full text screening stage. T~~t~~he level of agreement was characterised using a qualitative scale.[20] Discrepancies were resolved by discussion between the two reviewers, and if necessary referral to a third independent reviewer (DB) until consensus was reached.

Data extraction was also undertaken by CE and EP, independently using piloted forms. Data extracted included study details (such as year and journal of publication, country and study design); study characteristics (including setting, population, delivery methods and personnel); intervention details (including intervention type, duration and principal components) and outcome details (including adherence assessment measure, data and definition). A list of intervention components was independently extracted from the articles verbatim by two reviewers. Grouping of similar components was undertaken by one reviewer and verified by a second reviewer."

Accuracy of data collected was verified by comparison of the forms completed by the two independent reviewers. In cases of discrepancy, consensus was agreed through discussion

and where necessary, referral to a third independent reviewer (DB). For studies with missing data or ambiguities, the corresponding author was contacted for clarification.

Quality assessment

A quality assessment of all included studies was made using the Cochrane risk of bias tool.[18] The risk of bias was assessed in five domains deemed relevant to the included studies: random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data and selective reporting. Performance bias (blinding of participants and personnel) was not included as the nature of the interventions meant that blinding of participants and personnel was impossible in almost all studies. None of the included studies were found to contain additional sources of potential bias not represented by the five included domains. The risk of bias for each study, in each of the five domains was classified as low, uncertain or high, as recommended in the guidelines.[18] The quality assessment process was undertaken independently by two reviewers, with consensus on the final risk classifications reached through discussion.

Data analysis

The meta-analysis was conducted using STATA® (version 12.1). Given the broad inclusion criteria, we anticipated including studies from different populations, with different diseases and which used different ~~cognitive-based techniques~~CBCT. We therefore explored heterogeneity via calculation of theI^2statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance.[21 22] A random effects model (DerSimonian-Laird method) was employed to calculate a pooled effect size (Hedges' *g*) and 95% confidence interval for the included studies.[23] Calculation of the effect size as Hedges' *g* (standardised difference in means) enabled ~~continuous~~ adherence outcome measures of differing definition and measure, to be combined, transforming this data into a common metric. When standard deviation was missing, we estimated standard error of mean difference based on reported P values, means and the number of patients. Odds ratios were converted to standardised mean differences by using the formula SMD=lnOR*√3/π).[23]

Funnel plots were produced where appropriate to explore potential publication biases. STATA® (version 12.1) was used to conduct Egger's test[24] to test funnel plot asymmetry. ~~,and~~We used the trim and fill method~~s~~[25 26] to estimate a summary effect size after adjusting for asymmetric funnel plots. ~~These techniques enabled calculation of a pooled effect size that accounted for biases.~~

Variables of interest in influencing the effect size and informing intervention design were determined a priori and the following subgroup analyses undertaken using a random effects meta-regression: intervention components ~~type~~, setting ~~location~~, delivery personnel~~provider~~, delivery method and exposure, disease area ~~state~~and risk of bias ~~methodological quality~~ and outcome measure (objective compared to subjective). Objective outcome measures included electronic monitoring and pill counts, subject measures included all forms of self-report. Differences between subgroups were tested using STATA 'metareg' command for random-effects univariate meta-regression analysis.

Results

Study selection, characteristics and quality

Figure 1 shows the number of papers excluded at each stage of the review. Of the 4~~40~~2 abstracts screened, 8~~458~~ studies passed the abstract screening stage with moderate agreement between the two reviewers (k = 0·57~~15~~). Conflict in classifying an intervention as a ~~cognitive based technique~~CBCT accounted for 31.0~~55~~ 1% of discrepancies and was heavily influenced by a paucity of information in the abstracts. At the full text screening stage, agreement between the two independent reviewers was much higher, with~~as~~ a kappa value of 0.91, indicating~~ve of~~ almost perfect agreement. After examining 8~~458~~ full-text articles, we included 2~~63~~(31.0~~39.7~~%) in the meta-analysis.

The main characteristics of the 2~~63~~ included studies are summarised in Table 1. The studies provided a total sample size of 52164~~855~~ participants. Studies were primarily undertaken in the United States of America (USA) followed by the United Kingdom (UK) [27-29] Australia [30 31] and the Netherlands [32 33]. Dates of publication ranged from 1990 to 2012 with only two studies (7.7%) pre-dating 2000 [28 34]. Ten (38.5%) were published within the last five years (2008-2013).

The most common condition for which medications were prescribed was HIV, accounting for 14 (53.8%) studies. Other studies concerned treatments for a range of conditions including asthma [32 34 35] diabetes [27 31] and hypertension [30 36]. ~~Studies were primarily undertaken in the United States of America (USA) and this accounted for 15 (57.7%) studies. The United Kingdom (UK) was the setting for three (11.5%) studies[27-29] and Australia[30~~31~~] and the Netherlands[32~~33~~] each had two (7.7%) studies. Single studies came from Thailand[34], France[35], Belgium[36] and Spain[37]. Dates of publication ranged from 1990 to 2012. Almost all of the studies were published after the year 2000 with only two (7.7%) pre-dating this[28~~38~~]. Ten (38.5%) were published within the last five years (2008-2013).~~

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~~The most common condition for which medications were prescribed was HIV, accounting for 14 (53.8%) studies. Other studies concerned treatments for a range of conditions including three (11.5%) studieswhich focussed on asthma[32,36,38]. Adherence to medications for diabetes[27,31] and hypertension[30,39] each accounted for two (7.7%)studies and the were singular studies considering adherence in multiple sclerosis[40], epilepsy[29], tuberculosis[41], osteoporosis[42] and vitamin supplementation[28].~~

Just over half of the included studies(53.8~~2.2~~%) described an intervention with a clearly defined ~~cognitive-based technique~~CBCT; Motivational Interviewing (MI) was most commonly used and this was the case for 1~~0~~ (42.3~~3.5~~%) studies[30 31 36-44]. For 1~~2~~ (46.2~~7.8~~%) studies, a clearly defined ~~cognitive-based technique~~CBCT such as MI could not be identified[32-35 45-52]. Instead, this group comprised of ~~non-specific~~, multiple components such as 'providing education' or 'increasing patient knowledge' which was reported in nine (75.0%)~~10~~ (~~90.9%~~) studies in this group. Other components included 'increasing self-efficacy' and 'developing or improving problem solving skills' each reported in six (50.0~~4.5%~~) studies and 'identifying and resolving adherence barriers' and 'increasing social support' also each reported in six (50.0%)~~five (45.5%) studies~~. Detailed information regarding the identified intervention components extracted from each study are provided as a supplementary table. The majority of interventions had multiple components.

Interventions were most commonly delivered in person, from community based settings and by routine healthcare providers such as nurses, pharmacists and general medical practitioners. 'Non-routine' healthcare providers were considered to be those such as psychologists or psychotherapists, who would not ordinarily be involved in the patient's care in the absence of mental illness. The intervention period ranged from four (15·4%) studies reporting singular sessions, to six (23·1%) studies reporting multiple sessions over 12 months. The median (IQ) number of sessions over which interventions were delivered was5.0 (3.0 to 7.3) ~~4·0 (3.0 to 7.0)~~. The majority of interventions were delivered over a period of six months or less which was the case for 1~~7~~4 studies (65.4~~3.6~~%). The comparison group was 'standard care' for all studies; for 1~~3~~2 studies (50.0~~2.2~~%) standard care involved some form of technique to improve adherence such as education, encouragement or provision of adherence aids and in these studies, recipients of the intervention received further techniques such as MI.

Table 1: Characteristics of included studies in meta-analysis

Study	Study setting	Disease area	Intervention description*	Identified intervention components	Components received by control group	Sample size	Intervention delivery style (& personnel)	Intervention length (average)
Bailey et al 1990[34]	Hospital clinic, USA	Asthma	Comprehensive programme integrating a skills-orientated self-help workbook with one-to-one counselling & adherence-enhancing strategies.	Multiple components; non-specific techniques	Standard care; education via standardised set of pamphlets and routine physician encouragement	225	Telephone calls and in person (specialist)	240 minutes (4 x 60min sessions) over unknown period
Berger et al 2005[40]	Telephone calls to patients at home, USA	Multiple Sclerosis	Software supported intervention based on Transtheoretical model of change and MI	Motivational Interviewing (MI)	Standard care plus could telephone help line	367	Telephone calls (researcher)	9 sessions of unknown duration delivered over 3 months
Brown et al 2009[29]	Hospital clinic, UK	Epilepsy	Formation of III via completion of a self-administered questionnaire	Implementation Intention Interventions (III)	Standard care plus self-report questionnaires	69	Questionnaire completion (not in person)	One-off intervention of unknown duration
Dilorio et al 2003[41]	Community clinic, USA	HIV	One-to-one counselling sessions based on MI	Motivational Interviewing (MI)	Standard care; usual adherence education provided in the clinic	17	In person (routine HCP)	5 x 35 minutes sessions delivered over 12 months
Dilorio et al 2008[42]	Hospital clinic, USA	HIV	MI as individual counselling sessions	Motivational Interviewing (MI)	Standard care; usual (extensive) education provided at the clinic	213	Mostly in person with some telephone calls (routine HCP)	5 sessions of 35 minutes over 12 months
Farmer et al. 2012[27]	Community based clinic, UK	Type 2 diabetes	Brief intervention to elicit beliefs, resolve barriers and form 'if-then' plans.	If-then Planning (III)	Standard care plus additional clinic visits for blood tests	211	In person (clinic nurse)	One-off session lasting 30 minutes.
George et al 2010[30]	Community pharmacies, Australia and Tasmania	Hypertension	Community pharmacy intervention of one-to-one sessions, monitoring & medication review	Motivational Interviewing (MI)	Standard care	343	In person (routine HCP)	3 sessions of unknown duration over 6 months

Study	Study setting	Disease area	Intervention description*	Identified intervention components	Components received by control group	Sample size	Intervention delivery style (& personnel)	Intervention length (average)
Golin et al 2006[39]	Community clinic, USA	HIV	Multi-component MI based intervention.	Motivational Interviewing (MI)	General HIV information provided via audio tape, two one-to-one sessions and two mail shots.	117	In person (specialist)	2 sessions of unknown duration over 2 months
Hovell et al 2003[51]	Hospital clinic, USA	Tuberculosis	Adherence coaching involving interviewing, contingency contracting and shaping procedures	Multiple components; non-specific techniques	Standard care; routine advice at appointments	188	Telephone calls & in person (researcher)	12 sessions of 15-30 minutes over 6 months
Konkle-Parker et al. 2012[38]	Community based clinics and patients own homes, USA	HIV	Adherence intervention guided by the Information-Motivation-Behavioural Skills (IMB) model	Motivational Interviewing (MI)	Standard care; usual clinic appointments	36	Telephone calls and in person (nurse practitioner)	8 sessions over 24 weeks. Average overall duration 1h 30 minutes
Maneesriwongul et al 2012[37]	Hospital outpatients clinic & telephone calls to patients at home, Thailand	HIV	Motivational interviewing with counselling	Motivational Interviewing (MI)	Standard care; education and provision of leaflets at point of prescribing	60	Telephone calls & in person (researcher)	3 sessions approximately 30 minutes over a four week period
Murphy et al 2002[52]	Community based clinic, USA	HIV	Multi-component and multi-disciplinary intervention including behavioural strategies and cognitive behavioural therapy	Multiple components; non-specific techniques	Standard care; regular appointments with enquiries about adherence and an additional 30 minute appointment for those with problems where medication schedule is written down for them	33	In person (specialist)	5 sessions of unknown duration over 7 weeks
Ogedegbe et al 2008[36]	Community clinic, USA	Hypertension	Practice-based MI counselling	Motivational Interviewing (MI)	Standard care; usual appointments plus additional visits for MEMS downloads	160	In person (researcher)	4 sessions lasting 30-40 mins delivered over 12 months

Study	Study setting	Disease area	Intervention description*	Identified intervention components	Components received by control group	Sample size	Intervention delivery style (& personnel)	Intervention length (average)
Pradier et al 2003[50]	Hospital clinic, France	HIV	Educational & counselling intervention founded in the principles of motivational psychology and client-centred therapy	Multiple components; non-specific techniques	Standard care; routine follow up appointments	202	In person (routine HCP)	3 sessions of 45-60 minutes over 3 months
Put et al 2003[35]	Hospital clinic, Belgium	Asthma	Behavioural change intervention involving psycho-education with behavioural and cognitive techniques	Multiple components; non-specific techniques	Standard (no details provided)	23	In person (researcher)	360 hours (6 x 60 minutes sessions) over 3 months
Remien et al[49] 2005	Community based clinic, USA	HIV	Couples-based intervention grounded in Social action theory	Multiple components; non-specific techniques	Standard care; education at point of prescribing & follow up to check adherence & investigate/address underlying causes of any non-adherence	196	In person (routine HCP)	4 sessions of 45-60 minutes over 5 weeks
Safren et al 2001[44]	Community clinic, USA	HIV	Single session minimal treatment intervention using cognitive behavioural, motivational interviewing and problem solving techniques	Motivational Interviewing (MI)	Minimal contact intervention; daily diary used to record no. of pills prescribed & taken each day	53	In person (routine HCP)	One-off intervention of unknown duration
Sheeran et al 1999[28]	Visits to patients own home, UK	Vitamin Supplements	Formation of III via completion of a self-administered questionnaire	Implementation Intention Intervention (III)	Completion of same questionnaire but without formation of implementation intention	78	Questionnaire completion (not in person)	One-off intervention of unknown duration
Simoni et al. 2009[48]	Community based clinic & telephone calls to patient's at home, USA	HIV	Peer-led medication-related social support intervention.	Multiple-components; non-specific techniques	Standard care; education programme and social and health referrals as necessary	114	Group sessions and individualtelephone calls (peers)	18 sessions of unknown duration over 3 months

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Study	Study setting	Disease area	Intervention description*	Identified intervention components	Components received by control group	Sample size	Intervention delivery style (& personnel)	Intervention length (average)
Smith et al 2003[47]	Community based research office, USA	HIV	Self-management intervention based on feedback of adherence performance & principles of social cognitive theory	Multiple components; non-specific techniques	Standard care; usual medication counselling, educational leaflets, scheduling support reminder lists & discussion of adherence strategies	17	In person (routine HCP)	Four sessions of unknown duration over 12 weeks
Solomon et al 2012[43]	Telephone calls to patients own home, USA	Osteoporosis	Telephone based counselling programme rooted in motivational interviewing	Motivational Interviewing (MI)	Standard care plus seven information mailings on osteoarthritis care	2087	Telephones calls (health educator)	8 sessions of 14 minutes over 12 months
Tuldra et al 2000[46]	Hospital clinic, Spain	HIV	Psycheducative intervention based on Self-efficacy theory	Multiple components; non-specific techniques	Standard care; normal clinical follow-up	77	Unknown (routine HCP)	7 sessions of unknown duration ~~No details provided~~
Van Es et al 2001[32]	Hospital clinic, Netherlands	Asthma	Intervention programme to stimulate a positive attitude, increase social support and enhance self-efficacy.	Multiple components; non-specific techniques	Standard care; routine check-ups	67	In person (routine HCP)	7 sessions of 30-90 minutes over 12 months
Wagner et al 2006[45]	Community clinic, USA	HIV	Cognitive behavioural intervention with motivational components, based on the information-motivation-behavioural skills (IMB) model	Multiple components; non-specific techniques	Standard care practices for improving adherence; education, tailoring regimen, offering a pillbox, adherence checks & enquiries about side effects	135	In person (routine HCP)	5 sessions of 30-45 minutes over 48 weeks
Weber et al 2004[33]	Community, psychotherapy clinic, Netherlands	HIV	Cognitive behavioural intervention delivered by a psychotherapist.	Multiple components; non-specific techniques	Standard care (no details provided)	53	In person (specialist)	11 sessions of 45 minutes over 12 months

Study	Study setting	Disease area	Intervention description*	Identified intervention components	Components received by control group	Sample size	Intervention delivery style (& personnel)	Intervention length (average)
Williams et al. 2012[31]	Telephone calls and visits to patients own home, Australia	Diabetes	Multifactorial intervention consisting of self-monitoring of blood pressure, medicine review, educational DVDs and MI to support blood pressure control and optimal medication adherence	Motivational Interviewing (MI)	Standard care (no details provided)	75	In person and phone calls (specialist)	5 sessions, one of 89 minutes and 4 of an average of 11.75 minutes, over 3 months

* See supplementary table A for detailed breakdown of intervention components

Supplementary figures 1 and 2 show the results of the risk of bias assessment. Only Five (19.2%)~~three (13.0%)~~ studies[27 36 41 48 49] scored 'low risk' in all five bias categories. 198 (73.18~~.2~~%) were described as moderate overall risk, scoring 'low risk' in two to four of the categories and two (78~~.~~7%)[40 44] were described as 'high risk' scoring a low risk of bias in only one category. The most common source of bias was a lack of blinding of the outcome assessment; this is because the measure of adherence was frequently self-report. Self-report measures of adherence are commonly used but subject to patient bias. In the majority of cases the patients were not blind to their treatment group allocation and thus use of self-report measures leaves scope for bias.

Meta-analysis

263~~3~~ RCTs were pooled to assess the effect of ~~cognitive based techniques~~CBCT on medication adherence. Three studies showed non-significant negative effects on medication adherence but the remaining 230~~3~~ studies all showed improvements in medication adherence with receipt of intervention. The effect size calculated for each study is summarised in table 2.

Random effects meta-analysis showed evidence that ~~cognitive based techniques~~CBCTare associated with improved medication adherence. Figure 2 shows the forest plot for the 263~~3~~ studies and exemplifies the tendency towards positive adherence effects with intervention. A pooled estimate of effect size (95% CI) (reported as Hedges' ~~s~~*g*) of 0·3422 (0·232~~3~~26 to 0·4657~~8~~) was calculated when all studies were combined, although heterogeneity was high (I^2 = ~~70.2~~68%, 95% CI: 52% to 79%).

The funnel plot produced was indicative of publication bias (as shown in figure 3) and so further explored using Egger's test which confirmed statistically significant funnel plot asymmetry (p= 0.0054). The trim-and-fill technique was used to re-compute an effect size which accounted for this asymmetry, yielding a more conservative effect size estimate of 0.2105 (0.084~~7~~ to 0.3326~~3~~) (as shown in supplementary figure 3). This effect size suggests that ~~cognitive based techniques~~CBCT elicit small but statistically significant improvements in medication adherence (p = 0.0013~~3~~)relative to standard care. According to data from six studies that used the percentage of prescribed dose taken, the pooled standard deviation of this outcome was 30.7%. Then a standardised mean difference of 0.205 (0.084 to 0.326) is corresponding to a difference of 6.3% (2.6% to 10.0%) between the intervention and the control group in the percentage of dose taken.

Table 2: Study outcomes for studies included in meta-analysis

Study	Sample size (intervention, control)	Adherence definition (assessment measure)	Extracted data			Effect size (Hedges' g) (95% CI)
			Intervention group	Control group	P-value	
Bailey et al 1990	225 (124, 101)	% of patients scored as adherent on all 6 items of a self-report scale (based on Morisky's self-reported scale)	Mean = 91.9	Mean = 61.7	0.001	0.44 (0.18 to 0.71)
Berger et al 2005	367 (172, 195)	% of patients discontinuing treatment by study endpoint (patient interview)	Mean = 98.8	Mean = 91.3	0.001	0.35 (0.14 to 0.55)
Brown et al 2009	69 (36, 33)	% of prescribed doses taken over a month (electronic monitoring)	Mean (SD) = 93.4 (12.3)	Mean (SD) = 79.1 (28.1)		0.66 (0.18 to 1.14)
Dilorio et al 2003	17 (8, 9)	Mean number of missed medicines in the last 30 days (self-report questionnaire)	Mean (SD) = 0.13 (0.35)	Mean (SD) = 0.98 (1.48)		0.73 (-0.21 to 1.67)
Dilorio et al 2008	213 (107, 106)	% of doses taken during intervention period (electronic monitoring)	Mean = 64	Mean = 55	0.09	0.23 (-0.04 to 0.50)
Farmer et al. 2012	211 (126, 85)	% of days during a 12 week period in which medication was taken correctly (electronic monitoring)	Mean (SD) = 77.4 (26.3)	Mean (SD) = 64.0 (30.8)	0.04	0.47 (0.20 to 0.75)
George et al 2010	343 (170, 173)	% of participants classed as adherent (Morisky self-report scale)	Mean = 72.2	Mean = 63.8	0.09	0.18 (-0.03 to 0.39)
Golin et al 2006	117 (59, 58)	% of prescribed doses taken take in month prior to study endpoint (CAS)	Mean (SD) = 76 (27)	Mean (SD) = 71 (27)		0.18 (-0.18 to 0.54)
Hovell et al 2003	188 (92, 96)	Cumulative number of doses taken over 9 months (patient interview)	Mean (SD) = 179.93 (57.01)	Mean (SD) = 150.98 (73.75)		0.44 (0.15 to 0.72)
Konkle-Parker et al. 2012	36 (21,15)	% of patients taking >90% of their medications in the last 3-4 weeks (prescription refill data)	Mean (SD) = 0.93 (0.23)	Mean (SD) = 0.92 (0.27)		0.04 (-0.61 to 0.69)
Maneesriwongul et al 2012	60 (30, 30)	Mean % of doses taken over last 4 weeks (self-report using visual analogue scale)	Mean (SD) = 97.1 (3.3)	Mean (SD) = 89.8 (5.6)		1.55 (0.98 to 2.12)
Murphy et al 2002	33 (17, 16)	% of doses taken during intervention period (self-report questionnaire)	Mean (SD) = 0.86 (0.33)	Mean (SD) = 0.83 (0.36)		0.09 (-0.58 to 0.75)
Ogedegbe et al 2008	160 (79, 81)	% of days during a two month period in which medication was taken correctly (electronic monitoring)	Mean = 56.9	Mean = 42.9	0.027	0.35 (0.04 to 0.66)
Pradier et al 2003	202 (123, 121)	% of patients deemed to be adherent (taking 100% of doses) (self-report questionnaire)	Mean = 75	Mean = 61	0.04	0.34 (0.02 to 0.65)

Put et al 2003	23 (12, 11)	Frequency of non-adherent behaviour over the last 3 months (self-report questionnaire)	Mean (SD) = 6.9 (1.2)	Mean (SD) = 8.1 (3.1)		0.50 (-0.30 to 1.30)
Remien et al 2005	196 (106, 109)	% of doses taken during previous 2 weeks (electronic monitoring)	Mean (SD) = 76 (27)	Mean (SD) = 60 (34)		0.52 (0.25 to 0.79)
Safren et al 2001	53 (28, 25)	% of prescribed doses taken over the last 2 weeks (self-report questionnaire)	Mean (SD) = 93 (22)	Mean (SD) = 94 (10)		-0.06 (-0.59 to 0.47)
Sheeran et al 1999	78 (38, 40)	Number of once daily doses missed over a 3 week period (self-report questionnaire)	Mean = 2.68	Mean = 4.85	0.05	0.45 (0.00 to 0.89)
Simoni et al. 2009	114 (57, 57)	% of doses taken over last seven days (electronic monitoring)	Mean (SD) = 32.3 (42.5)	Mean (SD) = 29.1 (39.7)		0.08 (-0.29 to 0.44)
Smith et al 2003	17 (8, 9)	% of participants taking ≥ 80% of their weekly doses (electronic monitoring)	Odds ratio = 7.8 (2.2 to 28.1)			1.08 (0.41 to 1.74)
Solomon et al 2012	2087 (1046, 1041)	Median % medication possession ratio (prescription refill data)	Median = 49 IQR = 7 to 88	Median = 41 IQR = 2 to 86	0.07	0.08 (-0.01 to 0.17)
Tuldra et al 2000	77 (36, 41)	% of patients with monthly adherence ≥ 95% (self-reported number of pills taken)	Mean = 94	Mean = 69	0.008	0.62 (0.16 to 1.07)
Van Es et al 2001	67 (58, 54)	Adherence score on self-report scale based on how often medication was taken (never-always)	Mean = 7.7	Mean = 6.7	0.05	0.48 (0.00 to 0.96)
Wagner et al 2006	135 (154, 76)	% of doses taken during intervention period (electronic monitoring)	Mean = 83.5	Mean = 86.4	0.57	-0.08 (-0.35 to 0.20)
Weber et al 2004	53 (29, 24)	% of patients with monthly adherence ≥ 95% (electronic monitoring)	Mean = 70.8	Mean = 50	0.014	0.69 (0.14 to 1.24)
Williams et al 2012	75 (36, 39)	% of doses taken during intervention period (pill counts	Mean = 58.4	Mean = 66	0.162	-0.32 (-0.77 to 0.13)

Sub-group analyses via meta-regression

Table 3 summarises the results of the subgroup analyses to explore variation in effect size for the pre-determined variables. The regression co-efficient is the difference in ~~the~~ pooled Hedges'~~s~~ g between the two subgroups compared. A c~~C~~o-efficient >0 indicates that studies in subgroup-A reported greater treatment effects that those in subgroup-B. Interventions delivered from~~at~~ hospital settings were~~was~~ associated with greater treatment effect compared with interventions in community or other settings (difference 0.27, 95% CI 0.01 to 0.54, P=0.043). Differences in effect size between subgroups were statistically non-significant in all other~~all~~ cases. However, the subgroup analyses may have failed to detect important differences between subgroups because of the small number of studies included. ~~Differences in sub-groups were not found to account for any notable degree of the observed heterogeneity.~~

Table 3: Summary of sub-group analyses

Variable	Sub-group~~s~~-A vs. subgroup-B	No. of studies (no. of participants) in each sub-group	Co-efficient (95% CI)	P-value
Intervention setting	Hospital vs. community	9 (1124) Vs. 1~~7~~4 (40923~~731~~)	0.27~~5~~ (~~-0.014~~0.01 to 0.5465)	0.04~~361~~
Disease area	HIV vs. other conditions	1~~2~~2 (1323~~173~~) Vs. 1~~2~~1 (389~~3682~~)	0.05~~116~~ (-0.23195 to 0.33428)	0.72~~447~~
Intervention components	MI vs. no MI component	1~~0~~10 (353~~802~~) Vs. 15~~13~~ (167~~8353~~)	-0.17~~86~~ (-0.4485 to 0.09113)	0.193~~210~~
Intervention delivery method	Entirely in person vs. other methods	1~~5~~3 (166~~3416~~) Vs. 11~~ 0~~ (355~~3439~~)	-0.03~~06~~ (-0.3154 to 0.25366)	0.841~~973~~
	Entirely over the telephone vs. other methods	3 (2679) Vs. 2~~3~~0 (253~~7176~~)	-0.16~~005~~ (-0.59317 to 0.26327)	0.442~~976~~
	Both ~~i~~in person and~~/or~~ telephone vs. other	7~~2~~0 (775~~4631~~) Vs. 19~~3~~ (444~~1224~~)	-0.05~~0.985~~ (-0.2779 to 0.37476)	0.744~~593~~
Intervention delivery personnel	Routine HCP vs. others	1~~2~~0 (156~~7320~~) Vs. 1~~4~~3 (364~~9535~~)	-0.02~~42~~ (-0.3060 to 0.2677)	0.888~~789~~
	Specialist vs. others	5 (503) Vs. 2~~1~~18 (471~~3352~~)	-0.14~~73~~ (-0.51~~57~~ to 0.2212)	0.419~~360~~
Intervention exposure	Four sessions or fewer vs. five sessions or more	1~~2~~1 (173~~520~~) Vs. 1~~4~~2 (348~~5335~~)	0.22~~-0.912~~ (-0.0492 to 0.48106)	0.095~~193~~
Control group type	Explicit active controls vs. usual care (no adherence enhancing strategies)	1~~3~~2 (368~~3472~~) Vs. 1~~3~~1 (153~~3383~~)	0.09~~548~~ (-0.18~~2.609~~ to 0.37~~3.706~~)	0.493~~722~~
Risk of bias	Outcome assessment	1~~5~~2 (355~~5194~~) Vs. 11	0.05~~828~~ (-	0.736~~151~~

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	blinding vs. no outcome assessment blinding	(1661)	0.2432 to 0.3397)	
Outcome measures	Objective vs. subjective measured outcomes	14 (3850) Vs. 12 (1366)	-0.16 (-0.44 to 0.11)	0.225

~~Note to Table 3: Differences between subgroups were tested using STATA 'metareg' command for random-effects meta-regression analysis. Co-efficient refers to the difference in effect size between the two sub-groups.~~

Discussion

Principal~~Principle~~ findings

~~We found that r~~Receipt of a cognitive-based behavioural adherence intervention was associated with small but statistically significant improvements in medication adherence. Heterogeneity was high and notable publication bias was identified. However, techniques have been used to account for these biases resulting in a more conservative summary effect size ~~(95% CI)~~ of 0.205 (95% CI: 0.0847 to 0.3263; P=0.001).

In ~~over~~ half of the included studies, the standard care received by the ~~study~~ control group explicitly involved some form of 'adherence enhancing strategy' such as provision of education, monitoring or review. Such strategies form the mainstay of current medication adherence interventions and so our research suggests that ~~cognitive based techniques~~CBCT may be able to elicit adherence benefits beyond the techniques used in current practice.

The majority of interventions were complex and multifaceted, thus subgroup analysis to explore whether this is associated with greater effect could not be undertaken ~~(Haynes, 2008 #3)~~. The ~~S~~sub-group analyses performed revealed that the effect size ~~achieved~~ is greater when interventions were delivered in the hospital setting~~associated with setting (hospital or not)~~ compared with community, but not influenced by other variables such as the type of ~~cognitive based intervention~~CBCT, delivery method and personnel or duration. Further work is necessary to explore the effect of setting on effect size. ~~This suggests that the interventions studied in this meta-analysis may be generalizableacross a diverse range of settings.~~

Comparison with other studies

In 2003, Peterson *et al.* conducted a meta-analysis of educational and behavioural interventions to improve medication adherence in a range of illnesses.[53] The included studies were all RCTs delivered over similar time periods to those included in our study. The

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educational components and behavioural components such as changes in dosing schedule and reminders examined by Peterson *et al.* closely mirror those utilised in the studies from our meta-analysis which used control groups with 'active standard care'. Peterson *et al.* reported a correlation coefficient (*r*) equivalent to a Cohen's *d* effect size of 0·16 (0·08, 0·24). For our study, the effect size for all studies, when adjusting for publication bias and reported as Hedges' *g* was 0.205 (0.0847, 0.33263). This suggests that inclusion of ~~cognitive based techniques~~CBCT, strengthens the adherence improvements gained, if only marginally. Moreover, Peterson *et al.* report publication bias observed from a funnel plot of their included studies, but have not made allowances for this bias via re-computed effect sizes. T~~With this mind, t~~heir Cohen's *d* value of 0.16 is likely exaggerated by the noted publication bias and thus infers that the true difference in effect size between the two meta-analyses may be greater.

~~For studies using MI, a~~An effect size (Hedges' ~~s~~*g*) of 0.2546 (95% CI 0.0718, 0.4214) for studies using MI was calculated, compared with an effect size of 0.41 (95% CI 0.278 to 0.541) for non-MI interventions. After adjusting for bias, the estimated He~~i~~dges'~~s~~ g was 0.137 (95% CI -0.067 to 0.341) for studies using MI and 0.356 (95% CI 0.223 to 0.489) for studies using non-MI interventions. These estimated effect sizes ~~which~~ closely match~~es~~ the effect size calculated when MI is used as a behavioural intervention in ~~-~~other healthcare domains[14] and thus represents novel evidence for the wider application of MI techniques beyond the treatment of substance abuse and gambling.

Strengths and weaknesses of our work

This study represents the first meta-analysis of MI and other ~~cognitive based techniques~~CBCT as medication adherence interventions and has been undertaken with methodological rigour and in accordance with published guidance.[18] A notable strength of this work is the robust methodological techniques that have been applied to provide an estimate of effect size which accounts for publication biases and thus greater confidence can be placed in the estimate. The work is also strengthened by restriction to RCTs.

Whilst moderate agreement in abstract screening may be lower than ideal, this is largely attributable to paucity of detail reported in ~~studies~~ abstracts and complexities in intervention definitions which are known to be problematic in this domain.[11-13] The conservative approach to abstract screening prevented study exclusion if disagreement was associated with insufficient information and thus prevented exclusion in error. Heterogeneity between the included studies was high with an I^2 value of ~~70.2~~68% (95% CI: 52% to 79%) and thus raises the question as to whether the studies were sufficiently comparable to warrant pooling

in a meta-analysis. Whilst we defined our inclusion criteria to ensure studies were as similar as possible (i.e. all using a ~~cognitive-based behaviour change technique~~CBCT), heterogeneity was expected as other factors such as the populations and disease states studied were more difficult to control for. Interestingly, the ~~inclusion of one particular study which was vastly larger in sample size than all other studies greatly increased the heterogeneity~~largest study had a small standardized group difference compared to most of the other studies which contributed substantially to the heterogeneity.[43] Furthermore, results from all but three of the studies indicate positive effects of the intervention. Aside from these between study differences, the actual interventions ~~themselves~~ were variable, as were the definitions of adherence and assessment tools used. ~~According to the results of subgroup analyses, studies from hospital settings reported greater treatment effects compared with studies in other settings.~~ The differences between subgroups were statistically non-significant in terms of disease area, intervention components, delivery methods, delivery personnel, intensity, usual care and risk of bias ~~(Table 3)~~. However, the statistical power was limited by the small number of studies included in the subgroup analyses. The analyses may therefore have failed to detect some important subgroup differences.

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Despite these numerous between study differences, the core of each intervention was the use of a ~~cognitive-based technique~~CBCT to improve medication adherence which was comparable across all studies and thus we would argue that data pooling irrespective of heterogeneity was both intuitive and meaningful.

We have established that receipt of a cognitive-based behavioural medication adherence intervention is likely to elicit small improvements in medication adherence, but the clinical relevance and impact of this improvement remains unknown. Based on mean adherence rates in the control groups, mean standard deviations and the effect size calculated, it has been possible to estimate the increase in percentage of doses taken for the intervention groups. Based on the adjusted Hedges' *g* value of 0.205 (0.084~~7~~ to 0.3263), receipt of a ~~cognitive-based technique~~CBCT improved adherence (% of doses taken) by 6.29~~5.46~~% (2.58~~1.83~~% to 10.09~~.12~~%). For some medications, a 6~~5~~% increase in the percentage of doses taken may not be of clinical relevance. However, for ~~many~~ other medications such as antiretroviral therapy for HIV which requires very high levels of adherence or anti-epileptic therapies with narrow therapeutic windows, a 6~~5~~% increase in adherence may have notable clinical relevance. Whilst many included studies included data on clinical outcomes, pooling of this data from a diverse range of studies was not possible.

Implications

Motivational and ~~cognitive-based techniques~~CBCT can seemingly be delivered effectively by routine healthcare professionals, in both primary and secondary care settings, with efficacy applicable to a range of diseases. Efficacy was not related to intervention duration or follow-up period. Interestingly, the results also suggest that these interventions can be delivered via telephone or face-to-face with comparable efficacy. These are valuable traits for an adherence intervention which could be adaptable to a wide range of settings and amenable to tailoring to meet individual need.

The flexibility and adaptability of these techniques coupled with their frequent simplicity means that practitioners may wish to consider incorporation of ~~some of~~ these techniques into their consultations when faced with the need to facilitate medication related behaviour changes.

Recommendations and conclusions

Further investigation of these techniques as medication adherence interventions is warranted in order to further elucidate the characteristics most strongly associated with efficacy. Studies to determine both patient and healthcare practitioner acceptability of these techniques is also necessary to establish their role in routine healthcare.

Article summary

Article focus

- Medication non-adherence is widespread and represents a notable barrier to achieving optimal effects from therapeutic intervention.
- Despite the magnitude and consequences of non-adherence, a gold standard intervention to improve it remains elusive.
- Cognitive-based behaviour change techniques may represent a useful tool in improving medication adherence but their use in this domain had not been established using meta-analytic techniques.

Key messages

- Cognitive-based behaviour change techniques are effective interventions for improving medication adherence and capable of eliciting improvements in adherence beyond those achieved with educational and behavioural interventions which form the mainstay of current practice

- Cognitive-based behaviour change techniques can be effectively delivered by routine healthcare providers ~~in standard community based settings~~. Brief interventions are seemingly effective too.
- Health care providers may wish to consider incorporation of these techniques into their medication adherence consultations

Strengths and limitations of this study

- The studies pooled in this meta-analysis are restricted to RCTs which strengthens their robustness.
- Techniques to account for publication bias have been utilised to provide a conservative effect size estimate offering robustness to our estimate
- Notable heterogeneity was reported when studies were combined which may be a limitation.

Declaration of competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgements

CE would like to acknowledge Estelle Payerne for her invaluable contributions as the second reviewer for abstract screening and data extraction. CE would also like to acknowledge David Wright and John Wood for their comments on the protocol design, data analysis and methods of dissemination, and Steven Watson for his ~~ongoing~~on-going technical support in using the meta-analysis software and comments regarding data interpretation

Funding

This research has been supported by a PhD studentship awarded by the Dean of Science at the University of East Anglia.

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Figure 1: Flow diagram for selection of studies

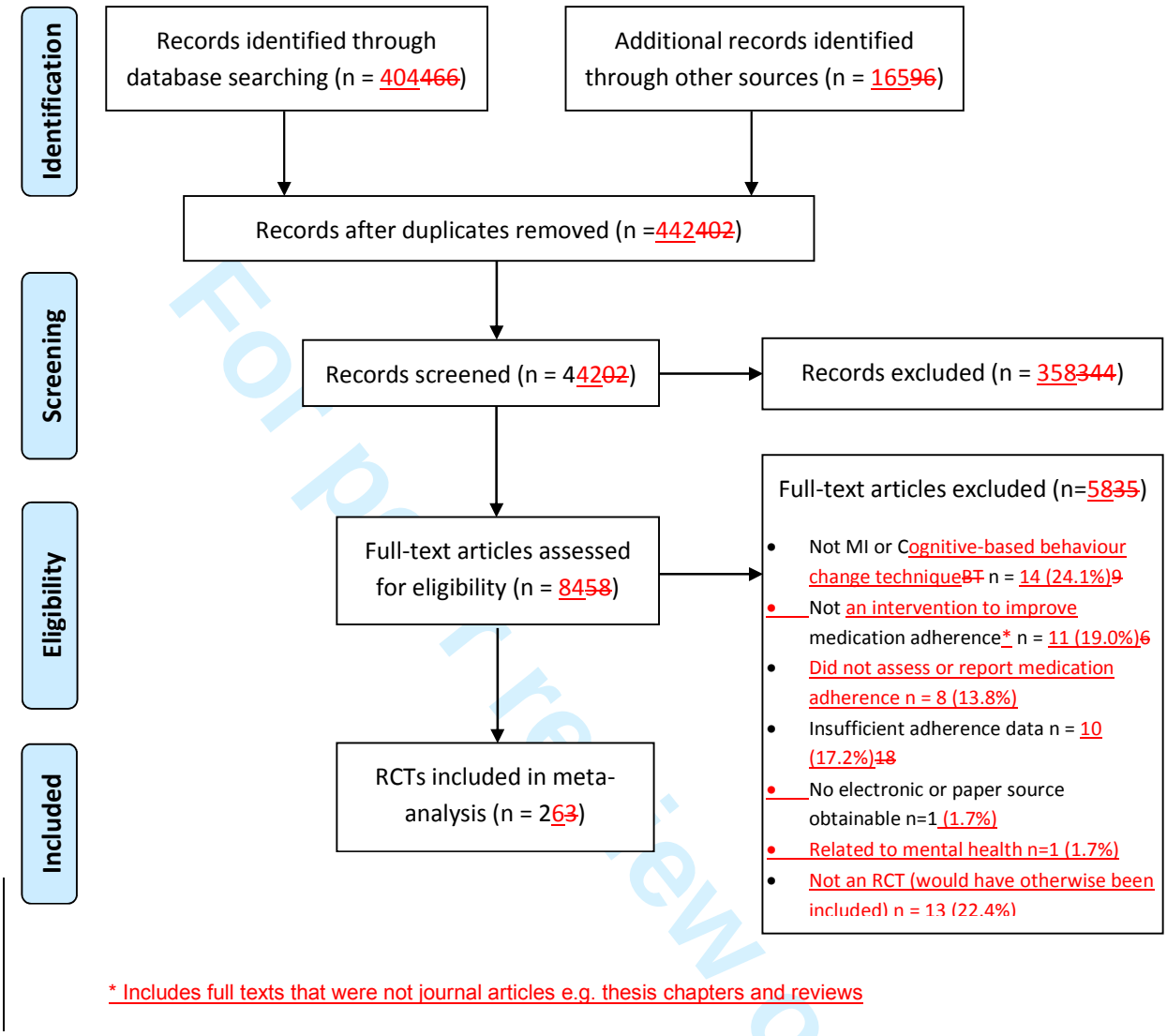


Figure 2: Forrest plot for studies included in meta-analysis

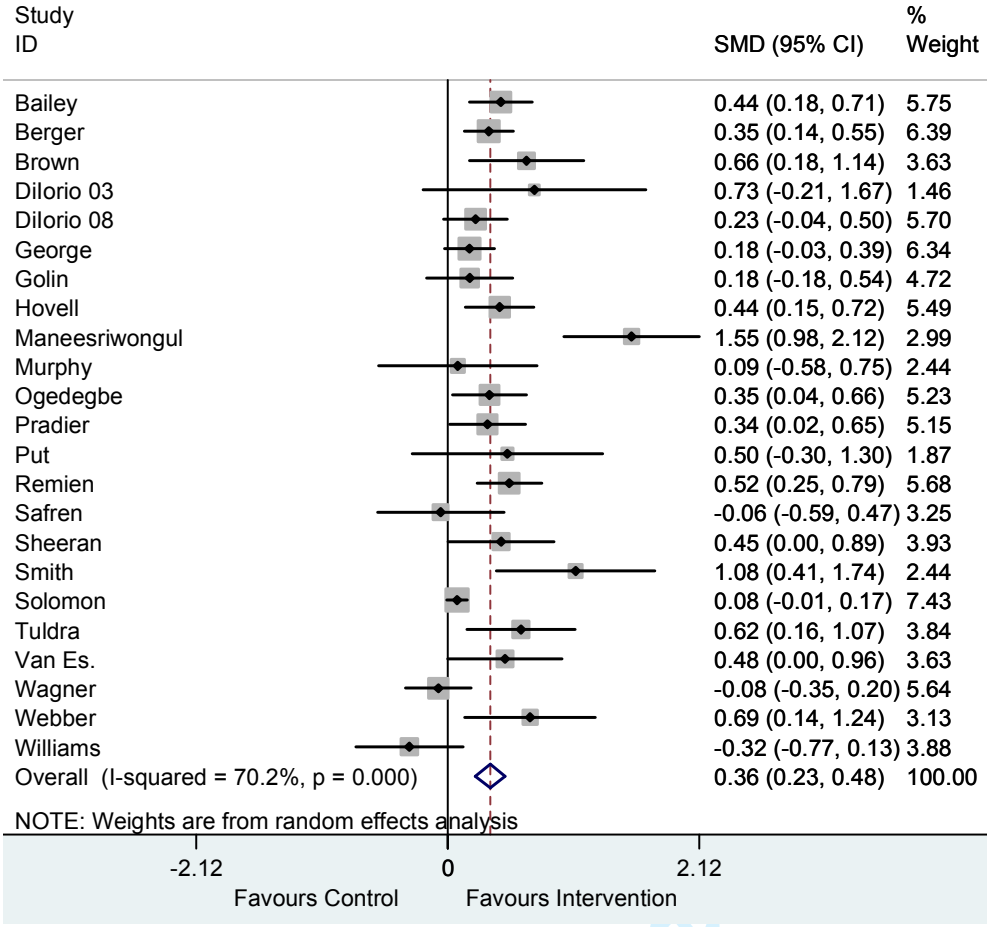
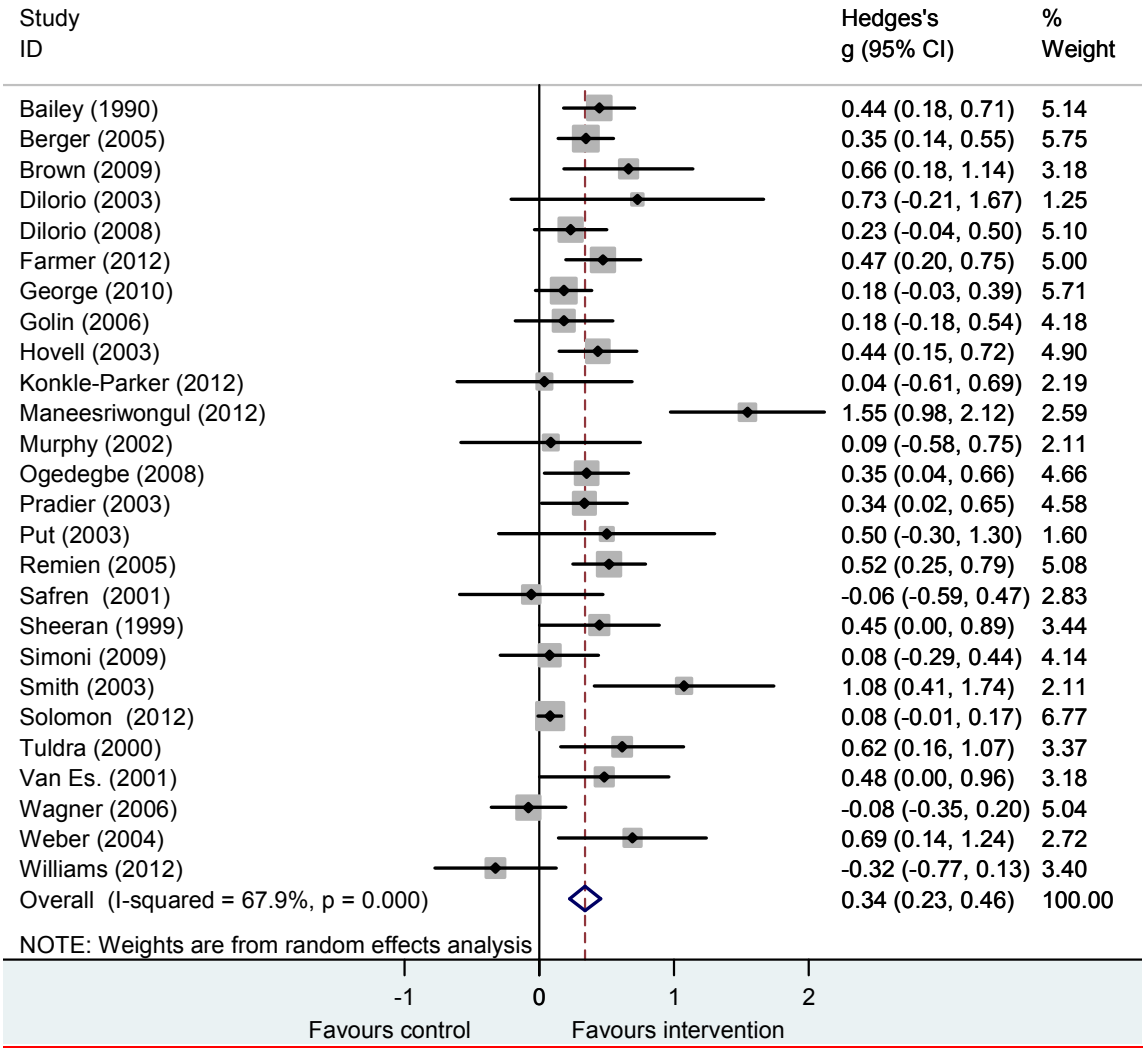


Figure 2: Forest plot for studies included in meta-analysis



~~Figure 3: Funnel plot for studies included in meta-analysis~~

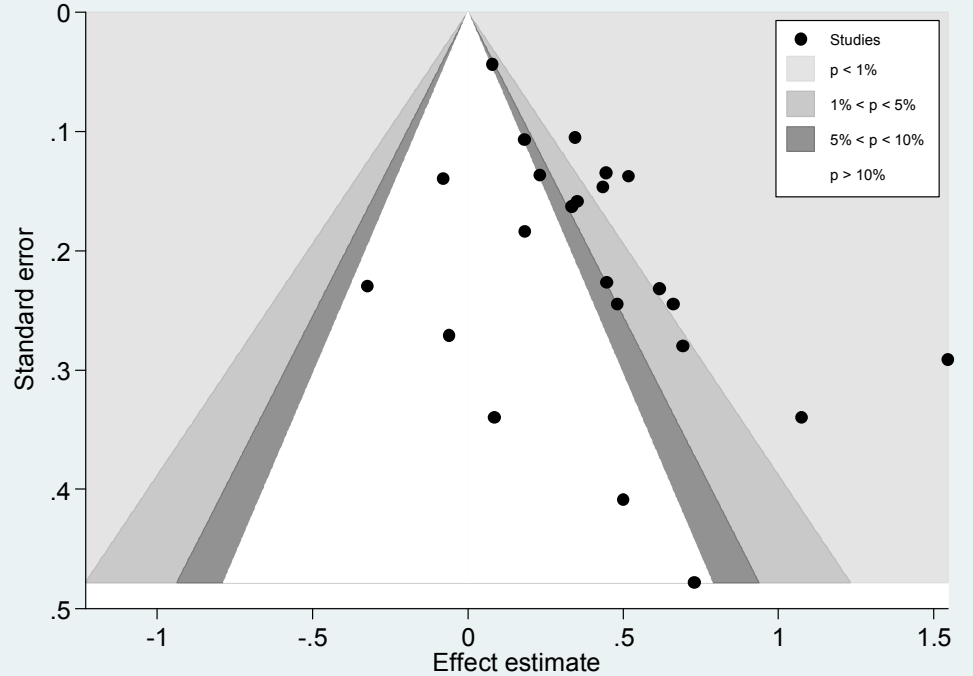
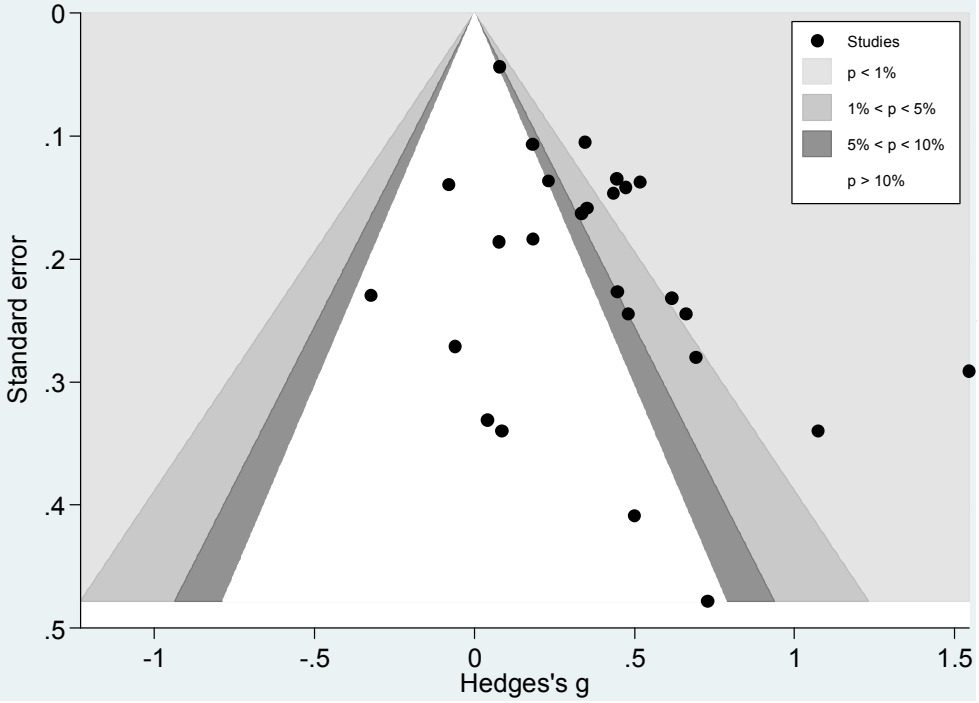


Figure 3: Funnel plot for studies included in meta-analysis



Appendix one: Search terms to be applied to databases

	Search terms
1	medication* adheren*.ti,ab
2	medication* complian*.ti,ab
3	medication* concordan*.ti,ab
4	medication* non-adheren*.ti,ab
5	medication* non adheren*.ti,ab.
6	medication* non-complian*.ti,ab
7	medication* non complian*.ti,ab.
8	medication* persist*.ti,ab.
9	drug* adheren*.ti,ab.
10	drug* complian*.ti,ab.
11	drug* concordan*.ti,ab
12	drug non-adheren*.ti,ab.
13	drug* non adheren*.ti,ab.
14	drug* non-complian*.ti,ab.
15	drug* non complian*.ti,ab.
16	drug* persist*.ti,ab
17	medicine adheren*.ti,ab.
18	medicine complian*.ti,ab.
19	medicine concordan*.ti,ab.
20	medicine non-adheren*.ti,ab.
21	medicine non adheren*.ti,ab
22	medicine non-complian*.ti,ab.
23	medicine non complian*.ti,ab
24	medicine persist*.ti,ab
25	patient adheren*.ti,ab.
26	patient complian*.ti,ab.
27	patient concordan*.ti,ab.
28	patient non-adheren*.ti,ab.
29	patient non adheren*.ti,ab.
30	patient non-complian*.ti,ab.
31	patient non complian*.ti,ab
32	patient persist*.ti,ab.
33	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34	motivation* interview*.ti,ab
35	motivation* enhancement therap*.ti,ab.
36	behavio?r change counsel?ing.ti,ab
37	implementation* intention*.ti,ab.
38	if-then plan*.ti,ab
39	if then plan*.ti,ab.
40	motivation* counsel?ing.ti,ab.
41	motivation* behavio?r.ti,ab.
42	motivation* change.ti,ab.
43	motivation* intervention*.ti,ab.
44	health behavio?r change*.ti,ab.
45	brief intervention*.ti,ab.
46	cognitive intervention*.ti,ab.
47	cognitive technique*.ti,ab
48	health behavio?r counsel?ing.ti,ab.
49	problem solving treatment*.ti,ab.
50	problem solving therap*.ti,ab
51	34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50
52	33 and 51
53	Remove duplicates from 52

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix one
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7-8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ open

A meta-analysis of cognitive-based behaviour change techniques as interventions to improve medication adherence

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-002749.R2
Article Type:	Research
Date Submitted by the Author:	01-Jul-2013
Complete List of Authors:	Easthall, Claire; University of East Anglia, School of Pharmacy Song, Fujian; University of East Anglia, School of Pharmacy Bhattacharya, Debi; University of East Anglia, School of Pharmacy
Primary Subject Heading:	Medical management
Secondary Subject Heading:	Medical management, Health services research, Patient-centred medicine
Keywords:	Medication adherence, Meta-analysis, Behaviour change, Motivational Interviewing, Adherence intervention

A meta-analysis of cognitive-based behaviour change techniques as interventions to improve medication adherence

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Abstract

Objective

To describe and evaluate the use of cognitive-based behaviour change techniques as interventions to improve medication adherence.

Design

Systematic review and meta-analysis of interventions to improve medication adherence.

Data sources

Search of Medline, Embase, PsycINFO, CINAHL and The Cochrane Library databases from the earliest year to April 2013 without language restriction. References of included studies were also screened to identify further relevant articles.

Review methods

We used pre-defined criteria to select Randomised Controlled Trials (RCTs) describing a medication adherence intervention that used Motivational Interviewing (MI) or other-cognitive based techniques. Data were extracted and risk of bias was assessed by two independent reviewers. We conducted the meta-analysis using a random effects model and Hedges' *g* as the measure of effect size.

Results

We included 26 studies (5216 participants) in the meta-analysis. Interventions most commonly used MI but many used techniques such as aiming to increase the patient's confidence and sense of self-efficacy, encouraging support seeking behaviours and challenging negative thoughts, which were not specifically categorised. Interventions were most commonly delivered from community based settings by routine healthcare providers such as GPs and nurses. An effect size (95% CI) of 0.34 (0.23 to 0.46) was calculated and was statistically significant (p = <0.001). Heterogeneity was high with an I^2 value of 68%. Adjustment for publication bias generated a more conservative estimate of summary effect size of 0.21 (0.08 to 0.33). The majority of sub-group analyses produced statistically non-significant results.

Conclusion

Cognitive-based behaviour change techniques are effective interventions eliciting improvements in medication adherence that are likely to be greater than the behavioural and

educational interventions largely used in current practice. Sub-group analyses suggest that these interventions are amenable to use across different populations and in differing manners without loss of efficacy. These factors may facilitate incorporation of these techniques into routine care.

Introduction

Estimates suggest that 30 to 50% of patients prescribed medications for chronic illnesses do not adhere to their prescribed medication regimen.[1] This non-adherence has been demonstrated to diminish treatment effect which can result in prolonged illness, additional investigations and prescribing that may otherwise have been unnecessary.[2] A link between poor adherence and an increased risk of mortality is also well established.[3] Consequently, the World Health Organisation (WHO) has described non-adherence as "a worldwide problem of striking magnitude" and a priority for healthcare researchers and policy makers.[1]

Despite both the magnitude and potential gravity of sub-optimal medication adherence, a gold standard intervention remains elusive; a recent Cochrane review highlighted the paucity of effective interventions in current practice.[4] Evidence suggests that complex, multi-faceted interventions, tailored to meet individual needs are most likely to be efficacious[4 5] which is intuitive given the complex, multi-stage process that is medication taking.

Non-adherent behaviour is traditionally categorised into unintentional and intentional. Unintentional non-adherence includes behaviours arising from forgetfulness, misunderstanding and confusion. Intentional non-adherence describes patient choice to deviate from the prescribed medication regimen. Unintentional and intentional non-adherence are not mutually exclusive thus an amalgam of these behaviours often exists in any one patient. An understanding of patient behaviour and its underpinning psychology plus the wealth of factors, both internal and external that may influence medication taking, is crucial to understanding how to change patient behaviour and thus improve medication adherence.[6]

Historically, adherence interventions have encompassed behaviour change techniques such as simplifying dosage regimens and providing adherence aids or education to address the practical issues of adherence in terms of knowing how and being able to take the medication as prescribed. Pooled data for such studies have demonstrated marginal effects[4] yet such interventions continue to form the cornerstone of routine healthcare provision.[2] These interventions may have particularly poor efficacy in cases of intentional non-adherence as the provision of persuasive advice may evoke further resistance to change.[7 8] Through an understanding of the challenges faced in changing behaviours and the motivation necessary to achieve change, novel, Cognitive-based Behaviour Change Techniques (CBCT) have emerged. These interventions aim to change a patient's behaviour by altering their thoughts, feelings, confidence or motivation to adhere. CBCT interventions can vary widely in content such as incorporating techniques to enhance patient sense of self-efficacy, problem solve and increase motivation to adhere.

Motivational interviewing (MI) is one of the most widely recognised CBCT and is designed to facilitate behaviour change by resolving patient ambivalence about change.[9] It therefore primarily targets intentional non-adherence but also enables patients to reflect on any unintentional barriers to adherence and seek out solutions. Systematic reviews and meta-analyses have reported MI efficacy in facilitating health related behaviour change such as smoking cessation and alcohol withdrawal[10-16] but have not explored its effects on medication adherence. Adaptations of MI such as Behaviour Change Counselling (BCC)[17]additionally allow the facilitator to educate and advise thus application to both intentional and unintentional non-adherence may be effective.

Best practice guidelines state that evidence of intervention efficacy should ideally be pooled from literature in a systematic review or meta-analysis wherever possible to offer a robust and cohesive evidence base.[18] This study provides a systematic review and meta-analysis of MI and other cognitive-based techniques as interventions to improve medication adherence.

Methods

We used standard systematic review methods[18 19] and registered the study protocol (PROSPERO register reference CRD42011001721). Randomised Controlled Trials (RCTs) reporting an adherence intervention using MI and/or other cognitive-based techniques with medication adherence as an outcome measure were eligible for inclusion. All definitions of adherence such as percentage of doses taken over a given time period and percentage of patients achieving a specified adherence level were considered. All adherence measures were also considered including self-report and electronic monitoring. Where multiple measures were reported, the percentage of patients achieving a specified adherence level was selected as this was common to more studies.

Any intervention using some form of psychological technique to change a patient's adherence behaviour and their thoughts, feelings, confidence, or motivation towards adhering was defined as a cognitive-based technique. Studies examining adherence to medications for the treatment of addiction and/or mental health conditions were excluded as these interventions tend to be specific to these domains.

Search strategies

We developed a search strategy to avoid restriction to pre-determined terms such as 'motivational interviewing' as many of the techniques of interest are not classified using specific or consistent terms. MeSH terms were also used to enhance retrieval of relevant studies. Truncations (*), wild cards ($), hyphens and other relevant Boolean operators were used where permitted. Scoping searches were conducted prior to finalising the search strategy to ensure suitability of terms in generating a good coverage of relevant material.

We applied the search strategy (as shown in appendix one) to the MEDLINE, EMBASE, PsychINFO, CINAHL and Cochrane databases in April 2013 without date or language restrictions. The reference lists of all screened full text articles were also used to identify further relevant articles.

Study selection and data extraction

Two researchers (CE and EP) independently screened titles and abstracts against the inclusion and exclusion criteria using a piloted abstract screening tool. Inter-reviewer agreement using Cohen's Kappa (K) was assessed for both the abstract and full text screening stage. The level of agreement was characterised using a qualitative scale.[20] Discrepancies were resolved by discussion between the two reviewers, and if necessary referral to a third independent reviewer (DB) until consensus was reached.

Data extraction was also undertaken by CE and EP, independently using piloted forms. Data extracted included study details (such as year and journal of publication, country and study design); study characteristics (including setting, population, delivery methods and personnel); intervention details (including intervention type, duration and principal components) and outcome details (including adherence assessment measure, data and definition). A list of intervention components was independently extracted from the articles verbatim by two reviewers. Grouping of similar components was undertaken by one reviewer and verified by a second reviewer.

Accuracy of data collected was verified by comparison of the forms completed by the two independent reviewers. In cases of discrepancy, consensus was agreed through discussion and where necessary, referral to a third independent reviewer (DB). For studies with missing data or ambiguities, the corresponding author was contacted for clarification.

Quality assessment

A quality assessment of all included studies was made using the Cochrane risk of bias tool.[18] The risk of bias was assessed in five domains deemed relevant to the included studies: random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data and selective reporting. Performance bias (blinding of participants and personnel) was not included as the nature of the interventions meant that blinding of participants and personnel was impossible in almost all studies. None of the included studies were found to contain additional sources of potential bias not represented by the five included domains. The risk of bias for each study, in each of the five domains was classified as low, uncertain or high, as recommended in the guidelines.[18] The quality assessment process was undertaken independently by two reviewers, with consensus on the final risk classifications reached through discussion.

Data analysis

The meta-analysis was conducted using STATA® (version 12.1). Given the broad inclusion criteria, we anticipated including studies from different populations, with different diseases and which used different CBCT. We therefore explored heterogeneity via calculation of the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance.[21 22] A random effects model (DerSimonian-Laird method) was employed to calculate a pooled effect size (Hedges' *g*) and 95% confidence interval for the included studies.[23] Calculation of the effect size as Hedges' *g* (standardised difference in means) enabled adherence outcome measures of differing definition and measure, to be combined, transforming this data into a common metric. When standard deviation was missing, we estimated standard error of mean difference based on reported P values, means and the number of patients. Odds ratios were converted to standardised mean differences by using the formula SMD=lnOR*√3/π).[23]

Funnel plots were produced where appropriate to explore potential publication biases. STATA® (version 12.1) was used to conduct Egger's test[24] to test funnel plot asymmetry. We used the trim and fill method[25 26] to estimate a summary effect size after adjusting for asymmetric funnel plots.

Variables of interest in influencing the effect size and informing intervention design were determined a priori and the following subgroup analyses undertaken using a random effects meta-regression: intervention components, setting , delivery personnel, delivery method and intervention exposure, disease area and risk of bias. The type of outcome measure used to assess adherence (objective compared to subjective) was added as a post-hoc sub-group analysis to further explore heterogeneity. Objective outcome measures included electronic

monitoring and pill counts, subjective measures included all forms of self-report. Differences between subgroups were tested using STATA 'metareg' command for random-effects univariate meta-regression analysis.

Results

Study selection, characteristics and quality

Figure 1 shows the number of papers excluded at each stage of the review. Of the 442 abstracts screened, 84 studies passed the abstract screening stage with moderate agreement between the two reviewers (k = 0·57). Conflict in classifying an intervention as a CBCT accounted for 31.0% of discrepancies and was heavily influenced by a paucity of information in the abstracts. At the full text screening stage, agreement between the two independent reviewers was much higher, with a kappa value of 0.91, indicating almost perfect agreement. After examining 84 full-text articles, we included 26(31.0%) in the meta-analysis.

The main characteristics of the 26 included studies are summarised in Table 1. The studies provided a total sample size of 5216 participants. Studies were primarily undertaken in the United States of America (USA) followed by the United Kingdom (UK),[27-29] Australia[30 31] and the Netherlands[32 33]. Dates of publication ranged from 1990 to 2012 with only two studies (7.7%) pre-dating 2000[28 34]. Ten (38.5%) were published within the last five years (2008-2013). The most common condition for which medications were prescribed was HIV, accounting for 14 (53.8%) studies. Other studies concerned treatments for a range of conditions including asthma[32 34 35] diabetes[27 31] and hypertension[30 36].

Just over half of the included studies(53.8%) described an intervention with a clearly defined CBCT; Motivational Interviewing (MI) was most commonly used and this was the case for 11 (42.3%) studies[30 31 36-44]. A further three (11.5%) studies used Implementation Intention Interventions (III, also known as if-then planning) as a clearly defined CBCT. For 12 (46.2%) studies, a clearly defined CBCT such as MI could not be identified[32-35 45-52], these studies are identified in table 1 as 'multiple components; non-specific techniques'. Instead, this group comprised of, multiple components such as 'providing education' or 'increasing patient knowledge' which was reported in nine (75.0%) studies in this group. Other components included 'increasing self-efficacy' and 'developing or improving problem solving skills' each reported in six (50.0) studies and 'identifying and resolving adherence barriers' and 'increasing social support' also each reported in six (50.0%). All studies within this group included one or more components that aimed to alter the patient's thoughts, feelings,

motivation or confidence towards adherence and that could therefore be classified as a cognitive-based behaviour change technique. Detailed information regarding the identified intervention components extracted from each study are provided as a supplementary table. The majority of interventions had multiple components. Many studies combined cognitive-based behaviour change techniques with more traditionally used educational (e.g. increasing patient knowledge) and behavioural (e.g. regimen simplification and provision of dosing aids) components.

Interventions were most commonly delivered in person, from community based settings and by routine healthcare providers such as nurses, pharmacists and general medical practitioners. 'Non-routine' healthcare providers were considered to be those such as psychologists or psychotherapists, who would not ordinarily be involved in the patient's care in the absence of mental illness.

The intervention period ranged from four (15·4%) studies reporting singular sessions, to six (23·1%) studies reporting multiple sessions over 12 months. The median (IQ) number of sessions over which interventions were delivered was 5.0 (3.0 to 7.3). The majority of interventions were delivered over a period of six months or less which was the case for 17 studies (65.4%). Intervention exposure as the total number of minutes spent delivering the intervention could be estimated for 16 studies. In the remaining 10 studies this data was not available. Intervention exposure ranged from thirty minutes to eight hours and fifteen minutes. The median (IQR) intervention exposure was 175 (118 to 263) minutes.

The comparison group was 'standard care' for all studies; for 13 studies (50.0%) standard care involved some form of technique to improve adherence such as education, encouragement or provision of adherence aids and in these studies, recipients of the intervention received further techniques such as MI.

Table 1: Characteristics of included studies in meta-analysis

Study	Study setting	Disease area	Intervention description*	Identified intervention components	Components received by control group	Sample size	Intervention delivery style (& personnel)	Intervention length (average)
Bailey et al 1990[34]	Hospital clinic, USA	Asthma	Comprehensive programme integrating a skills-orientated self-help workbook with one-to-one counselling & adherence-enhancing strategies.	Multiple components; non-specific techniques	Standard care; education via standardised set of pamphlets and routine physician encouragement	225	Telephone calls and in person (specialist)	240 minutes (4 x 60min sessions) over unknown period
Berger et al 2005[40]	Telephone calls to patients at home, USA	Multiple Sclerosis	Software supported intervention based on Transtheoretical model of change and MI	Motivational Interviewing (MI)	Standard care plus could telephone help line	367	Telephone calls (researcher)	9 sessions of unknown duration delivered over 3 months
Brown et al 2009[29]	Hospital clinic, UK	Epilepsy	Formation of III via completion of a self-administered questionnaire	Implementation Intention Interventions (III)	Standard care plus self-report questionnaires	69	Questionnaire completion (not in person)	One-off intervention of unknown duration
DiIorio et al 2003[41]	Community clinic, USA	HIV	One-to-one counselling sessions based on MI	Motivational Interviewing (MI)	Standard care; usual adherence education provided in the clinic	17	In person (routine HCP)	5 x 35 minutes sessions delivered over 12 months
DiIorio et al 2008[42]	Hospital clinic, USA	HIV	MI as individual counselling sessions	Motivational Interviewing (MI)	Standard care; usual (extensive) education provided at the clinic	213	Mostly in person with some telephone calls (routine HCP)	5 sessions of 35 minutes over 12 months
Farmer et al. 2012[27]	Community based clinic, UK	Type 2 diabetes	Brief intervention to elicit beliefs, resolve barriers and form 'if-then' plans.	If-then Planning (III)	Standard care plus additional clinic visits for blood tests	211	In person (clinic nurse)	One-off session lasting 30 minutes.
George et al 2010[30]	Community pharmacies, Australia and Tasmania	Hypertension	Community pharmacy intervention of one-to-one sessions, monitoring & medication review	Motivational Interviewing (MI)	Standard care	343	In person (routine HCP)	3 sessions of unknown duration over 6 months

Study	Study setting	Disease area	Intervention description*	Identified intervention components	Components received by control group	Sample size	Intervention delivery style (& personnel)	Intervention length (average)
Golin et al 2006[39]	Community clinic, USA	HIV	Multi-component MI based intervention.	Motivational Interviewing (MI)	General HIV information provided via audio tape, two one-to-one sessions and two mail shots.	117	In person (specialist)	2 sessions of unknown duration over 2 months
Hovell et al 2003[51]	Hospital clinic, USA	Tuberculosis	Adherence coaching involving interviewing, contingency contracting and shaping procedures	Multiple components; non-specific techniques	Standard care; routine advice at appointments	188	Telephone calls & in person (researcher)	12 sessions of 15-30 minutes over 6 months
Konkle-Parker et al. 2012[38]	Community based clinics and patients own homes, USA	HIV	Adherence intervention guided by the Information-Motivation-Behavioural Skills (IMB) model	Motivational Interviewing (MI)	Standard care; usual clinic appointments	36	Telephone calls and in person (nurse practitioner)	8 sessions over 24 weeks. Average overall duration 1h 30 minutes
Maneesriwongul et al 2012[37]	Hospital outpatients clinic & telephone calls to patients at home, Thailand	HIV	Motivational interviewing with counselling	Motivational Interviewing (MI)	Standard care; education and provision of leaflets at point of prescribing	60	Telephone calls & in person (researcher)	3 sessions approximately 30 minutes over a four week period
Murphy et al 2002[52]	Community based clinic, USA	HIV	Multi-component and multi-disciplinary intervention including behavioural strategies and cognitive behavioural therapy	Multiple components; non-specific techniques	Standard care; regular appointments with enquiries about adherence and an additional 30 minute appointment for those with problems where medication schedule is written down for them	33	In person (specialist)	5 sessions of unknown duration over 7 weeks
Ogedegbe et al 2008[36]	Community clinic, USA	Hypertension	Practice-based MI counselling	Motivational Interviewing (MI)	Standard care; usual appointments plus additional visits for MEMS downloads	160	In person (researcher)	4 sessions lasting 30-40 mins delivered over 12 months

Study	Study setting	Disease area	Intervention description*	Identified intervention components	Components received by control group	Sample size	Intervention delivery style (& personnel)	Intervention length (average)
Pradier et al 2003[50]	Hospital clinic, France	HIV	Educational & counselling intervention founded in the principles of motivational psychology and client-centred therapy	Multiple components; non-specific techniques	Standard care; routine follow up appointments	202	In person (routine HCP)	3 sessions of 45-60 minutes over 3 months
Put et al 2003[35]	Hospital clinic, Belgium	Asthma	Behavioural change intervention involving psycho-education with behavioural and cognitive techniques	Multiple components; non-specific techniques	Standard (no details provided)	23	In person (researcher)	360 minutes (6 x 60 minutes sessions) over 3 months
Remien et al[49] 2005	Community based clinic, USA	HIV	Couples-based intervention grounded in Social action theory	Multiple components; non-specific techniques	Standard care; education at point of prescribing & follow up to check adherence & investigate/address underlying causes of any non-adherence	196	In person (routine HCP)	4 sessions of 45-60 minutes over 5 weeks
Safren et al 2001[44]	Community clinic, USA	HIV	Single session minimal treatment intervention using cognitive behavioural, motivational interviewing and problem solving techniques	Motivational Interviewing (MI)	Minimal contact intervention; daily diary used to record no. of pills prescribed & taken each day	53	In person (routine HCP)	One-off intervention of unknown duration
Sheeran et al 1999[28]	Visits to patients own home, UK	Vitamin Supplements	Formation of III via completion of a self-administered questionnaire	Implementation Intention Intervention (III)	Completion of same questionnaire but without formation of implementation intention	78	Questionnaire completion (not in person)	One-off intervention of unknown duration
Simoni et al. 2009[48]	Community based clinic & telephone calls to patient's at home, USA	HIV	Peer-led medication-related social support intervention.	Multiple-components; non-specific techniques	Standard care; education programme and social and health referrals as necessary	114	Group sessions and individual telephone calls (peers)	18 sessions of unknown duration over 3 months

Study	Study setting	Disease area	Intervention description*	Identified intervention components	Components received by control group	Sample size	Intervention delivery style (& personnel)	Intervention length (average)
Smith et al 2003[47]	Community based research office, USA	HIV	Self-management intervention based on feedback of adherence performance & principles of social cognitive theory	Multiple components; non-specific techniques	Standard care; usual medication counselling, educational leaflets, scheduling support reminder lists & discussion of adherence strategies	17	In person (routine HCP)	Four sessions of unknown duration over 12 weeks
Solomon et al 2012[43]	Telephone calls to patients own home, USA	Osteoporosis	Telephone based counselling programme rooted in motivational interviewing	Motivational Interviewing (MI)	Standard care plus seven information mailings on osteoarthritis care	2087	Telephones calls (health educator)	8 sessions of 14 minutes over 12 months
Tuldra et al 2000[46]	Hospital clinic, Spain	HIV	Psycheducative intervention based on Self-efficacy theory	Multiple components; non-specific techniques	Standard care; normal clinical follow-up	77	Unknown (routine HCP)	7 sessions of unknown duration
Van Es et al 2001[32]	Hospital clinic, Netherlands	Asthma	Intervention programme to stimulate a positive attitude, increase social support and enhance self-efficacy.	Multiple components; non-specific techniques	Standard care; routine check-ups	67	In person (routine HCP)	7 sessions of 30-90 minutes over 12 months
Wagner et al 2006[45]	Community clinic, USA	HIV	Cognitive behavioural intervention with motivational components, based on the information-motivation-behavioural skills (IMB) model	Multiple components; non-specific techniques	Standard care practices for improving adherence; education, tailoring regimen, offering a pillbox, adherence checks & enquiries about side effects	135	In person (routine HCP)	5 sessions of 30-45 minutes over 48 weeks
Weber et al 2004[33]	Community, psychotherapy clinic, Netherlands	HIV	Cognitive behavioural intervention delivered by a psychotherapist.	Multiple components; non-specific techniques	Standard care (no details provided)	53	In person (specialist)	11 sessions of 45 minutes over 12 months

Study	Study setting	Disease area	Intervention description*	Identified intervention components	Components received by control group	Sample size	Intervention delivery style (& personnel)	Intervention length (average)
Williams et al. 2012[31]	Telephone calls and visits to patients own home, Australia	Diabetes	Multifactorial intervention consisting of self-monitoring of blood pressure, medicine review, educational DVDs and MI to support blood pressure control and optimal medication adherence	Motivational Interviewing (MI)	Standard care (no details provided)	75	In person and phone calls (specialist)	5 sessions, one of 89 minutes and 4 of an average of 11.75 minutes, over 3 months

* See supplementary table A for detailed breakdown of intervention components

Supplementary figures 1 and 2 show the results of the risk of bias assessment. Only Five (19.2%)studies[27 36 41 48 49] scored 'low risk' in all five bias categories. 19 (73.1%) were described as moderate overall risk, scoring 'low risk' in two to four of the categories and two (7.7%)[40 44] were described as 'high risk' scoring a low risk of bias in only one category. The most common source of bias was a lack of blinding of the outcome assessment; this is because the measure of adherence was frequently self-report. Self-report measures of adherence are commonly used but subject to patient bias. In the majority of cases the patients were not blind to their treatment group allocation and thus use of self-report measures leaves scope for bias.

Meta-analysis

26 RCTs were pooled to assess the effect of CBCT on medication adherence. Three studies showed non-significant negative effects on medication adherence but the remaining 23 studies all showed improvements in medication adherence with receipt of intervention. The effect size calculated for each study is summarised in table 2.

Random effects meta-analysis showed evidence that CBCT are associated with improved medication adherence. Figure 2 shows the forest plot for the 26 studies and exemplifies the tendency towards positive adherence effects with intervention. A pooled estimate of effect size (95% CI) (reported as Hedges' *g)* of 0·34 (0·23 to 0·46) was calculated when all studies were combined, although heterogeneity was high (I^2 = 68%, 95% CI: 52% to 79%).

The funnel plot produced was indicative of publication bias (as shown in figure 3) and so further explored using Egger's test which confirmed statistically significant funnel plot asymmetry (p= 0.005). The trim-and-fill technique was used to re-compute an effect size which accounted for this asymmetry, yielding a more conservative effect size estimate of 0.21 (0.08 to 0.33) (as shown in supplementary figure 3). This effect size suggests that CBCT elicit small but statistically significant improvements in medication adherence (p = 0.001) relative to standard care. According to data from six studies that used the percentage of prescribed dose taken, the pooled standard deviation of this outcome was 30.7%. Then a standardised mean difference of 0.205 (0.084 to 0.326) is corresponding to a difference of 6.3% (2.6% to 10.0%) between the intervention and the control group in the percentage of dose taken.

Table 2: Study outcomes for studies included in meta-analysis

Study	Sample size (intervention, control)	Adherence definition (assessment measure)	Extracted data			Effect size (Hedges's g) (95% CI)
			Intervention group	Control group	P-value	
Bailey et al 1990	225 (124, 101)	% of patients scored as adherent on all 6 items of a self-report scale (based on Morisky's self-reported scale)	Mean = 91.9	Mean = 61.7	0.001	0.44 (0.18 to 0.71)
Berger et al 2005	367 (172, 195)	% of patients discontinuing treatment by study endpoint (patient interview)	Mean = 98.8	Mean = 91.3	0.001	0.35 (0.14 to 0.55)
Brown et al 2009	69 (36, 33)	% of prescribed doses taken over a month (electronic monitoring)	Mean (SD) = 93.4 (12.3)	Mean (SD) = 79.1 (28.1)		0.66 (0.18 to 1.14)
Dilorio et al 2003	17 (8, 9)	Mean number of missed medicines in the last 30 days (self-report questionnaire)	Mean (SD) = 0.13 (0.35)	Mean (SD) = 0.98 (1.48)		0.73 (-0.21 to 1.67)
Dilorio et al 2008	213 (107, 106)	% of doses taken during intervention period (electronic monitoring)	Mean = 64	Mean = 55	0.09	0.23 (-0.04 to 0.50)
Farmer et al. 2012	211 (126, 85)	% of days during a 12 week period in which medication was taken correctly (electronic monitoring)	Mean (SD) = 77.4 (26.3)	Mean (SD) = 64.0 (30.8)	0.04	0.47 (0.20 to 0.75)
George et al 2010	343 (170, 173)	% of participants classed as adherent (Morisky self-report scale)	Mean = 72.2	Mean = 63.8	0.09	0.18 (-0.03 to 0.39)
Golin et al 2006	117 (59, 58)	% of prescribed doses taken take in month prior to study endpoint (CAS)	Mean (SD) = 76 (27)	Mean (SD) = 71 (27)		0.18 (-0.18 to 0.54)
Hovell et al 2003	188 (92, 96)	Cumulative number of doses taken over 9 months (patient interview)	Mean (SD) = 179.93 (57.01)	Mean (SD) = 150.98 (73.75)		0.44 (0.15 to 0.72)
Konkle-Parker et al. 2012	36 (21,15)	% of patients taking >90% of their medications in the last 3-4 weeks (prescription refill data)	Mean (SD) = 0.93 (0.23)	Mean (SD) = 0.92 (0.27)		0.04 (-0.61 to 0.69)
Maneesriwongul et al 2012	60 (30, 30)	Mean % of doses taken over last 4 weeks (self-report using visual analogue scale)	Mean (SD) = 97.1 (3.3)	Mean (SD) = 89.8 (5.6)		1.55 (0.98 to 2.12)
Murphy et al 2002	33 (17, 16)	% of doses taken during intervention period (self-report questionnaire)	Mean (SD) = 0.86 (0.33)	Mean (SD) = 0.83 (0.36)		0.09 (-0.58 to 0.75)
Ogedegbe et al 2008	160 (79, 81)	% of days during a two month period in which medication was taken correctly (electronic monitoring)	Mean = 56.9	Mean = 42.9	0.027	0.35 (0.04 to 0.66)
Pradier et al 2003	202 (123, 121)	% of patients deemed to be adherent (taking 100% of doses) (self-report questionnaire)	Mean = 75	Mean = 61	0.04	0.34 (0.02 to 0.65)

Put et al 2003	23 (12, 11)	Frequency of non-adherent behaviour over the last 3 months (self-report questionnaire)	Mean (SD) = 6.9 (1.2)	Mean (SD) = 8.1 (3.1)		0.50 (-0.30 to 1.30)
Remien et al 2005	196 (106, 109)	% of doses taken during previous 2 weeks (electronic monitoring)	Mean (SD) = 76 (27)	Mean (SD) = 60 (34)		0.52 (0.25 to 0.79)
Safren et al 2001	53 (28, 25)	% of prescribed doses taken over the last 2 weeks (self-report questionnaire)	Mean (SD) = 93 (22)	Mean (SD) = 94 (10)		-0.06 (-0.59 to 0.47)
Sheeran et al 1999	78 (38, 40)	Number of once daily doses missed over a 3 week period (self-report questionnaire)	Mean = 2.68	Mean = 4.85	0.05	0.45 (0.00 to 0.89)
Simoni et al. 2009	114 (57, 57)	% of doses taken over last seven days (electronic monitoring)	Mean (SD) = 32.3 (42.5)	Mean (SD) = 29.1 (39.7)		0.08 (-0.29 to 0.44)
Smith et al 2003	17 (8, 9)	% of participants taking ≥ 80% of their weekly doses (electronic monitoring)	Odds ratio = 7.8 (2.2 to 28.1)			1.08 (0.41 to 1.74)
Solomon et al 2012	2087 (1046, 1041)	Median % medication possession ratio (prescription refill data)	Median = 49 IQR = 7 to 88	Median = 41 IQR = 2 to 86	0.07	0.08 (-0.01 to 0.17)
Tuldra et al 2000	77 (36, 41)	% of patients with monthly adherence ≥ 95% (self-reported number of pills taken)	Mean = 94	Mean = 69	0.008	0.62 (0.16 to 1.07)
Van Es et al 2001	67 (58, 54)	Adherence score on self-report scale based on how often medication was taken (never-always)	Mean = 7.7	Mean = 6.7	0.05	0.48 (0.00 to 0.96)
Wagner et al 2006	135 (154, 76)	% of doses taken during intervention period (electronic monitoring)	Mean = 83.5	Mean = 86.4	0.57	-0.08 (-0.35 to 0.20)
Weber et al 2004	53 (29, 24)	% of patients with monthly adherence ≥ 95% (electronic monitoring)	Mean = 70.8	Mean = 50	0.014	0.69 (0.14 to 1.24)
Williams et al 2012	75 (36, 39)	% of doses taken during intervention period (pill counts	Mean = 58.4	Mean = 66	0.162	-0.32 (-0.77 to 0.13)

Sub-group analyses via meta-regression

Table 3 summarises the results of the subgroup analyses to explore variation in effect size for the pre-determined variables. The regression co-efficient is the difference in pooled Hedges' g between the two subgroups compared. A co-efficient >0 indicates that studies in subgroup-A reported greater treatment effects that those in subgroup-B.

The classification of studies into sub-groups was largely intuitive. However, as a continuous rather than categorical variable, 'total intervention exposure' was less amenable to intuitive dichotomisation. In such instances, it is standard practice to create two sub-groups by distributing a roughly equal number of studies to each group. An arbitrary cut off point of three hours was therefore used to split the data into two sub-groups.

Interventions delivered from hospital settings were associated with greater treatment effect compared with interventions in community or other settings (difference 0.27, 95% CI 0.01 to 0.54, P=0.043). Differences in effect size between subgroups were statistically non-significant in all other cases. However, the subgroup analyses may have failed to detect important differences between subgroups because of the small number of studies included.

Table 3: Summary of sub-group analyses

Variable	Sub-group-A vs. subgroup-B	No. of studies (no. of participants) in each sub-group	Co-efficient (95% CI)	P-value
Intervention setting	Hospital vs. community	9 (1124) Vs. 17 (4092)	0.27 (0.01 to 0.54)	0.043
Disease area	HIV vs. other conditions	14 (1323) Vs. 12 (3893)	0.05 (-0.23 to 0.33)	0.72
Intervention components	MI vs. no MI component	11 (3538) Vs. 15 (1678)	-0.17 (-0.44 to 0.09)	0.193
Intervention delivery method	Entirely in person vs. other methods	15 (1663) Vs. 11 (3553)	-0.03 (-0.31 to 0.25)	0.841
	Entirely over the telephone vs. other methods	3 (2679) Vs. 23 (2537)	-0.16 (-0.59 to 0.26)	0.442
	Both in person and telephone vs. other	7 (775) Vs. 19 (4441)	-0.05 (-0.27 to 0.37)	0.744
Intervention delivery personnel	Specialist vs. Routine HCP	5 (503) Vs. 12 (1567)	-0.01 (-0.46 to 0.26)	0.561
Total intervention exposure	≤3 hours vs. >3 hours	9 (3061) vs. 7 (887)	0.07 (-0.35 to 0.50)	0.728
Control group type	Explicit active controls vs. usual care (no adherence enhancing strategies)	13 (3683) Vs. 13 (1533)	0.09 (-0.18 to 0.37)	0.493
Risk of bias	Outcome assessment blinding vs. no outcome assessment blinding	15 (3555) Vs. 11 (1661)	0.05 (-0.24 to 0.33)	0.736
Outcome measures	Objective vs. subjective measured outcomes	14 (3850) Vs. 12 (1366)	-0.16 (-0.44 to 0.11)	0.225

As the variable 'intervention exposure' was a continuous variable, an additional post-hoc analysis was undertaken. This allowed the variable to be analysed in it 'natural' continuous state rather than two sub-groups. This exploratory analysis was undertaken to ensure that the arbitrary cut off point of three hours had not adversely influenced the data. A co-efficient value (95% CI) of 0.001 (-0.001 to 0.002) suggested that there was no association between intervention exposure and effect size. A non-significant p-value of 0.540 confirmed this and demonstrates comparable results to the sub-group analysis for this variable.

Discussion

Principal findings

Receipt of a cognitive-based behavioural adherence intervention was associated with small but statistically significant improvements in medication adherence. Heterogeneity was high and notable publication bias was identified. However, techniques have been used to account for this bias resulting in a more conservative summary effect size of 0.21 (95% CI: 0.08 to 0.33; P=0.001).

In half of the included studies, the standard care received by the control group explicitly involved some form of 'adherence enhancing strategy' such as provision of education, monitoring or review. Such strategies form the mainstay of current medication adherence interventions and so our research suggests that CBCT may be able to elicit adherence benefits beyond the techniques used in current practice.

The majority of interventions were complex and multifaceted, thus subgroup analysis to explore whether this is associated with greater effect could not be undertaken. The sub-group analyses performed revealed that the effect size is greater when interventions were delivered in the hospital setting compared with community, but not influenced by other variables such as the type of CBCT, delivery method and personnel or duration. Further work is necessary to explore the effect of setting on effect size.

Comparison with other studies

In 2003, Peterson *et al.* conducted a meta-analysis of educational and behavioural interventions to improve medication adherence in a range of illnesses.[53] The included studies were all RCTs delivered over similar time periods to those included in our study. The educational components and behavioural components such as changes in dosing schedule and reminders examined by Peterson *et al.* closely mirror those utilised in the studies from

our meta-analysis which used control groups with 'active standard care'. Peterson *et al.* reported a correlation coefficient (*r*) equivalent to a Cohen's *d* effect size of 0·16 (0·08, 0·24). For our study, the effect size for all studies, when adjusting for publication bias and reported as Hedges' *g* was 0.20 (0.08, 0.33). This suggests that inclusion of CBCT, strengthens the adherence improvements gained, if only marginally. Moreover, Peterson *et al.* report publication bias observed from a funnel plot of their included studies, but have not made allowances for this bias via re-computed effect sizes. Their Cohen's *d* value of 0.16 is likely exaggerated by the noted publication bias and thus implies that the true difference in effect size between the two meta-analyses may be greater.

An effect size (Hedges' *g*) of 0.25 (95% CI 0.07, 0.42) for studies using MI was calculated, compared with an effect size of 0.41 (95% CI 0.278 to 0.541) for non-MI interventions. After adjusting for bias, the estimated Hedges' g was 0.137 (95% CI -0.067 to 0.341) for studies using MI and 0.356 (95% CI 0.223 to 0.489) for studies using non-MI interventions. These estimated effect sizes closely match the effect size calculated when MI is used as a behavioural intervention in other healthcare domains[14] and thus represents novel evidence for the wider application of MI techniques beyond the treatment of substance abuse and gambling. The overlapping confidence intervals of the effect sizes calculated for MI-based and non-MI based interventions suggests that MI-based interventions are unlikely to be superior in their efficacy compared to those based on other cognitive-based behaviour change techniques.

Strengths and weaknesses of our work

This study represents the first meta-analysis of MI and other CBCT as medication adherence interventions and has been undertaken with methodological rigour and in accordance with published guidance.[18] A notable strength of this work is the robust methodological techniques that have been applied to provide an estimate of effect size which accounts for publication biases and thus greater confidence can be placed in the estimate. The work is also strengthened by restriction to RCTs.

Whilst moderate agreement in abstract screening may be lower than ideal, this is largely attributable to paucity of detail reported in abstracts and complexities in intervention definitions which are known to be problematic in this domain.[11-13] The conservative approach to abstract screening prevented study exclusion if disagreement was associated with insufficient information and thus prevented exclusion in error. Heterogeneity between the included studies was high with an I^2 value of 68% (95% CI: 52% to 79%) and thus raises the question as to whether the studies were sufficiently comparable to warrant pooling in a

meta-analysis. Whilst we defined our inclusion criteria to ensure studies were as similar as possible (i.e. all using a CBCT), heterogeneity was expected as other factors such as the populations and disease states studied were more difficult to control for. Interestingly, the largest study had a small standardized group difference compared to most of the other studies which contributed substantially to the heterogeneity.[43] Furthermore, results from all but three of the studies indicate positive effects of the intervention. Aside from these between study differences, the actual interventions were variable, as were the definitions of adherence and assessment tools used.

The differences between subgroups were statistically non-significant in terms of disease area, intervention components, delivery methods, delivery personnel, intensity, usual care and risk of bias. However, the statistical power was limited by the small number of studies included in the subgroup analyses. The analyses may therefore have failed to detect some important subgroup differences. Moreover, for variables such as the intervention exposure, meaningful conclusions are difficult to draw. Whilst the analyses both infer that intervention exposure did not influence effect size, it is important to remember a whole host variables are at large. It is possible that briefer interventions used different techniques or were delivered to different types of recipients compared to the longer interventions and so comparisons may not be wholly meaningful. Further work may be necessary to explore whether otherwise identical interventions (same technique, same population, same delivery personnel and so forth) differ in effect size when delivered with different exposure.

Despite these numerous between study differences, the core of each intervention was the use of a CBCT to improve medication adherence which was comparable across all studies and thus we would argue that data pooling irrespective of heterogeneity was both intuitive and meaningful.

We have established that receipt of a cognitive-based behavioural medication adherence intervention is likely to elicit small improvements in medication adherence, but the clinical relevance and impact of this improvement remains unknown. Based on mean adherence rates in the control groups, mean standard deviations and the effect size calculated, it has been possible to estimate the increase in percentage of doses taken for the intervention groups. Based on the adjusted Hedges' *g* value of 0.205 (0.084 to 0.326), receipt of a CBCT improved adherence (% of doses taken) by 6.29% (2.58% to 10.0%). For some medications, a 6% increase in the percentage of doses taken may not be of clinical relevance. However, for other medications such as antiretroviral therapy for HIV which requires very high levels of adherence or anti-epileptic therapies with narrow therapeutic windows, a 6% increase in adherence may have notable clinical relevance. Whilst many

included studies included data on clinical outcomes, pooling of this data from a diverse range of studies was not possible.

Implications

Motivational and CBCT can seemingly be delivered effectively by routine healthcare professionals, with efficacy applicable to a range of diseases. Efficacy was not related to intervention exposure. Interestingly, the results also suggest that these interventions can be delivered via telephone or face-to-face with comparable efficacy. These are valuable traits for an adherence intervention which could be adaptable to a wide range of settings and amenable to tailoring to meet individual need.

The flexibility and adaptability of these techniques coupled with their frequent simplicity means that practitioners may wish to consider incorporation of these techniques into their consultations when faced with the need to facilitate medication related behaviour changes.

Recommendations and conclusions

Further investigation of these techniques as medication adherence interventions is warranted in order to further elucidate the characteristics most strongly associated with efficacy. Studies to determine both patient and healthcare practitioner acceptability of these techniques is also necessary to establish their role in routine healthcare.

Article summary

Article focus

- Medication non-adherence is widespread and represents a notable barrier to achieving optimal effects from therapeutic intervention.
- Despite the magnitude and consequences of non-adherence, a gold standard intervention to improve it remains elusive.
- Cognitive-based behaviour change techniques may represent a useful tool in improving medication adherence but their use in this domain had not been established using meta-analytic techniques.

Key messages

- Cognitive-based behaviour change techniques are effective interventions for improving medication adherence and capable of eliciting improvements in adherence beyond those achieved with educational and behavioural interventions which form the mainstay of current practice.

- According to the results of sub-group analyses, cognitive-based behaviour change techniques can be effectively delivered by routine healthcare providers, and the effectiveness of interventions is not associated with intervention exposure
- Health care providers may wish to consider incorporation of these techniques into their medication adherence consultations.

Strengths and limitations of this study

- The studies pooled in this meta-analysis are restricted to RCTs which strengthens their robustness.
- Techniques to account for publication bias have been utilised to provide a conservative effect size estimate offering robustness to our estimate
- Notable heterogeneity was reported when studies were combined which may be a limitation.

Declaration of competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgements

CE would like to acknowledge Estelle Payerne for her invaluable contributions as the second reviewer for abstract screening and data extraction. CE would also like to acknowledge David Wright and John Wood for their comments on the protocol design, data analysis and methods of dissemination, and Steven Watson for his on-going technical support in using the meta-analysis software and comments regarding data interpretation

Funding

This research has been supported by a PhD studentship awarded by the Dean of Science at the University of East Anglia.

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A meta-analysis of cognitive-based behaviour change techniques as interventions to improve medication adherence

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Keywords: Medication adherence, Motivational Interviewing, Meta-analysis, Behaviour change, Adherence intervention

Abstract

Objective

To describe and evaluate the use of cognitive-based behaviour change techniques as interventions to improve medication adherence.

Design

Systematic review and meta-analysis of interventions to improve medication adherence.

Data sources

Search of Medline, Embase, PsycINFO, CINAHL and The Cochrane Library databases from the earliest year to April 2013 without language restriction. References of included studies were also screened to identify further relevant articles.

Review methods

We used pre-defined criteria to select Randomised Controlled Trials (RCTs) describing a medication adherence intervention that used Motivational Interviewing (MI) or other-cognitive based techniques. Data were extracted and risk of bias was assessed by two independent reviewers. We conducted the meta-analysis using a random effects model and Hedges' *g* as the measure of effect size.

Results

We included 26 studies (5216 participants) in the meta-analysis. Interventions most commonly used MI but many used techniques such as aiming to increase the patient's confidence and sense of self-efficacy, encouraging support seeking behaviours and challenging negative thoughts, which were not specifically categorised. Interventions were most commonly delivered from community based settings by routine healthcare providers such as GPs and nurses. An effect size (95% CI) of 0.34 (0.23 to 0.46) was calculated and ~~the overall effect of these interventions~~ was statistically significant (p = <0.001). Heterogeneity was high with an I^2 value of 68%. Adjustment for publication bias generated a more conservative estimate of summary effect size of 0.21 (0.08 to 0.33). ~~No statistically significant differences were observed in a range of subgroup analyses.~~ The majority of sub-group analyses produced statistically non-significant results.

Conclusion

Cognitive-based behaviour change techniques are effective interventions eliciting improvements in medication adherence that are likely to be greater than the behavioural and educational interventions largely used in current practice. ~~Results of subgroup analyses indicated that these interventions can be delivered in routine healthcare settings by non-specialist healthcare providers.~~ Sub-group analyses suggest that these interventions are amenable to use across different populations and in differing manners without loss of efficacy. These factors may facilitate incorporation of these techniques into routine care.

Introduction

Estimates suggest that 30 to 50% of patients prescribed medications for chronic illnesses do not adhere to their prescribed medication regimen.[1] This non-adherence has been demonstrated to diminish treatment effect which can result in prolonged illness, additional investigations and prescribing that may otherwise have been unnecessary.[2] A link between poor adherence and an increased risk of mortality is also well established.[3] Consequently, the World Health Organisation (WHO) has described non-adherence as "a worldwide problem of striking magnitude" and a priority for healthcare researchers and policy makers.[1]

Despite both the magnitude and potential gravity of sub-optimal medication adherence, a gold standard intervention remains elusive; a recent Cochrane review highlighted the paucity of effective interventions in current practice.[4] Evidence suggests that complex, multi-faceted interventions, tailored to meet individual needs are most likely to be efficacious[4 5] which is intuitive given the complex, multi-stage process that is medication taking.

Non-adherent behaviour is traditionally categorised into unintentional and intentional. Unintentional non-adherence includes behaviours arising from forgetfulness, misunderstanding and confusion. Intentional non-adherence describes patient choice to deviate from the prescribed medication regimen. Unintentional and intentional non-adherence are not mutually exclusive thus an amalgam of these behaviours often exists in any one patient. An understanding of patient behaviour and its underpinning psychology plus the wealth of factors, both internal and external that may influence medication taking, is crucial to understanding how to change patient behaviour and thus improve medication adherence.[6]

Historically, adherence interventions have encompassed behaviour change techniques such as simplifying dosage regimens and providing adherence aids or education to address the practical issues of adherence in terms of knowing how and being able to take the medication as prescribed. Pooled data for such studies have demonstrated marginal effects[4] yet such interventions continue to form the cornerstone of routine healthcare provision.[2] These interventions may have particularly poor efficacy in cases of intentional non-adherence as the provision of persuasive advice may evoke further resistance to change.[7 8] Through an understanding of the challenges faced in changing behaviours and the motivation necessary to achieve change, novel, Cognitive-based Behaviour Change Techniques (CBCT) have emerged. These interventions aim to change a patient's behaviour by altering their thoughts, feelings, confidence or motivation to adhere. CBCT interventions can vary widely

in content such as incorporating techniques to enhance patient sense of self-efficacy, problem solve and increase motivation to adhere.

Motivational interviewing (MI) is one of the most widely recognised CBCT and is designed to facilitate behaviour change by resolving patient ambivalence about change.[9] It therefore primarily targets intentional non-adherence but also enables patients to reflect on any unintentional barriers to adherence and seek out solutions. Systematic reviews and meta-analyses have reported MI efficacy in facilitating health related behaviour change such as smoking cessation and alcohol withdrawal[10-16] but have not explored its effects on medication adherence. Adaptations of MI such as Behaviour Change Counselling (BCC)[17]additionally allow the facilitator to educate and advise thus application to both intentional and unintentional non-adherence may be effective.

Best practice guidelines state that evidence of intervention efficacy should ideally be pooled from literature in a systematic review or meta-analysis wherever possible to offer a robust and cohesive evidence base.[18] This study provides a systematic review and meta-analysis of MI and other cognitive-based techniques as interventions to improve medication adherence.

Methods

We used standard systematic review methods[18 19] and registered the study protocol (PROSPERO register reference CRD42011001721). Randomised Controlled Trials (RCTs) reporting an adherence intervention using MI and/or other cognitive-based techniques with medication adherence as an outcome measure were eligible for inclusion. All definitions of adherence such as percentage of doses taken over a given time period and percentage of patients achieving a specified adherence level were considered. All adherence measures were also considered including self-report and electronic monitoring. Where multiple measures were reported, the percentage of patients achieving a specified adherence level was selected as this was common to more studies.

Any intervention using some form of psychological technique to change a patient's adherence behaviour and their thoughts, feelings, confidence, or motivation towards adhering was defined as a cognitive-based technique. Studies examining adherence to medications for the treatment of addiction and/or mental health conditions were excluded as these interventions tend to be specific to these domains.

Search strategies

We developed a search strategy to avoid restriction to pre-determined terms such as 'motivational interviewing' as many of the techniques of interest are not classified using specific or consistent terms. MeSH terms were also used to enhance retrieval of relevant studies. Truncations (*), wild cards ($), hyphens and other relevant Boolean operators were used where permitted. Scoping searches were conducted prior to finalising the search strategy to ensure suitability of terms in generating a good coverage of relevant material.

We applied the search strategy (as shown in appendix one) to the MEDLINE, EMBASE, PsychINFO, ~~and~~ CINAHL and Cochrane~~, and~~ databases in April 2013 without date or language restrictions. The reference lists of all screened full text articles were also used to identify further relevant articles.

Study selection and data extraction

Two researchers (CE and EP) independently screened titles and abstracts against the inclusion and exclusion criteria using a piloted abstract screening tool. Inter-reviewer agreement using Cohen's Kappa (K) was assessed for both the abstract and full text screening stage. The level of agreement was characterised using a qualitative scale.[20] Discrepancies were resolved by discussion between the two reviewers, and if necessary referral to a third independent reviewer (DB) until consensus was reached.

Data extraction was also undertaken by CE and EP, independently using piloted forms. Data extracted included study details (such as year and journal of publication, country and study design); study characteristics (including setting, population, delivery methods and personnel); intervention details (including intervention type, duration and principal components) and outcome details (including adherence assessment measure, data and definition). A list of intervention components was independently extracted from the articles verbatim by two reviewers. Grouping of similar components was undertaken by one reviewer and verified by a second reviewer.

Accuracy of data collected was verified by comparison of the forms completed by the two independent reviewers. In cases of discrepancy, consensus was agreed through discussion and where necessary, referral to a third independent reviewer (DB). For studies with missing data or ambiguities, the corresponding author was contacted for clarification.

Quality assessment

A quality assessment of all included studies was made using the Cochrane risk of bias tool.[18] The risk of bias was assessed in five domains deemed relevant to the included studies:

random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data and selective reporting. Performance bias (blinding of participants and personnel) was not included as the nature of the interventions meant that blinding of participants and personnel was impossible in almost all studies. None of the included studies were found to contain additional sources of potential bias not represented by the five included domains. The risk of bias for each study, in each of the five domains was classified as low, uncertain or high, as recommended in the guidelines.[18] The quality assessment process was undertaken independently by two reviewers, with consensus on the final risk classifications reached through discussion.

Data analysis

The meta-analysis was conducted using STATA® (version 12.1). Given the broad inclusion criteria, we anticipated including studies from different populations, with different diseases and which used different CBCT. We therefore explored heterogeneity via calculation of the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance.[21 22] A random effects model (DerSimonian-Laird method) was employed to calculate a pooled effect size (Hedges' *g*) and 95% confidence interval for the included studies.[23] Calculation of the effect size as Hedges' *g* (standardised difference in means) enabled adherence outcome measures of differing definition and measure, to be combined, transforming this data into a common metric. When standard deviation was missing, we estimated standard error of mean difference based on reported P values, means and the number of patients. Odds ratios were converted to standardised mean differences by using the formula SMD=lnOR*√3/π).[23]

Funnel plots were produced where appropriate to explore potential publication biases. STATA® (version 12.1) was used to conduct Egger's test[24] to test funnel plot asymmetry. We used the trim and fill method[25 26] to estimate a summary effect size after adjusting for asymmetric funnel plots.

Variables of interest in influencing the effect size and informing intervention design were determined a priori and the following subgroup analyses undertaken using a random effects meta-regression: intervention components, setting , delivery personnel, delivery method and intervention exposure~~exposure~~, disease area and risk of bias. ~~and~~ The type of outcome measure used to assess adherence (objective compared to subjective) was added as a post-hoc sub-group analysis to further explore heterogeneity. Objective outcome measures included electronic monitoring and pill counts, subjective measures included all forms of self-

report. Differences between subgroups were tested using STATA 'metareg' command for random-effects univariate meta-regression analysis.

Results

Study selection, characteristics and quality

Figure 1 shows the number of papers excluded at each stage of the review. Of the 442 abstracts screened, 84 studies passed the abstract screening stage with moderate agreement between the two reviewers (k = 0·57). Conflict in classifying an intervention as a CBCT accounted for 31.0% of discrepancies and was heavily influenced by a paucity of information in the abstracts. At the full text screening stage, agreement between the two independent reviewers was much higher, with a kappa value of 0.91, indicating almost perfect agreement. After examining 84 full-text articles, we included 26(31.0%) in the meta-analysis.

The main characteristics of the 26 included studies are summarised in Table 1. The studies provided a total sample size of 5216 participants. Studies were primarily undertaken in the United States of America (USA) followed by the United Kingdom (UK),[27-29] Australia[30 31] and the Netherlands[32 33]. Dates of publication ranged from 1990 to 2012 with only two studies (7.7%) pre-dating 2000[28 34]. Ten (38.5%) were published within the last five years (2008-2013). The most common condition for which medications were prescribed was HIV, accounting for 14 (53.8%) studies. Other studies concerned treatments for a range of conditions including asthma[32 34 35] diabetes[27 31] and hypertension[30 36].

Just over half of the included studies(53.8%) described an intervention with a clearly defined CBCT; Motivational Interviewing (MI) was most commonly used and this was the case for 11 (42.3%) studies[30 31 36-44]. A further three (11.5%) studies used Implementation Intention Interventions (III, also known as if-then planning) as a clearly defined CBCT. For 12 (46.2%) studies, a clearly defined CBCT such as MI could not be identified[32-35 45-52], these studies are identified in table 1 as 'multiple components; non-specific techniques'. Instead, this group comprised of, multiple components such as 'providing education' or 'increasing patient knowledge' which was reported in nine (75.0%) (studies in this group. Other components included 'increasing self-efficacy' and 'developing or improving problem solving skills' each reported in six (50.0) studies and 'identifying and resolving adherence barriers' and 'increasing social support' also each reported in six (50.0%). All studies within this group included one or more components that aimed to alter the patient's thoughts, feelings, motivation or confidence towards adherence and that could therefore be classified as a

cognitive-based behaviour change technique. Detailed information regarding the identified intervention components extracted from each study are provided as a supplementary table. The majority of interventions had multiple components. Many studies combined cognitive-based behaviour change techniques with more traditionally used educational (e.g. increasing patient knowledge) and behavioural (e.g. regimen simplification and provision of dosing aids) components.

Interventions were most commonly delivered in person, from community based settings and by routine healthcare providers such as nurses, pharmacists and general medical practitioners. 'Non-routine' healthcare providers were considered to be those such as psychologists or psychotherapists, who would not ordinarily be involved in the patient's care in the absence of mental illness.

The intervention period ranged from four (15·4%) studies reporting singular sessions, to six (23·1%) studies reporting multiple sessions over 12 months. The median (IQ) number of sessions over which interventions were delivered was 5.0 (3.0 to 7.3). The majority of interventions were delivered over a period of six months or less which was the case for 17 studies (65.4%). Intervention exposure as the total number of minutes spent delivering the intervention could be estimated for 16 studies. In the remaining 10 studies this data was not available. Intervention exposure ranged from thirty minutes to eight hours and fifteen minutes. The median (IQR) intervention exposure was 175 (118 to 263) minutes.

The comparison group was 'standard care' for all studies; for 13 studies (50.0%) standard care involved some form of technique to improve adherence such as education, encouragement or provision of adherence aids and in these studies, recipients of the intervention received further techniques such as MI.

Table 1: Characteristics of included studies in meta-analysis

Study	Study setting	Disease area	Intervention description*	Identified intervention components	Components received by control group	Sample size	Intervention delivery style (& personnel)	Intervention length (average)
Bailey et al 1990[34]	Hospital clinic, USA	Asthma	Comprehensive programme integrating a skills-orientated self-help workbook with one-to-one counselling & adherence-enhancing strategies.	Multiple components; non-specific techniques	Standard care; education via standardised set of pamphlets and routine physician encouragement	225	Telephone calls and in person (specialist)	240 minutes (4 x 60min sessions) over unknown period
Berger et al 2005[40]	Telephone calls to patients at home, USA	Multiple Sclerosis	Software supported intervention based on Transtheoretical model of change and MI	Motivational Interviewing (MI)	Standard care plus could telephone help line	367	Telephone calls (researcher)	9 sessions of unknown duration delivered over 3 months
Brown et al 2009[29]	Hospital clinic, UK	Epilepsy	Formation of III via completion of a self-administered questionnaire	Implementation Intention Interventions (III)	Standard care plus self-report questionnaires	69	Questionnaire completion (not in person)	One-off intervention of unknown duration
DiIorio et al 2003[41]	Community clinic, USA	HIV	One-to-one counselling sessions based on MI	Motivational Interviewing (MI)	Standard care; usual adherence education provided in the clinic	17	In person (routine HCP)	5 x 35 minutes sessions delivered over 12 months
DiIorio et al 2008[42]	Hospital clinic, USA	HIV	MI as individual counselling sessions	Motivational Interviewing (MI)	Standard care; usual (extensive) education provided at the clinic	213	Mostly in person with some telephone calls (routine HCP)	5 sessions of 35 minutes over 12 months
Farmer et al. 2012[27]	Community based clinic, UK	Type 2 diabetes	Brief intervention to elicit beliefs, resolve barriers and form 'if-then' plans.	If-then Planning (III)	Standard care plus additional clinic visits for blood tests	211	In person (clinic nurse)	One-off session lasting 30 minutes.
George et al 2010[30]	Community pharmacies, Australia and Tasmania	Hypertension	Community pharmacy intervention of one-to-one sessions, monitoring & medication review	Motivational Interviewing (MI)	Standard care	343	In person (routine HCP)	3 sessions of unknown duration over 6 months

Study	Study setting	Disease area	Intervention description*	Identified intervention components	Components received by control group	Sample size	Intervention delivery style (& personnel)	Intervention length (average)
Golin et al 2006[39]	Community clinic, USA	HIV	Multi-component MI based intervention.	Motivational Interviewing (MI)	General HIV information provided via audio tape, two one-to-one sessions and two mail shots.	117	In person (specialist)	2 sessions of unknown duration over 2 months
Hovell et al 2003[51]	Hospital clinic, USA	Tuberculosis	Adherence coaching involving interviewing, contingency contracting and shaping procedures	Multiple components; non-specific techniques	Standard care; routine advice at appointments	188	Telephone calls & in person (researcher)	12 sessions of 15-30 minutes over 6 months
Konkle-Parker et al. 2012[38]	Community based clinics and patients own homes, USA	HIV	Adherence intervention guided by the Information-Motivation-Behavioural Skills (IMB) model	Motivational Interviewing (MI)	Standard care; usual clinic appointments	36	Telephone calls and in person (nurse practitioner)	8 sessions over 24 weeks. Average overall duration 1h 30 minutes
Maneesriwongul et al 2012[37]	Hospital outpatients clinic & telephone calls to patients at home, Thailand	HIV	Motivational interviewing with counselling	Motivational Interviewing (MI)	Standard care; education and provision of leaflets at point of prescribing	60	Telephone calls & in person (researcher)	3 sessions approximately 30 minutes over a four week period
Murphy et al 2002[52]	Community based clinic, USA	HIV	Multi-component and multi-disciplinary intervention including behavioural strategies and cognitive behavioural therapy	Multiple components; non-specific techniques	Standard care; regular appointments with enquiries about adherence and an additional 30 minute appointment for those with problems where medication schedule is written down for them	33	In person (specialist)	5 sessions of unknown duration over 7 weeks
Ogedegbe et al 2008[36]	Community clinic, USA	Hypertension	Practice-based MI counselling	Motivational Interviewing (MI)	Standard care; usual appointments plus additional visits for MEMS downloads	160	In person (researcher)	4 sessions lasting 30-40 mins delivered over 12 months

Study	Study setting	Disease area	Intervention description*	Identified intervention components	Components received by control group	Sample size	Intervention delivery style (& personnel)	Intervention length (average)
Pradier et al 2003[50]	Hospital clinic, France	HIV	Educational & counselling intervention founded in the principles of motivational psychology and client-centred therapy	Multiple components; non-specific techniques	Standard care; routine follow up appointments	202	In person (routine HCP)	3 sessions of 45-60 minutes over 3 months
Put et al 2003[35]	Hospital clinic, Belgium	Asthma	Behavioural change intervention involving psycho-education with behavioural and cognitive techniques	Multiple components; non-specific techniques	Standard (no details provided)	23	In person (researcher)	360 minutes ~~hours~~ (6 x 60 minutes sessions) over 3 months
Remien et al[49] 2005	Community based clinic, USA	HIV	Couples-based intervention grounded in Social action theory	Multiple components; non-specific techniques	Standard care; education at point of prescribing & follow up to check adherence & investigate/address underlying causes of any non-adherence	196	In person (routine HCP)	4 sessions of 45-60 minutes over 5 weeks
Safren et al 2001[44]	Community clinic, USA	HIV	Single session minimal treatment intervention using cognitive behavioural, motivational interviewing and problem solving techniques	Motivational Interviewing (MI)	Minimal contact intervention; daily diary used to record no. of pills prescribed & taken each day	53	In person (routine HCP)	One-off intervention of unknown duration
Sheeran et al 1999[28]	Visits to patients own home, UK	Vitamin Supplements	Formation of III via completion of a self-administered questionnaire	Implementation Intention Intervention (III)	Completion of same questionnaire but without formation of implementation intention	78	Questionnaire completion (not in person)	One-off intervention of unknown duration
Simoni et al. 2009[48]	Community based clinic & telephone calls to patient's at home, USA	HIV	Peer-led medication-related social support intervention.	Multiple-components; non-specific techniques	Standard care; education programme and social and health referrals as necessary	114	Group sessions and individual telephone calls (peers)	18 sessions of unknown duration over 3 months

Study	Study setting	Disease area	Intervention description*	Identified intervention components	Components received by control group	Sample size	Intervention delivery style (& personnel)	Intervention length (average)
Smith et al 2003[47]	Community based research office, USA	HIV	Self-management intervention based on feedback of adherence performance & principles of social cognitive theory	Multiple components; non-specific techniques	Standard care; usual medication counselling, educational leaflets, scheduling support reminder lists & discussion of adherence strategies	17	In person (routine HCP)	Four sessions of unknown duration over 12 weeks
Solomon et al 2012[43]	Telephone calls to patients own home, USA	Osteoporosis	Telephone based counselling programme rooted in motivational interviewing	Motivational Interviewing (MI)	Standard care plus seven information mailings on osteoarthritis care	2087	Telephones calls (health educator)	8 sessions of 14 minutes over 12 months
Tuldra et al 2000[46]	Hospital clinic, Spain	HIV	Psycheducative intervention based on Self-efficacy theory	Multiple components; non-specific techniques	Standard care; normal clinical follow-up	77	Unknown (routine HCP)	7 sessions of unknown duration
Van Es et al 2001[32]	Hospital clinic, Netherlands	Asthma	Intervention programme to stimulate a positive attitude, increase social support and enhance self-efficacy.	Multiple components; non-specific techniques	Standard care; routine check-ups	67	In person (routine HCP)	7 sessions of 30-90 minutes over 12 months
Wagner et al 2006[45]	Community clinic, USA	HIV	Cognitive behavioural intervention with motivational components, based on the information-motivation-behavioural skills (IMB) model	Multiple components; non-specific techniques	Standard care practices for improving adherence; education, tailoring regimen, offering a pillbox, adherence checks & enquiries about side effects	135	In person (routine HCP)	5 sessions of 30-45 minutes over 48 weeks
Weber et al 2004[33]	Community, psychotherapy clinic, Netherlands	HIV	Cognitive behavioural intervention delivered by a psychotherapist.	Multiple components; non-specific techniques	Standard care (no details provided)	53	In person (specialist)	11 sessions of 45 minutes over 12 months

Study	Study setting	Disease area	Intervention description*	Identified intervention components	Components received by control group	Sample size	Intervention delivery style (& personnel)	Intervention length (average)
Williams et al. 2012[31]	Telephone calls and visits to patients own home, Australia	Diabetes	Multifactorial intervention consisting of self-monitoring of blood pressure, medicine review, educational DVDs and MI to support blood pressure control and optimal medication adherence	Motivational Interviewing (MI)	Standard care (no details provided)	75	In person and phone calls (specialist)	5 sessions, one of 89 minutes and 4 of an average of 11.75 minutes, over 3 months

* See supplementary table A for detailed breakdown of intervention components

Supplementary figures 1 and 2 show the results of the risk of bias assessment. Only Five (19.2%)studies[27 36 41 48 49] scored 'low risk' in all five bias categories. 19 (73.1%) were described as moderate overall risk, scoring 'low risk' in two to four of the categories and two (7.7%)[40 44] were described as 'high risk' scoring a low risk of bias in only one category. The most common source of bias was a lack of blinding of the outcome assessment; this is because the measure of adherence was frequently self-report. Self-report measures of adherence are commonly used but subject to patient bias. In the majority of cases the patients were not blind to their treatment group allocation and thus use of self-report measures leaves scope for bias.

Meta-analysis

26 RCTs were pooled to assess the effect of CBCT on medication adherence. Three studies showed non-significant negative effects on medication adherence but the remaining 23 studies all showed improvements in medication adherence with receipt of intervention. The effect size calculated for each study is summarised in table 2.

Random effects meta-analysis showed evidence that CBCT are associated with improved medication adherence. Figure 2 shows the forest plot for the 26 studies and exemplifies the tendency towards positive adherence effects with intervention. A pooled estimate of effect size (95% CI) (reported as Hedges' *g)* of 0·34 (0·23 to 0·46) was calculated when all studies were combined, although heterogeneity was high (I^2 = 68%, 95% CI: 52% to 79%).

The funnel plot produced was indicative of publication bias (as shown in figure 3) and so further explored using Egger's test which confirmed statistically significant funnel plot asymmetry (p= 0.005). The trim-and-fill technique was used to re-compute an effect size which accounted for this asymmetry, yielding a more conservative effect size estimate of 0.21 (0.08 to 0.33) (as shown in supplementary figure 3). This effect size suggests that CBCT elicit small but statistically significant improvements in medication adherence (p = 0.001) relative to standard care. According to data from six studies that used the percentage of prescribed dose taken, the pooled standard deviation of this outcome was 30.7%. Then a standardised mean difference of 0.205 (0.084 to 0.326) is corresponding to a difference of 6.3% (2.6% to 10.0%) between the intervention and the control group in the percentage of dose taken.

Table 2: Study outcomes for studies included in meta-analysis

Study	Sample size (intervention, control)	Adherence definition (assessment measure)	Extracted data			Effect size (Hedges's g) (95% CI)
			Intervention group	Control group	P-value	
Bailey et al 1990	225 (124, 101)	% of patients scored as adherent on all 6 items of a self-report scale (based on Morisky's self-reported scale)	Mean = 91.9	Mean = 61.7	0.001	0.44 (0.18 to 0.71)
Berger et al 2005	367 (172, 195)	% of patients discontinuing treatment by study endpoint (patient interview)	Mean = 98.8	Mean = 91.3	0.001	0.35 (0.14 to 0.55)
Brown et al 2009	69 (36, 33)	% of prescribed doses taken over a month (electronic monitoring)	Mean (SD) = 93.4 (12.3)	Mean (SD) = 79.1 (28.1)		0.66 (0.18 to 1.14)
Dilorio et al 2003	17 (8, 9)	Mean number of missed medicines in the last 30 days (self-report questionnaire)	Mean (SD) = 0.13 (0.35)	Mean (SD) = 0.98 (1.48)		0.73 (-0.21 to 1.67)
Dilorio et al 2008	213 (107, 106)	% of doses taken during intervention period (electronic monitoring)	Mean = 64	Mean = 55	0.09	0.23 (-0.04 to 0.50)
Farmer et al. 2012	211 (126, 85)	% of days during a 12 week period in which medication was taken correctly (electronic monitoring)	Mean (SD) = 77.4 (26.3)	Mean (SD) = 64.0 (30.8)	0.04	0.47 (0.20 to 0.75)
George et al 2010	343 (170, 173)	% of participants classed as adherent (Morisky self-report scale)	Mean = 72.2	Mean = 63.8	0.09	0.18 (-0.03 to 0.39)
Golin et al 2006	117 (59, 58)	% of prescribed doses taken take in month prior to study endpoint (CAS)	Mean (SD) = 76 (27)	Mean (SD) = 71 (27)		0.18 (-0.18 to 0.54)
Hovell et al 2003	188 (92, 96)	Cumulative number of doses taken over 9 months (patient interview)	Mean (SD) = 179.93 (57.01)	Mean (SD) = 150.98 (73.75)		0.44 (0.15 to 0.72)
Konkle-Parker et al. 2012	36 (21,15)	% of patients taking >90% of their medications in the last 3-4 weeks (prescription refill data)	Mean (SD) = 0.93 (0.23)	Mean (SD) = 0.92 (0.27)		0.04 (-0.61 to 0.69)
Maneesriwongul et al 2012	60 (30, 30)	Mean % of doses taken over last 4 weeks (self-report using visual analogue scale)	Mean (SD) = 97.1 (3.3)	Mean (SD) = 89.8 (5.6)		1.55 (0.98 to 2.12)
Murphy et al 2002	33 (17, 16)	% of doses taken during intervention period (self-report questionnaire)	Mean (SD) = 0.86 (0.33)	Mean (SD) = 0.83 (0.36)		0.09 (-0.58 to 0.75)
Ogedegbe et al 2008	160 (79, 81)	% of days during a two month period in which medication was taken correctly (electronic monitoring)	Mean = 56.9	Mean = 42.9	0.027	0.35 (0.04 to 0.66)
Pradier et al 2003	202 (123, 121)	% of patients deemed to be adherent (taking 100% of doses) (self-report questionnaire)	Mean = 75	Mean = 61	0.04	0.34 (0.02 to 0.65)

Put et al 2003	23 (12, 11)	Frequency of non-adherent behaviour over the last 3 months (self-report questionnaire)	Mean (SD) = 6.9 (1.2)	Mean (SD) = 8.1 (3.1)		0.50 (-0.30 to 1.30)
Remien et al 2005	196 (106, 109)	% of doses taken during previous 2 weeks (electronic monitoring)	Mean (SD) = 76 (27)	Mean (SD) = 60 (34)		0.52 (0.25 to 0.79)
Safren et al 2001	53 (28, 25)	% of prescribed doses taken over the last 2 weeks (self-report questionnaire)	Mean (SD) = 93 (22)	Mean (SD) = 94 (10)		-0.06 (-0.59 to 0.47)
Sheeran et al 1999	78 (38, 40)	Number of once daily doses missed over a 3 week period (self-report questionnaire)	Mean = 2.68	Mean = 4.85	0.05	0.45 (0.00 to 0.89)
Simoni et al. 2009	114 (57, 57)	% of doses taken over last seven days (electronic monitoring)	Mean (SD) = 32.3 (42.5)	Mean (SD) = 29.1 (39.7)		0.08 (-0.29 to 0.44)
Smith et al 2003	17 (8, 9)	% of participants taking ≥ 80% of their weekly doses (electronic monitoring)	Odds ratio = 7.8 (2.2 to 28.1)			1.08 (0.41 to 1.74)
Solomon et al 2012	2087 (1046, 1041)	Median % medication possession ratio (prescription refill data)	Median = 49 IQR = 7 to 88	Median = 41 IQR = 2 to 86	0.07	0.08 (-0.01 to 0.17)
Tuldra et al 2000	77 (36, 41)	% of patients with monthly adherence ≥ 95% (self-reported number of pills taken)	Mean = 94	Mean = 69	0.008	0.62 (0.16 to 1.07)
Van Es et al 2001	67 (58, 54)	Adherence score on self-report scale based on how often medication was taken (never-always)	Mean = 7.7	Mean = 6.7	0.05	0.48 (0.00 to 0.96)
Wagner et al 2006	135 (154, 76)	% of doses taken during intervention period (electronic monitoring)	Mean = 83.5	Mean = 86.4	0.57	-0.08 (-0.35 to 0.20)
Weber et al 2004	53 (29, 24)	% of patients with monthly adherence ≥ 95% (electronic monitoring)	Mean = 70.8	Mean = 50	0.014	0.69 (0.14 to 1.24)
Williams et al 2012	75 (36, 39)	% of doses taken during intervention period (pill counts	Mean = 58.4	Mean = 66	0.162	-0.32 (-0.77 to 0.13)

Sub-group analyses via meta-regression

Table 3 summarises the results of the subgroup analyses to explore variation in effect size for the pre-determined variables. The regression co-efficient is the difference in pooled Hedges' g between the two subgroups compared. A co-efficient >0 indicates that studies in subgroup-A reported greater treatment effects that those in subgroup-B.

The classification of studies into sub-groups was largely intuitive. However, as a continuous rather than categorical variable, 'total intervention exposure' was less amenable to intuitive dichotomisation. In such instances, it is standard practice to create two sub-groups by distributing a roughly equal number of studies to each group. An arbitrary cut off point of three hours was therefore used to split the data into two sub-groups.

Interventions delivered from hospital settings were associated with greater treatment effect compared with interventions in community or other settings (difference 0.27, 95% CI 0.01 to 0.54, P=0.043). Differences in effect size between subgroups were statistically non-significant in all other cases. However, the subgroup analyses may have failed to detect important differences between subgroups because of the small number of studies included.

Table 3: Summary of sub-group analyses

Variable	Sub-group-A vs. subgroup-B	No. of studies (no. of participants) in each sub-group	Co-efficient (95% CI)	P-value
Intervention setting	Hospital vs. community	9 (1124) Vs. 17 (4092)	0.27 (0.01 to 0.54)	0.043
Disease area	HIV vs. other conditions	14 (1323) Vs. 12 (3893)	0.05 (-0.23 to 0.33)	0.72
Intervention components	MI vs. no MI component	11 (3538) Vs. 15 (1678)	-0.17 (-0.44 to 0.09)	0.193
Intervention delivery method	Entirely in person vs. other methods	15 (1663) Vs. 11 (3553)	-0.03 (-0.31 to 0.25)	0.841
	Entirely over the telephone vs. other methods	3 (2679) Vs. 23 (2537)	-0.16 (-0.59 to 0.26)	0.442
	Both in person and telephone vs. other	7 (775) Vs. 19 (4441)	-0.05 (-0.27 to 0.37)	0.744
Intervention delivery personnel	~~Routine HCP vs. others~~	~~12 (1567) Vs. 14 (3649)~~	~~-0.02 (-0.30 to 0.26)~~	~~0.888~~
	~~Specialist vs. others~~	~~5 (503) Vs. 21 (4713)~~	~~-0.14 (-0.51 to 0.22)~~	~~0.419~~
	Specialist vs. Routine HCP	5 (503) Vs. 12 (1567)	-0.01 (-0.46 to 0.26)	0.561
~~Intervention exposure~~Total intervention exposure	~~Four sessions or fewer vs. five sessions or more~~ ≤3 hours vs. >3 hours	~~12 (1731) Vs. 14 (3485)~~ 9 (3061) vs. 7 (887)	~~0.22 (-0.04 to 0.48)~~ 0.07 (-0.35 to 0.50)	~~0.095~~ 0.728
Control group type	Explicit active controls vs. usual care (no adherence enhancing strategies)	13 (3683) Vs. 13 (1533)	0.09 (-0.18 to 0.37)	0.493

Risk of bias	Outcome assessment blinding vs. no outcome assessment blinding	15 (3555) Vs. 11 (1661)	0.05 (-0.24 to 0.33)	0.736
Outcome measures	Objective vs. subjective measured outcomes	14 (3850) Vs. 12 (1366)	-0.16 (-0.44 to 0.11)	0.225

As the variable 'intervention exposure' was a continuous variable, an additional post-hoc analysis was undertaken. This allowed the variable to be analysed in it 'natural' continuous state rather than two sub-groups. This exploratory analysis was undertaken to ensure that the arbitrary cut off point of three hours had not adversely influenced the data. A co-efficient value (95% CI) of 0.001 (-0.001 to 0.002) suggested that there was no association between intervention exposure and effect size. A non-significant p-value of 0.540 confirmed this and demonstrates comparable results to the sub-group analysis for this variable.

Discussion

Principal findings

Receipt of a cognitive-based behavioural adherence intervention was associated with small but statistically significant improvements in medication adherence. Heterogeneity was high and notable publication bias was identified. However, techniques have been used to account for this bias~~these biases~~ resulting in a more conservative summary effect size of 0.21 (95% CI: 0.08 to 0.33; P=0.001).

In half of the included studies, the standard care received by the control group explicitly involved some form of 'adherence enhancing strategy' such as provision of education, monitoring or review. Such strategies form the mainstay of current medication adherence interventions and so our research suggests that CBCT may be able to elicit adherence benefits beyond the techniques used in current practice.

The majority of interventions were complex and multifaceted, thus subgroup analysis to explore whether this is associated with greater effect could not be undertaken. The sub-group analyses performed revealed that the effect size is greater when interventions were delivered in the hospital setting compared with community, but not influenced by other variables such as the type of CBCT, delivery method and personnel or duration. Further work is necessary to explore the effect of setting on effect size.

Comparison with other studies

In 2003, Peterson *et al.* conducted a meta-analysis of educational and behavioural interventions to improve medication adherence in a range of illnesses.[53] The included studies were all RCTs delivered over similar time periods to those included in our study. The educational components and behavioural components such as changes in dosing schedule and reminders examined by Peterson *et al.* closely mirror those utilised in the studies from our meta-analysis which used control groups with 'active standard care'. Peterson *et al.* reported a correlation coefficient (*r*) equivalent to a Cohen's *d* effect size of 0·16 (0·08, 0·24). For our study, the effect size for all studies, when adjusting for publication bias and reported as Hedges' *g* was 0.20 (0.08, 0.33). This suggests that inclusion of CBCT, strengthens the adherence improvements gained, if only marginally. Moreover, Peterson *et al.* report publication bias observed from a funnel plot of their included studies, but have not made allowances for this bias via re-computed effect sizes. Their Cohen's *d* value of 0.16 is likely exaggerated by the noted publication bias and thus implies ~~infers~~ that the true difference in effect size between the two meta-analyses may be greater.

An effect size (Hedges' *g*) of 0.25 (95% CI 0.07, 0.42) for studies using MI was calculated, compared with an effect size of 0.41 (95% CI 0.278 to 0.541) for non-MI interventions. After adjusting for bias, the estimated Hedges' g was 0.137 (95% CI -0.067 to 0.341) for studies using MI and 0.356 (95% CI 0.223 to 0.489) for studies using non-MI interventions. These estimated effect sizes closely match the effect size calculated when MI is used as a behavioural intervention in other healthcare domains[14] and thus represents novel evidence for the wider application of MI techniques beyond the treatment of substance abuse and gambling. The overlapping confidence intervals of the effect sizes calculated for MI-based and non-MI based interventions suggests that MI-based interventions are unlikely to be superior in their efficacy compared to those based on other cognitive-based behaviour change techniques.

Strengths and weaknesses of our work

This study represents the first meta-analysis of MI and other CBCT as medication adherence interventions and has been undertaken with methodological rigour and in accordance with published guidance.[18] A notable strength of this work is the robust methodological techniques that have been applied to provide an estimate of effect size which accounts for publication biases and thus greater confidence can be placed in the estimate. The work is also strengthened by restriction to RCTs.

Whilst moderate agreement in abstract screening may be lower than ideal, this is largely attributable to paucity of detail reported in abstracts and complexities in intervention

definitions which are known to be problematic in this domain.[11-13] The conservative approach to abstract screening prevented study exclusion if disagreement was associated with insufficient information and thus prevented exclusion in error. Heterogeneity between the included studies was high with an I^2 value of 68% (95% CI: 52% to 79%) and thus raises the question as to whether the studies were sufficiently comparable to warrant pooling in a meta-analysis. Whilst we defined our inclusion criteria to ensure studies were as similar as possible (i.e. all using a CBCT), heterogeneity was expected as other factors such as the populations and disease states studied were more difficult to control for. Interestingly, the largest study had a small standardized group difference compared to most of the other studies which contributed substantially to the heterogeneity.[43] Furthermore, results from all but three of the studies indicate positive effects of the intervention. Aside from these between study differences, the actual interventions were variable, as were the definitions of adherence and assessment tools used.

The differences between subgroups were statistically non-significant in terms of disease area, intervention components, delivery methods, delivery personnel, intensity, usual care and risk of bias. However, the statistical power was limited by the small number of studies included in the subgroup analyses. The analyses may therefore have failed to detect some important subgroup differences. Moreover, for variables such as the intervention exposure, meaningful conclusions are difficult to draw. Whilst the analyses both infer that intervention exposure did not influence effect size, it is important to remember a whole host variables are at large. It is possible that briefer interventions used different techniques or were delivered to different types of recipients compared to the longer interventions and so comparisons may not be wholly meaningful. Further work may be necessary to explore whether otherwise identical interventions (same technique, same population, same delivery personnel and so forth) differ in effect size when delivered with different exposure.

Despite these numerous between study differences, the core of each intervention was the use of a CBCT to improve medication adherence which was comparable across all studies and thus we would argue that data pooling irrespective of heterogeneity was both intuitive and meaningful.

We have established that receipt of a cognitive-based behavioural medication adherence intervention is likely to elicit small improvements in medication adherence, but the clinical relevance and impact of this improvement remains unknown. Based on mean adherence rates in the control groups, mean standard deviations and the effect size calculated, it has been possible to estimate the increase in percentage of doses taken for the intervention groups. Based on the adjusted Hedges' *g* value of 0.205 (0.084 to 0.326), receipt of a CBCT

improved adherence (% of doses taken) by 6.29% (2.58% to 10.0%). For some medications, a 6% increase in the percentage of doses taken may not be of clinical relevance. However, for other medications such as antiretroviral therapy for HIV which requires very high levels of adherence or anti-epileptic therapies with narrow therapeutic windows, a 6% increase in adherence may have notable clinical relevance. Whilst many included studies included data on clinical outcomes, pooling of this data from a diverse range of studies was not possible.

Implications

Motivational and CBCT can seemingly be delivered effectively by routine healthcare professionals, ~~in both primary and secondary care settings,~~ with efficacy applicable to a range of diseases. Efficacy was not related to intervention exposure. ~~duration or follow-up period.~~ Interestingly, the results also suggest that these interventions can be delivered via telephone or face-to-face with comparable efficacy. These are valuable traits for an adherence intervention which could be adaptable to a wide range of settings and amenable to tailoring to meet individual need.

The flexibility and adaptability of these techniques coupled with their frequent simplicity means that practitioners may wish to consider incorporation of these techniques into their consultations when faced with the need to facilitate medication related behaviour changes.

Recommendations and conclusions

Further investigation of these techniques as medication adherence interventions is warranted in order to further elucidate the characteristics most strongly associated with efficacy. Studies to determine both patient and healthcare practitioner acceptability of these techniques is also necessary to establish their role in routine healthcare.

Article summary

Article focus

- Medication non-adherence is widespread and represents a notable barrier to achieving optimal effects from therapeutic intervention.
- Despite the magnitude and consequences of non-adherence, a gold standard intervention to improve it remains elusive.
- Cognitive-based behaviour change techniques may represent a useful tool in improving medication adherence but their use in this domain had not been established using meta-analytic techniques.

Key messages

- Cognitive-based behaviour change techniques are effective interventions for improving medication adherence and capable of eliciting improvements in adherence beyond those achieved with educational and behavioural interventions which form the mainstay of current practice.
- According to the results of sub-group analyses, cognitive-based behaviour change techniques can be effectively delivered by routine healthcare providers, and the effectiveness of interventions is not associated with intervention exposure
- Health care providers may wish to consider incorporation of these techniques into their medication adherence consultations.

Strengths and limitations of this study

- The studies pooled in this meta-analysis are restricted to RCTs which strengthens their robustness.
- Techniques to account for publication bias have been utilised to provide a conservative effect size estimate offering robustness to our estimate
- Notable heterogeneity was reported when studies were combined which may be a limitation.

Declaration of competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgements

CE would like to acknowledge Estelle Payerne for her invaluable contributions as the second reviewer for abstract screening and data extraction. CE would also like to acknowledge David Wright and John Wood for their comments on the protocol design, data analysis and methods of dissemination, and Steven Watson for his on-going technical support in using the meta-analysis software and comments regarding data interpretation

Funding

This research has been supported by a PhD studentship awarded by the Dean of Science at the University of East Anglia.

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1. I would add a sentence in the Results section of the abstract stating that there was high heterogeneity and reporting the I-squared value.

   Thank you for this suggestion, this has been added to the relevant section.

2. The last sentence of the Conclusions section of the Abstract should be removed or re-worded. “Can be delivered” implies feasibility rather than efficacy. If a conclusion is to be drawn from the subgroup analyses, the relevant results should be included in the Results section of the Abstract. The statement in the Results that “No statistically significant differences were observed in a range of subgroup analyses” is misleading.

   Thank you for these comments; they are useful in improving our manuscript. The statement “no statistically significant differences were observed in a range of sub-group analyses” has been removed as we agree that this was misleading. Instead this statement has been replaced with:

   “The majority of sub-group analyses produced statistically non-significant results”

   We would like to add:

   “for example, there were no significant differences between interventions delivered by specialists compared to interventions delivered by routine healthcare providers (co-efficient value (95% CI) = -0.10 (-0.46 to 0.26) P=0.561) and intervention exposure was not statistically associated with efficacy (co-efficient value (95% CI) =0.07 (-0.35 to 0.50) P=0.728)”.

   However, the strict word limit for the abstract means this level of detail could not be added.

   The conclusion has also been revised accordingly. The sentence containing the words “can be delivered” has been removed as we agree this relates to feasibility not efficacy. It has been replaced with:

   “Sub-group analyses suggest that these interventions are amenable to use across different populations and in differing manners without loss of efficacy. These factors may facilitate incorporation of these techniques into routine care.”

3. The Cochrane Library should be added to the list of databases on page 6.

   Thank you for spotting this omission, this has been added.

4. Page 7.The subgroup analysis by outcome measure should be described as post hoc or exploratory (not pre-specified like the other subgroup analyses).

   Thank you for this suggestion, the wording of this section has been amended accordingly.

5. Page 8. In 12 studies a clearly defined CBCT could not be identified. It is not clear how/why such interventions were classified as using cognitive-based behaviour change techniques.

Thank you for highlighting to us that this section is not clear. The following sentence has been added to improve clarity:

" All studies within this group included one or more components that aimed to alter the patients, thoughts, feelings, motivation or confidence towards adherence and that could therefore be classified as a cognitive-based behaviour change technique"

6. Page 8. As I mentioned in my previous review, it is confusing to include 'providing education' and 'increasing patient knowledge' as cognitive based behaviour change techniques (CBCT), given the distinction that has been made between CBCT and education. Perhaps include a sentence of explanation.

Thanks again for highlighting this source of ambiguity. The following sentence has been added to the end of the aforementioned paragraph:

"Many studies combined cognitive-based behaviour change techniques with more traditionally used educational (e.g. increasing patient knowledge) and behavioural (e.g. regimen simplification and provision of dosing aids) components"

7. Page 8. Aren't implementation intentions and if-then plans clearly defined CBCTs? Why aren't they mentioned in the paragraph that describes the intervention components?

We agree that III are clearly defined CBCTs. In this paragraph we aimed to summarise the most commonly used techniques to provide an overview of the data. As only three studies used III it did not seem intuitive to specifically mention this. However having reconsidered this point in light of this comment, we agree that it may be useful information to our readers. The following sentence has therefore been added:

"A further three (11.5%) studies used Implementation Intention Interventions (III, also known as if-then planning) as a clearly defined CBCT"

8. In Table 1, several interventions are described as involving non-specific techniques. This needs to be explained.

We have added a sentence to the relevant part of the text to reference the table and make it clear to which studies these relate. The full sentence now reads:

"For 12 (46.2%) studies, a clearly defined CBCT such as MI could not be identified[32-3545-52], these studies are identified in table 1 as 'multiple components; non-specific techniques'."

9. Page 19. 1st para. Should be "this bias" not "these biases". And, further down, "implies" not "infers".

Both of these have been amended as suggested.

10. Page 19-20. It's fine to compare the findings for MI with those in other healthcare domains but it's perhaps also worth emphasising that the non-MI interventions appeared to be no less effective.

Thank you for this suggestion. The following sentence has been added to the end of the paragraph:

"The overlapping confidence intervals of the effect sizes calculated for MI-based and non-MI based interventions suggests that MI based interventions are unlikely to be superior in their efficacy compared to those based on other cognitive-based behaviour change techniques".

11. Key messages. "Brief interventions are seemingly effective too". The subgroup analysis for intervention exposure compared four sessions or fewer with five sessions or more. I'm not sure that it is appropriate to describe four sessions or fewer as "brief".

Thank you for highlighting this problem to us. We agree that the classification of brief interventions as four sessions or fewer is inappropriate. The majority of studies provided information regarding the number of sessions over which the interventions were delivered but this is not a reliable proxy for intervention exposure as an intervention of ten half hour sessions would be equivalent to an intervention of five one hour sessions in terms of 'exposure time'. The total number of minutes spent delivering the intervention is therefore a more reliable measure of intervention exposure but this information was inconsistently reported in the studies. However, for 16 studies a reasonable estimate of the number of minutes spent on the intervention could be calculated. The following paragraph has been added to the first part of the results section to reflect the analysis as intervention exposure by number of minutes:

"Intervention exposure as the total number of minutes spent delivering the intervention could be estimated for 16 studies. In the remaining 10 studies this data was not available. Intervention exposure ranged from thirty minutes to eight hours and fifteen minutes. The median (IQR) intervention exposure was 175 (118 to 263) minutes"

As there is currently no widely accepted definition for what constitutes a brief intervention, determining an appropriate cut-off point for classification of interventions as brief or otherwise has been problematic. This difficulty is augmented by the paucity and variability of data that could be extracted from the various studies. An arbitrary cut off of three hours has however been used to create two subgroups of roughly equal study number to explore this. The appropriate section explains that this is common meta-analytical practice.

"The classification of studies into sub-groups was largely intuitive. However, as a continuous rather than categorical variable, 'total intervention exposure' was less

amenable to intuitive dichotomisation. In such instances, it is standard practice to create two sub-groups by distributing a roughly equal number of studies to each group. An arbitrary cut off point of three hours was therefore used to split the data into two sub-groups".

We are mindful that this arbitrary cut off of three hours may not seem intuitive and so have undertaken an additional post hoc meta-regression to explore the variable 'intervention exposure' as a continuous variable. The following has been added to the results section:

"As the variable 'intervention exposure' was a continuous variable, an additional post-hoc analysis was undertaken. This allowed the variable to be analysed in it 'natural' continuous state rather than two sub-groups. This exploratory analysis was undertaken to ensure that the arbitrary cut off point of three hours had not adversely influenced the data. A co-efficient value (95% CI) of 0.001 (-0.001 to 0.002) suggested that there was no association between intervention exposure and effect size. A non-significant p-value of 0.540 confirmed this and demonstrates comparable results to the sub-group analysis for this variable".

As there is no clear cut-off that constitutes a brief intervention, as advised, the message has been revised as:

"According to the results of sub-group analyses, cognitive-based behaviour change techniques can be effectively delivered by routine healthcare providers, and the effectiveness of interventions is not associated with intervention exposure."

12. Consistency between Abstract, Discussion and Key messages could be improved.

Thank you for highlighting these discrepancies. We have endeavoured to improve the consistencies.

Figure 1: Flow diagram for selection of studies

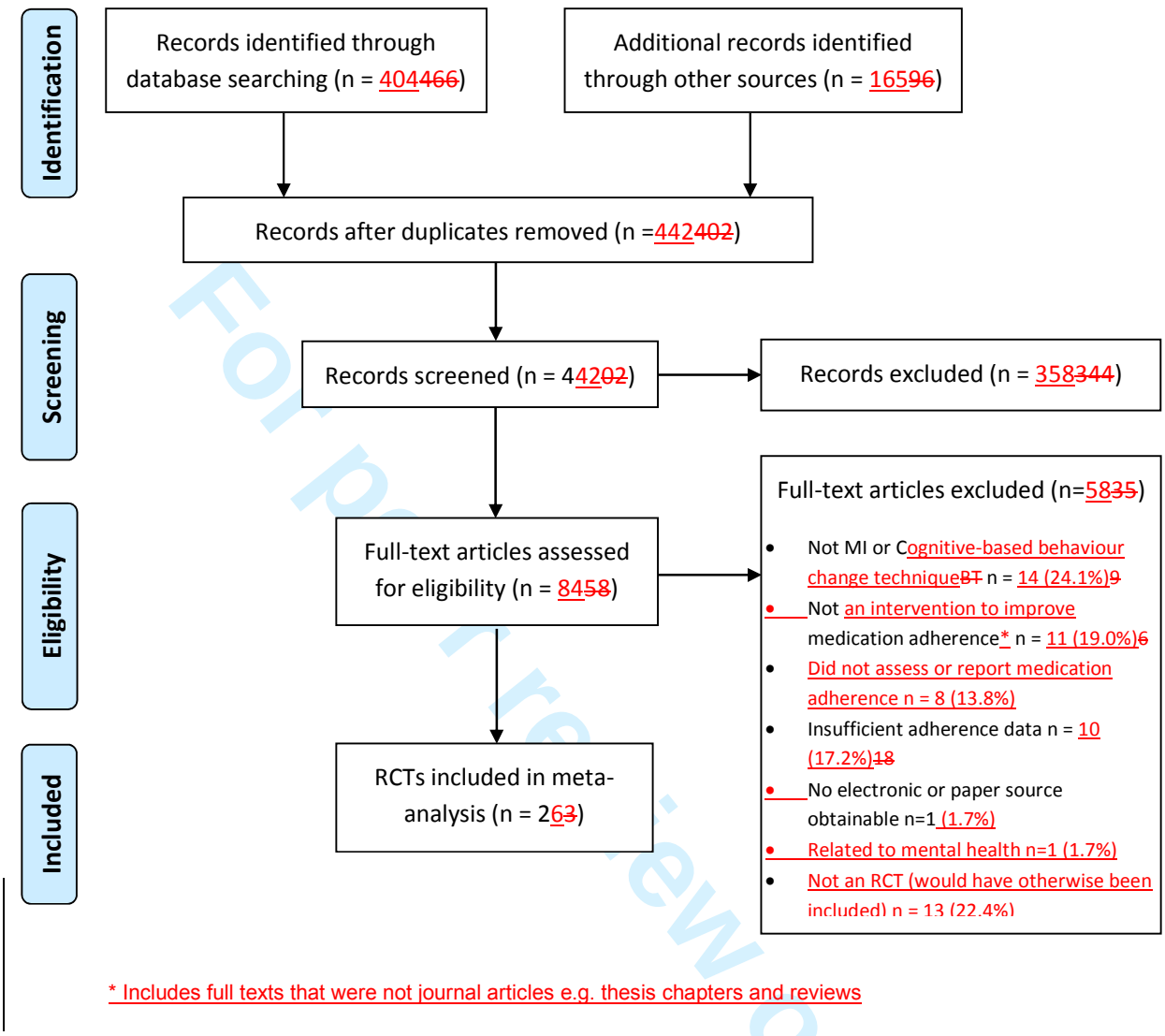


Figure 2: Forrest plot for studies included in meta-analysis

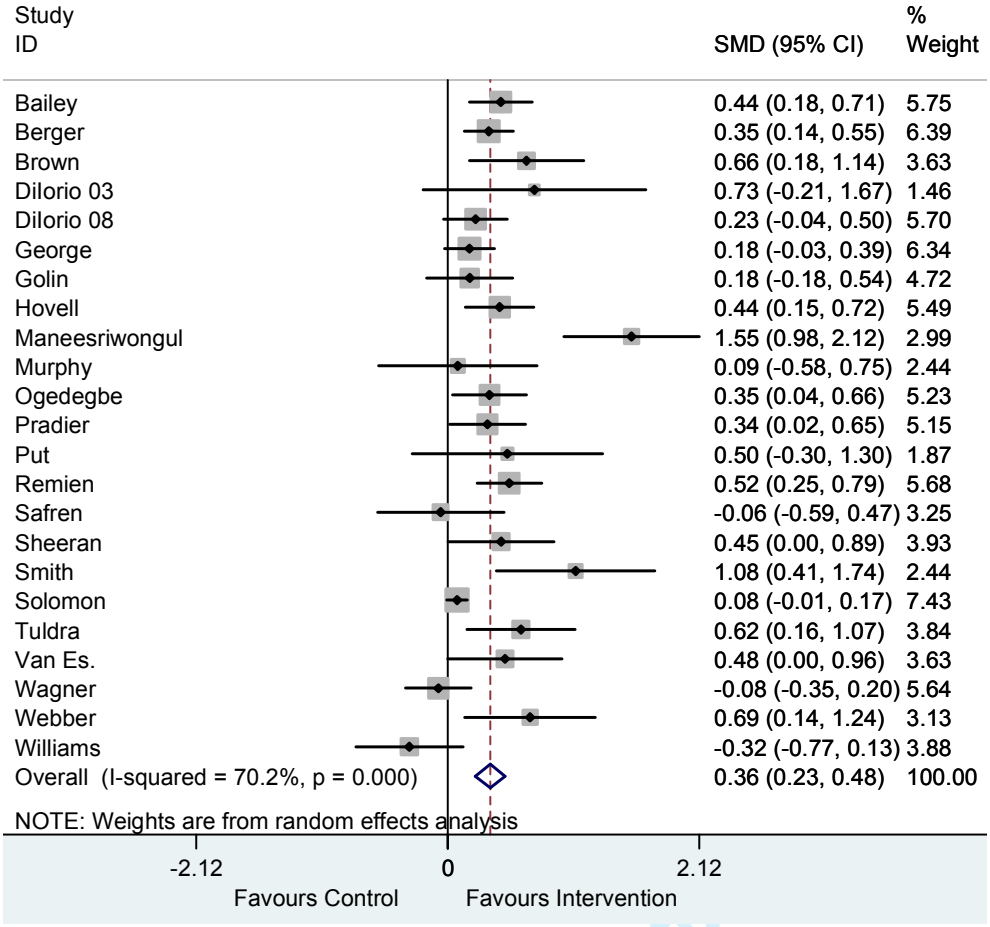
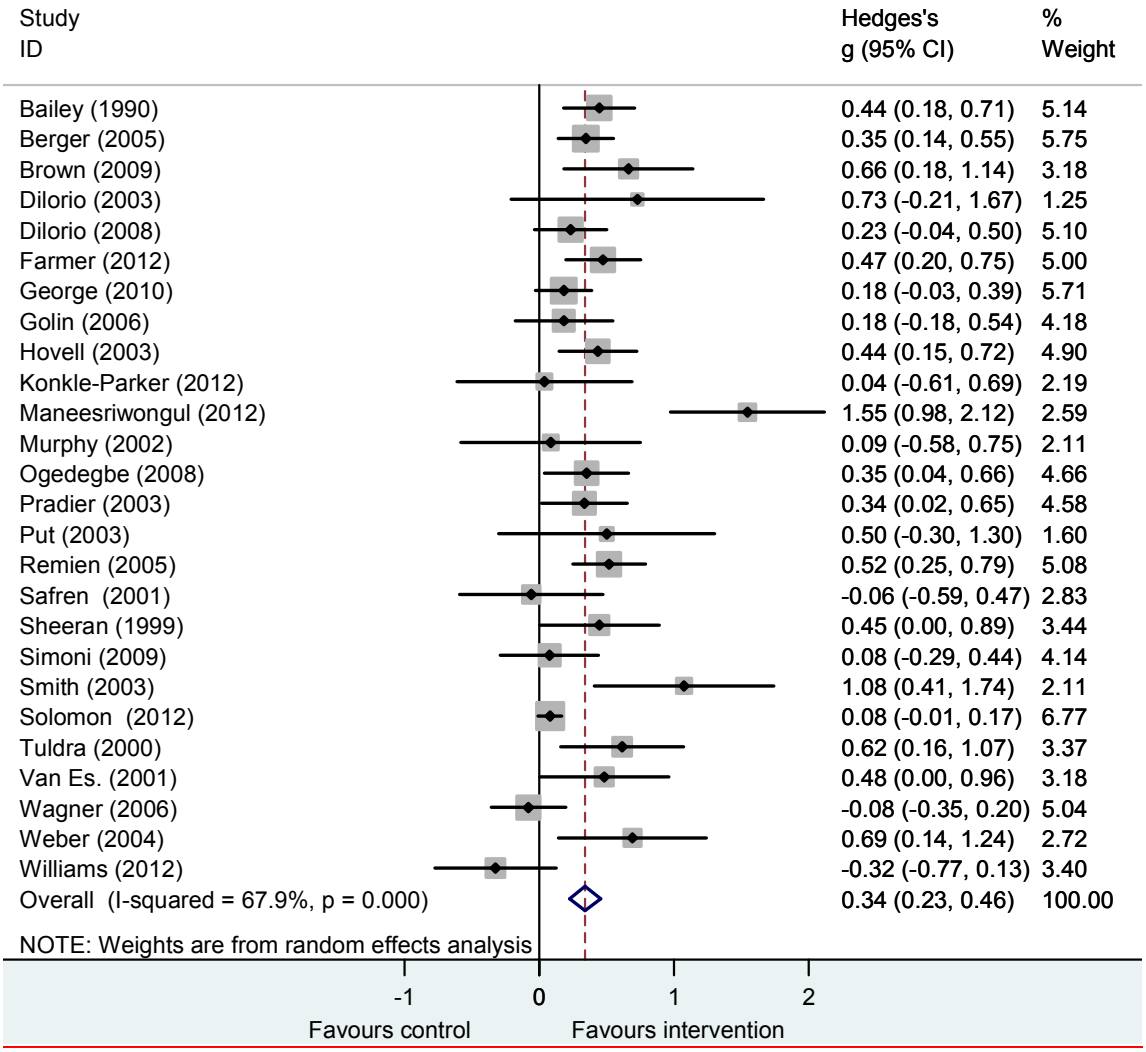


Figure 2: Forest plot for studies included in meta-analysis



~~Figure 3: Funnel plot for studies included in meta-analysis~~

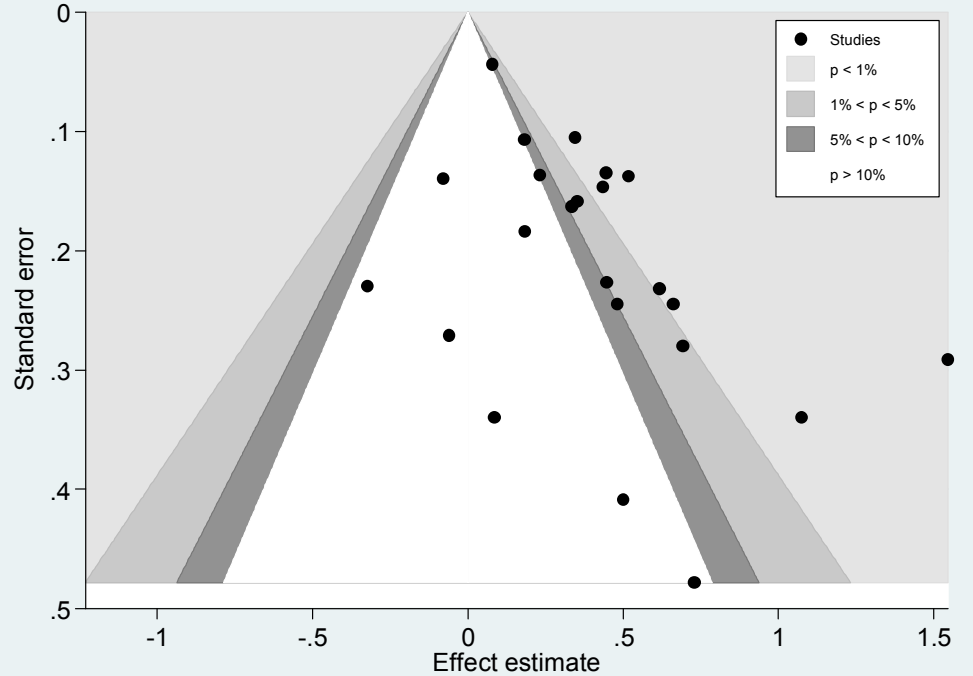
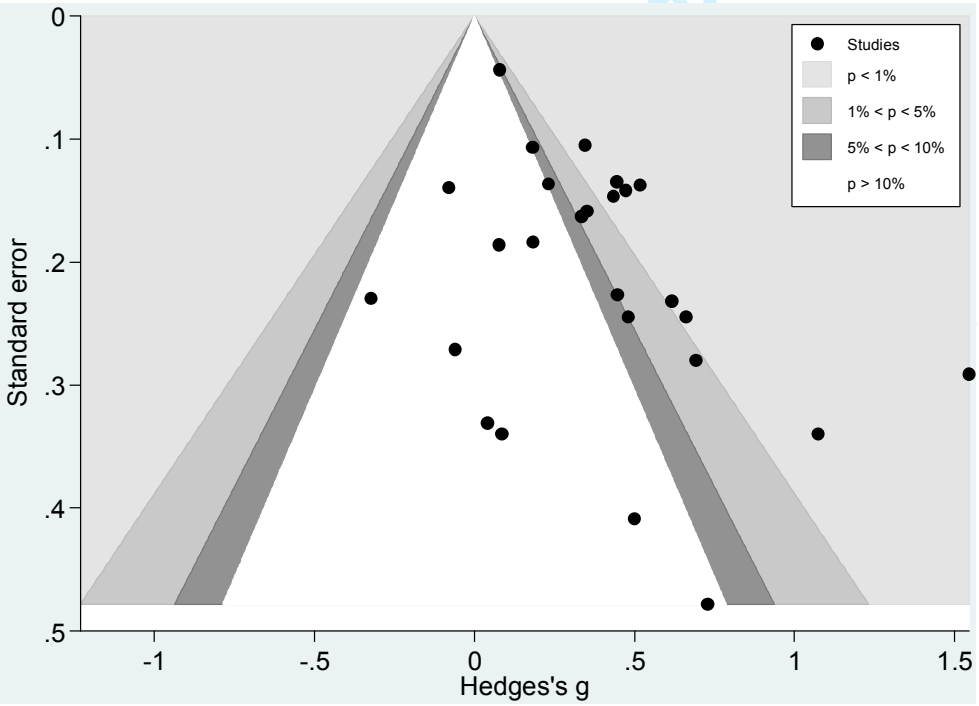
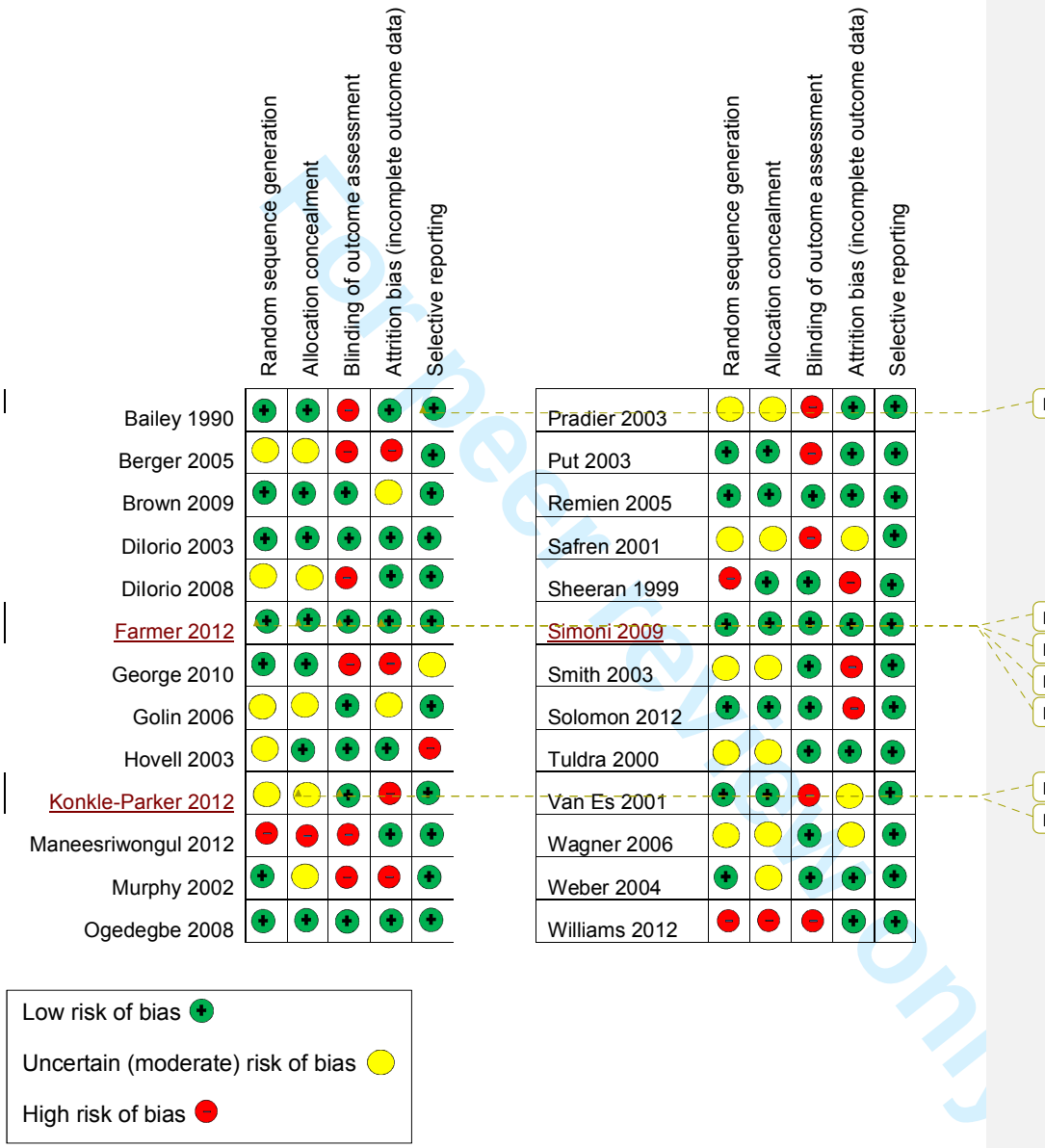


Figure 3: Funnel plot for studies included in meta-analysis



Supplementary figure 1 **Outcome of risk of bias assessment by paper**



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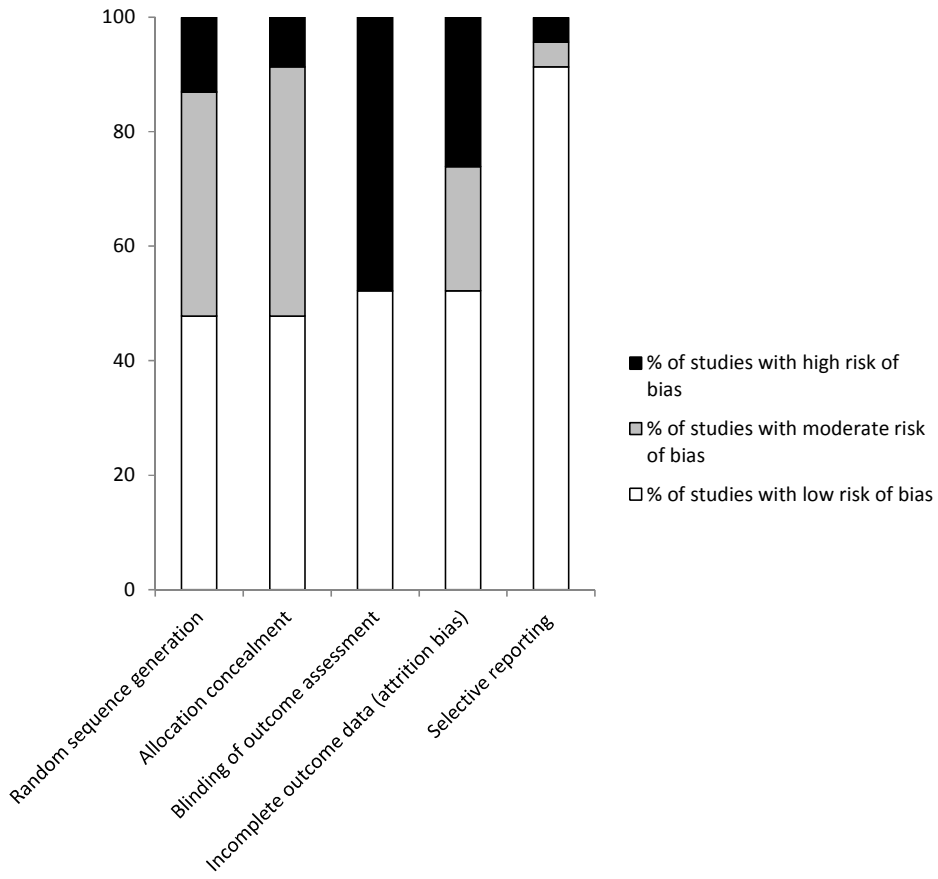
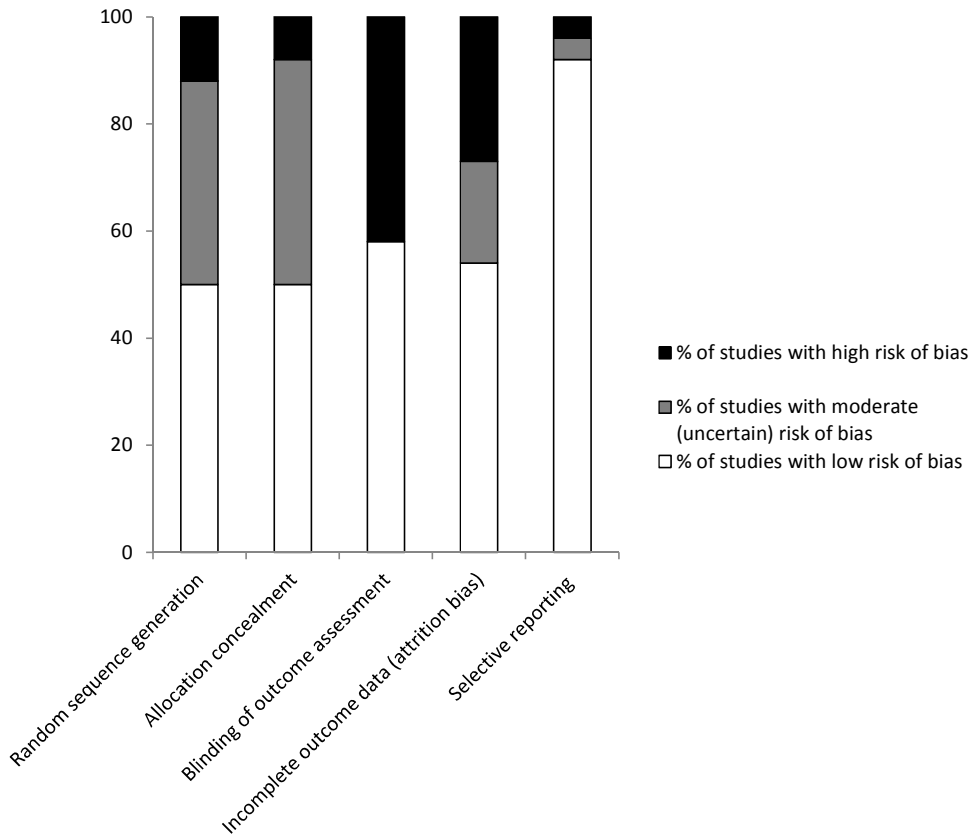
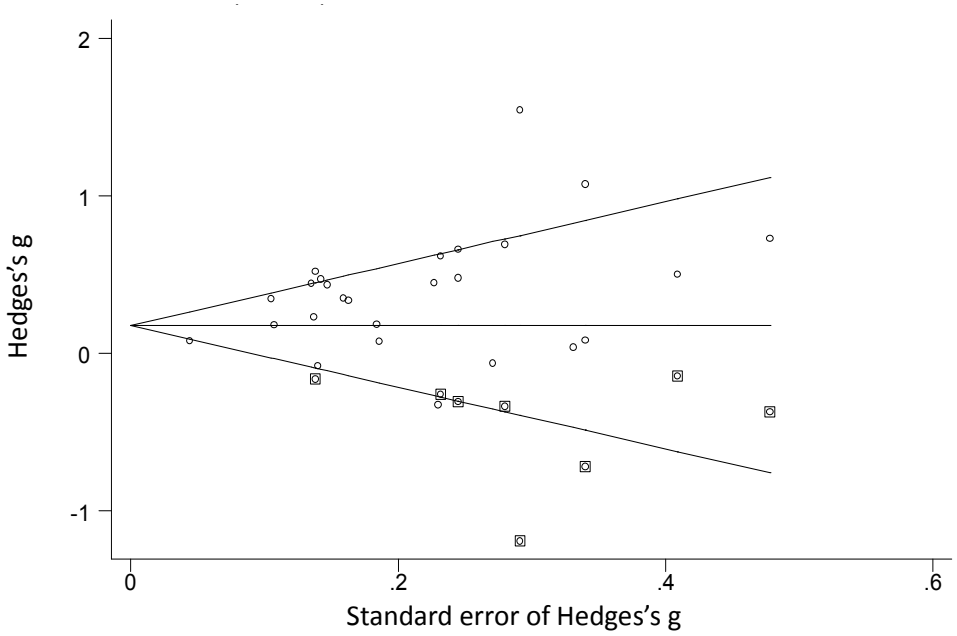
Supplementary figure 2 Outcome of risk of bias assessment by type of bias



Supplementary figure 2 Outcome of risk of bias assessment by type of bias



Supplementary figure 3 Filled funnel plot with pseudo 95% confidence limits



Supplementary table 1: Detailed information of intervention components

Study	Education/ Increasing patient knowledge	Motivational interviewing (MI)	Identifying and resolving adherence barriers	Developing/improving problem solving skills	Diary keeping/ self-monitoring	Increasingly sense of self-efficacy	Improving social support/ promoting support seeking	Goal setting/ action planning	Challenging negative thoughts/ changing attitudes	Improving communication with healthcare providers	Increasing confidence	Medication review	Identifying and addressing concerns	Rehearsing the behaviour	Simplifying/ tailoring medication regimen	Pill reminders/ dosing aids/ adherence cues	Formation of Implementation Intentions	Improving self-management/self-care skills	Improving adherence skills	Praising and encouraging	Increasing sense of control over own health	Increasing cognitive skills	Increasing self-awareness	Increasing motivation (not specifically MI)	Eliciting illness representations	Psychotherapy
Bailey 1990	✓		✓				✓		✓	✓								✓				✓				
Berger 2005	✓	✓																								
Brown 2009																	✓									
Dilorio 2003	✓	✓			✓																					
Dilorio 2008	✓	✓	✓					✓			✓															
Farmer 2012			✓					✓	✓								✓			✓				✓	✓	
George 2010	✓	✓			✓							✓				✓										

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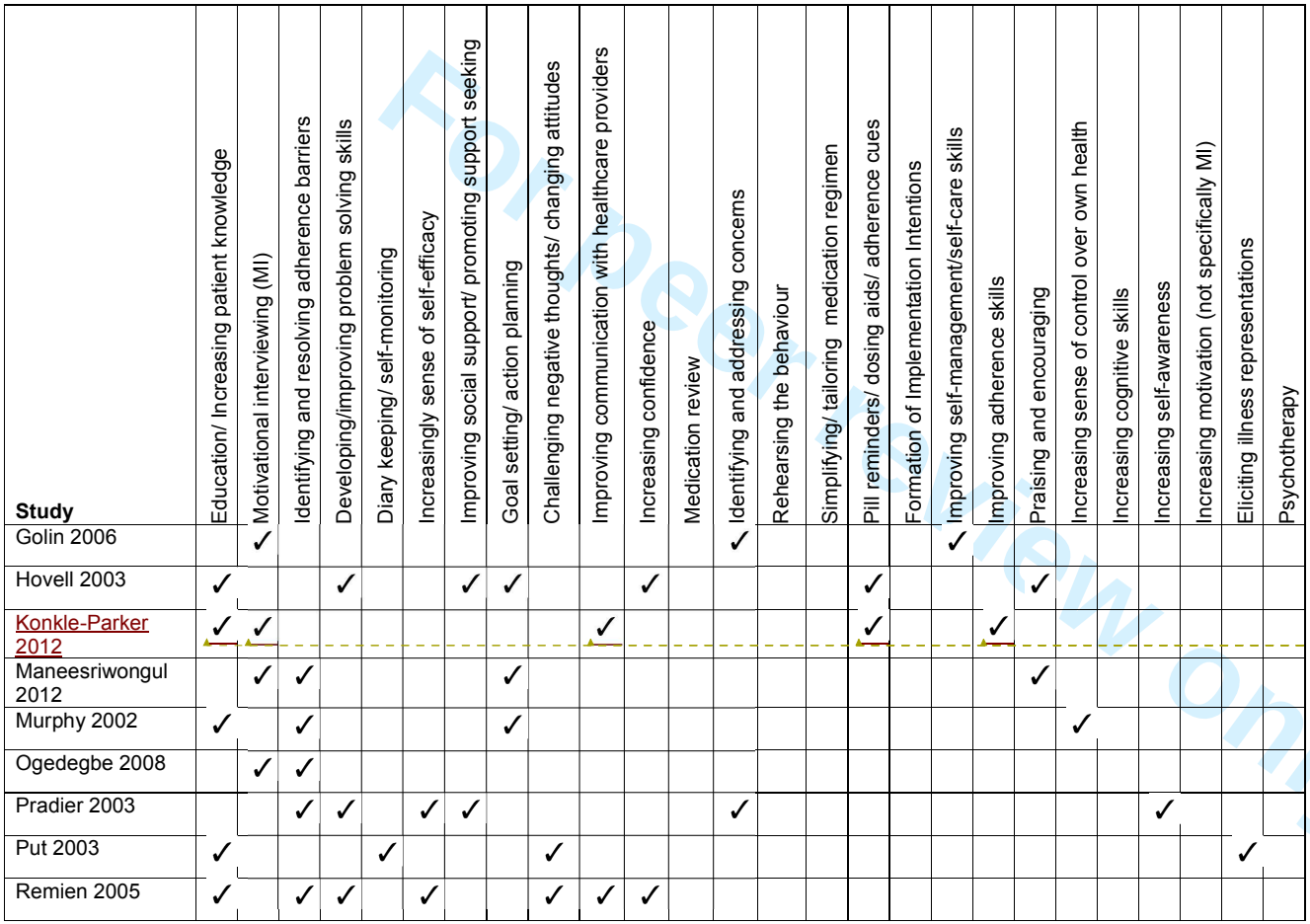

Study	Education/ Increasing patient knowledge	Motivational interviewing (MI)	Identifying and resolving adherence barriers	Developing/improving problem solving skills	Diary keeping/ self-monitoring	Increasingly sense of self-efficacy	Improving social support/ promoting support seeking	Goal setting/ action planning	Challenging negative thoughts/ changing attitudes	Improving communication with healthcare providers	Increasing confidence	Medication review	Identifying and addressing concerns	Rehearsing the behaviour	Simplifying/ tailoring medication regimen	Pill reminders/ dosing aids/ adherence cues	Formation of Implementation Intentions	Improving self-management/self-care skills	Improving adherence skills	Praising and encouraging	Increasing sense of control over own health	Increasing cognitive skills	Increasing self-awareness	Increasing motivation (not specifically MI)	Eliciting illness representations	Psychotherapy
Golin 2006		✓											✓					✓								
Hovell 2003	✓			✓			✓	✓			✓					✓				✓						
Konkle-Parker 2012	✓	✓								✓						✓			✓							
Maneesriwongul 2012		✓	✓					✓												✓						
Murphy 2002	✓		✓					✓													✓					
Ogedegbe 2008		✓	✓																							
Pradier 2003			✓	✓		✓	✓						✓										✓			
Put 2003	✓				✓				✓																✓	
Remien 2005	✓		✓	✓		✓			✓	✓	✓															

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Study	Education/ Increasing patient knowledge	Motivational interviewing (MI)	Identifying and resolving adherence barriers	Developing/improving problem solving/coping skills	Diary keeping/ self-monitoring	Increasingly sense of self-efficacy	Improving social support/ promoting support seeking	Goal setting/ action planning	Challenging negative thoughts/ changing attitudes	Improving communication with healthcare providers	Increasing confidence	Medication review	Identifying and addressing concerns	Rehearsing the behaviour	Simplifying/ tailoring medication regimen	Pill reminders/ dosing aids/ adherence cues	Formation of Implementation Intentions	Improving self-management/self-care skills	Improving adherence skills	Praising and encouraging	Increasing sense of control over own health	Increasing cognitive skills	Increasing self-awareness	Increasing motivation (not specifically MI)	Eliciting illness representations	Psychotherapy
Safren 2001	✓	✓		✓	✓					✓				✓												
Sheeran 1999																	✓									
Simoni 2009	✓		✓				✓		✓							✓				✓						
Smith 2003	✓				✓	✓			✓			✓							✓							
Solomon 2012	✓	✓	✓																							
Tuldra 2000	✓			✓		✓							✓		✓				✓							
Van Es 2001	✓			✓		✓	✓		✓	✓																
Wagner 2006	✓		✓	✓		✓	✓		✓					✓	✓									✓		
Weber 2004								✓																		✓

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Williams 2012	✓	✓			✓							✓														

Appendix one: Search terms to be applied to databases

	Search terms
1	medication* adheren*.ti,ab
2	medication* complian*.ti,ab
3	medication* concordan*.ti,ab
4	medication* non-adheren*.ti,ab
5	medication* non adheren*.ti,ab.
6	medication* non-complian*.ti,ab
7	medication* non complian*.ti,ab.
8	medication* persist*.ti,ab.
9	drug* adheren*.ti,ab.
10	drug* complian*.ti,ab.
11	drug* concordan*.ti,ab
12	drug non-adheren*.ti,ab.
13	drug* non adheren*.ti,ab.
14	drug* non-complian*.ti,ab.
15	drug* non complian*.ti,ab.
16	drug* persist*.ti,ab
17	medicine adheren*.ti,ab.
18	medicine complian*.ti,ab.
19	medicine concordan*.ti,ab.
20	medicine non-adheren*.ti,ab.
21	medicine non adheren*.ti,ab
22	medicine non-complian*.ti,ab.
23	medicine non complian*.ti,ab
24	medicine persist*.ti,ab
25	patient adheren*.ti,ab.
26	patient complian*.ti,ab.
27	patient concordan*.ti,ab.
28	patient non-adheren*.ti,ab.
29	patient non adheren*.ti,ab.
30	patient non-complian*.ti,ab.
31	patient non complian*.ti,ab
32	patient persist*.ti,ab.
33	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34	motivation* interview*.ti,ab
35	motivation* enhancement therap*.ti,ab.
36	behavio?r change counsel?ing.ti,ab
37	implementation* intention*.ti,ab.
38	if-then plan*.ti,ab
39	if then plan*.ti,ab.
40	motivation* counsel?ing.ti,ab.
41	motivation* behavio?r.ti,ab.
42	motivation* change.ti,ab.
43	motivation* intervention*.ti,ab.
44	health behavio?r change*.ti,ab.
45	brief intervention*.ti,ab.
46	cognitive intervention*.ti,ab.
47	cognitive technique*.ti,ab
48	health behavio?r counsel?ing.ti,ab.
49	problem solving treatment*.ti,ab.
50	problem solving therap*.ti,ab
51	34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50
52	33 and 51
53	Remove duplicates from 52

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix one
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7-8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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