El Tractament de Manteniment per a la Dependència Dual d'Heroïna i Cocaïna i per a la Dependència de Cocaïna

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ABREVIATURES

ACA: assaig clínic aleatoritzat

ATC: Anatomical Therapeutic Chemical classification (classificació Anatòmica Terapèutica Química)

CCDAG: Cochrane Collaborative Drugs and Alcohol Review Group

CENTRAL: Cochrane Central Register of Controlled Clinical Trials

DA: dopamina

DAT: transportador de la dopamina

EUA: Estats Units d'Amèrica

IC95%: interval de confiança al 95%

IV: invers de la variança

LAAM: levo-alfa-acetilmetadol

MH: Mantel-Haenszel

NA: no aplicable

ND: no disponible

NIH: National Institutes of Health

NNT: *number needed to reat* (nombre necessari de pacients per tractar)

OR: *odds ratio*

PET: *positron emission tomography* (tomografia per emissió de positrons)

PO: *per os* (via oral)

RAR: reducció absoluta de risc

RR: risc relatiu

RSMA: revisió sistemàtica amb metanàlisi

SAO: síndrome d'abstinència d'opiacis

SL: sublingual

TMO: tractament de manteniment amb opioids

UE: Unió Europea

VHC: virus de l’hepatitis C

VIH: virus de la immunodeficiència huma

PRESENTACIÓ

El tractament de manteniment amb metadona representa una fita històrica en la terapèutica de la dependència d'heroïna ja que va permetre disposar d'un tractament farmacològic eficaç per als pacients que fracassaven en programes de desintoxicació d'heroïna. A més, va significar un canvi de mentalitat en els objectius terapèutics del tractament dels pacients amb dependència d'heroïna que, fins aleshores, se centraven en l'abstinència mentre que, amb el tractament de manteniment amb metadona, passaven a ser-ho la reducció dels danys associats al consum d'heroïna i la rehabilitació social dels pacients. Posteriorment, es va demostrar que altres opioids com el levo-alfa-acetilmetadol (LAAM) i la buprenorfina eren també eficaços. Una aproximació terapèutica similar al tractament de manteniment amb opioids (TMO) també ha proporcionat resultats positius per a la dependència de tabac.

La dependència de cocaïna és un trastorn de prevalença creixent per al qual no es disposa de cap tractament farmacològic aprovat. Els bons resultats del tractament substitutiu per a la dependència d'heroïna i de tabac han esperonat la investigació d'un abordatge similar per a la dependència de cocaïna amb l'administració de psicoestimulants.

El consum de cocaïna, a més, és freqüent entre els pacients dependents d'heroïna i se sol acompanyar d'una davallada de l'eficàcia del tractament de manteniment amb metadona, fet que ha generat dubtes sobre la seva eficàcia per al tractament de pacients dependents d'heroïna que presenten una dependència de cocaïna comòrbida.

Aquesta tesi ha investigat l'eficàcia del tractament de manteniment per a la dependència dual d'heroïna i cocaïna i per a la dependència de cocaïna. Aquest objectiu general s'ha dividit en 4 objectius específics: determinar si 1) el TMO és eficaç per a la dependència dual d'heroïna i cocaïna, 2) hi ha diferències d'eficàcia entre la metadona i la buprenorfina, 3) el tractament de manteniment amb psicoestimulants és eficaç per a la dependència de cocaïna i 4) el tractament de manteniment doble amb opioids i psicoestimulants és més eficaç que el TMO en pacients amb una dependència dual d'heroïna i cocaïna. La metodologia d'estudi emprada ha esta la

revisió sistemàtica amb metanàlisi (RSMA). En aquesta memòria s'hi recullen els resultats més importants i la resta es poden trobar als annexes on s'hi inclouen les 3 publicacions que han originat els estudis que constitueixen aquesta tesi (Castells et al. 2007; Castells et al. 2009; Castells et al. 2010).

Els dos primers objectius específics es troben publicats en el primer article inclòs als annexes (Castells et al. 2009) el qual, a més, conté l'estudi de l'eficàcia dels tractaments adjuvants al TMO que no s'inclou en aquesta memòria ja que no constitueix l'eix vertebrador d'aquesta tesi. Els objectius tercer i quart estan desenvolupats en els altres dos articles (Castells et al. 2007; Castells et al. 2010). De fet, el segon article (Castells et al. 2010) és una ampliació i millora del primer a proposta de la *Cochrane Collaboration*. Aquest fet va permetre una anàlisi qualitativa més rigorosa dels estudis inclosos, així com, emprar una metodologia metanalítica més adequada. A més, atès que les revisions Cochrane no presenten restriccions d'espai, es va incloure un major nombre de subanàlisis i de variables dependents que va permetre un estudi més complet de l'eficàcia dels psicoestimulants per a la dependència de cocaïna.

Aquesta memòria no és completament fidel a les publicacions incloses als annexes i s'han introduït alguns canvis. S'ha actualitzat la cerca bibliogràfica a fi de permetre la inclusió dels assaigs clínics aleatoritzats (ACA) que s'han publicat recentment. Això s'ha traduït en la inclusió d'un nou ACA en la RSMA de l'eficàcia dels psicoestimulants per a la dependència de cocaïna. A més, s'han calculat mesures de benefici absolut com la reducció absoluta de risc (RAR) i el *number needed to treat* (NNT). Finalment, a la discussió s'ha inclòs una anàlisi de les evidències generades amb aquestes RSMAs. Aquesta secció aporta continguts completament nous ja que una anàlisi qualitativa d'aquest tipus no es va realitzar en cap dels articles publicats. Tots aquests canvis s'han acompanyat d'una ampliació substancial de la introducció.

INTRODUCCIÓ

El tractament de manteniment amb agonistes per a la dependència de substàncies

La dependència de substàncies és un malaltia crònica i recurrent que es caracteritza per un consum desajustat d'una substància que es manifesta clínicament per una combinació de tolerància als seus efectes, síndrome d'abstinència i pèrdua de control en el consum que desemboca en un deteriorament de la vida social i de la salut del pacient. S'entén per tolerància a la necessitat de consumir quantitats creixents de la substància/droga a fi de mantenir els mateixos efectes o, la disminució d'efecte amb la mateixa quantitat de substància. L'abstinència és el conjunt de manifestacions clíniques que apareixen quan s'interromp el consum de la substància (American Psychiatric Association 2000).

La tolerància als efectes d'una substància és un fenomen amplament descrit per als fàrmacs amb accions agonistes i sembla que es produeix com a conseqüència de la dessensibilització dels receptors on actua el fàrmac. Aquesta dessensibilització podria ser un mecanisme cel·lular adaptatiu per compensar l'excés d'estimulació. La tolerància als efectes d'un fàrmac que actua sobre un receptor pot afectar a la resta de fàrmacs que tenen accions agonistes sobre aquest mateix receptor. Quan això s'esdevé parlem de tolerància encreuada. El tractament de manteniment amb agonistes utilitza aquest fenomen farmacològic de la tolerància encreuada amb finalitats terapèutiques (Dole et al. 1966).

Conceptualment, el tractament de manteniment amb agonistes descansa sobre 3 pilars (Dole et al. 1966). L'administració per via oral de dosis creixents d'un fàrmac amb accions agonistes sobre el mateix receptor que la droga d'abús:

- provoca l'estimulació dels mateixos receptors sobre els que actua la droga d'abús i, d'aquesta manera, s'evita l'aparició de la síndrome d'abstinència i disminueix el desig de consum de la droga,

- no provoca efectes euforitzants i per tant el potencial d'abús d'aquests medicaments és baix. Això s'explica perquè la velocitat d'absorció per via oral és lenta en comparació amb la intravenosa o intrapulmonar,

- desencadena una tolerància als efectes del fàrmac agonista i una tolerància encreuada als efectes de la droga pròpiament dita. Aquest fet es tradueix en una pèrdua dels efectes reforçadors de la droga quan s'administra de forma concomitant amb el tractament de manteniment amb agonistes.

Per tant, amb el tractament de manteniment amb agonistes no es produeixen els efectes reforçadors negatius i positius de la droga quan aquesta s'administra de forma concomitant al tractament.

Antecedents. La referència ineludible del tractament de manteniment amb metadona per a la dependència d'heroïna

Els principis generals de la terapèutica amb fàrmacs agonistes es varen conceptualitzar durant la dècada dels 60 en paral·lel amb el desenvolupament del tractament de manteniment amb metadona per a la dependència d'heroïna. És interessant recordar que en aquella època no es coneixien encara l'existència dels receptors opioids i per tant tampoc se sabia que els opioids eren agonistes d'aquests receptors. Tanmateix, se sospitava que els opioids eren substàncies agonistes ja que, com altres agonistes, el seu ús continuat s'acompanyava de tolerància als seus efectes, fenomen que ja es coneixia en aquella època.

Els primers estudis que es van fer varen anar encaminats a demostrar que amb l'administració de dosis elevades de metadona es produiria, per un mecanisme de tolerància encreuada, un bloqueig dels efectes euforitzants de l'heroïna. En un primer estudi es van seleccionar 6 pacients dependents d'heroïna, se'ls va administrar metadona i, un cop estabilitzats, se'ls va administrar heroïna per via intravenosa i es va observar que els efectes euforitzants eren de poca intensitat (Dole et al. 1965). Posteriorment, en un segon estudi, a 7 pacients se'ls va administrar entre 80 i 100 mg/d de metadona durant 4 mesos. Durant aquest temps es va administrar heroïna en 3 ocasions i es varen mesurar els efectes euforitzants que produïa. Es va observar que aquests disminuïen progressivament a mesura que els pacients duien més temps amb dosis estables de metadona. La interpretació d'aquestes dades va ser que amb l'administració de dosis elevades de metadona es produïa de forma progressiva un fenomen de tolerància encreuada als efectes euforitzants de l'heroïna. Aquest fenomen es va anomenar bloqueig narcòtic (Dole et al. 1966).

Posteriorment, s'han realitzat més estudis de laboratori que han permès descriure amb més detall la teoria del bloqueig narcòtic. S'ha observat que el fenomen de la tolerància encreuada és dosi dependent, de manera que els efectes euforitzants (Donny et al. 2002; Volavka et al. 1978), la miosi (Volavka et al. 1978) i l'autoadministració d'heroïna (Donny et al. 2005) disminueixen a mesura que augmenta la dosis de manteniment amb metadona. A més, el fenomen de la tolerància encreuada amb l'heroïna es reprodueix si, enlloc d'heroïna, s'empren altres agonistes del receptor μ com la hidromorfona (Melichar et al. 2003).

Estudis de neuroimatge emprant la tomografia per emissió de positrons (PET) han permès comprendre una mica millor el mecanisme d'acció del tractament de manteniment amb metadona. S'ha observat que la disponibilitat dels receptors μ es correlaciona inversament amb la concentració plasmàtica de metadona i que pot ser fins a un 32% menor en pacients que reben tractament de manteniment amb metadona respecte als controls sans (Kling et al. 2000). Aquesta menor disponibilitat de receptors μ ha permès explicar a nivell receptorial el fenomen de la tolerància encreuada i, per tant, de la davallada dels efectes farmacològics de l'heroïna amb dosis creixents de metadona (Donny et al. 2002; Donny et al. 2005; Volavka et al. 1978).

Nombrosos estudis controlats i revisions sistemàtiques han investigat l'eficàcia del tractament de manteniment amb metadona. S'ha observat que l'abstinència d'heroïna és més elevada entre els pacients que reben metadona que entre els que reben placebo o que no reben tractament (Farré et al. 2002; Mattick et al. 2009). Així mateix, s'ha comprovat que l'eficàcia de la metadona sobre el consum d'heroïna augmenta amb la dosi (Amato et al. 2005; Faggiano et al. 2003; Farré et al. 2002). Pel que fa a la retenció a l'estudi s'han obtingut uns resultats similars. La proporció de pacients que completen l'estudi, és més gran entre els que han rebut metadona que entre els que han rebut placebo (Farré et al. 2002; Mattick et al. 2009). La influència de la dosi sobre la retenció no és del tot clara. Mentre alguns estudis mostren un augment de la retenció amb dosis elevades de metadona (Faggiano et al. 2003), d'altres no troben diferències (Farré et al. 2002).

A més, s'ha suggerit que el manteniment amb metadona estaria associat a una reducció de la criminalitat (Johansson et al. 2007; Marsch 1998), de les conductes (Marsch 1998) i del risc de transmissió del VIH (Hartel et al. 1998; Serpelloni et al. 1994). De fet, en alguns països, un dels arguments per a la facilitació de la inclusió dels pacients en programes de manteniment amb metadona va ser frenar la pandèmia del VIH (Torrens et al. 1994). Finalment, nombrosos estudis observacionals han mostrat que el tractament de manteniment amb metadona o amb altres opioids s'associa a una davallada de la mortalitat allí on s'han introduït aquests programes, com el Regne Unit (Kimber et al. 2010), Suècia (Romelsjö et al. 2010), Israel (Peles

et al. 2010), Austràlia (Caplehorn et al. 1996; Gibson et al. 2008), Itàlia (Davoli et al. 2007) o Catalunya (Brugal et al. 2005), entre d'altres.

La importància del tractament de manteniment amb metadona va més enllà de la seva eficàcia ja que va suposar un canvi en la comprensió de l'addicció a substàncies que, fins aleshores, es veia com una necessitat d'escapar de la realitat o una cerca autoindulgent d'eufòria; en definitiva, com una debilitat del caràcter. Des d'aquest punt de vista, el tractament de l'addicció havia de ser necessàriament l'abstinència. El manteniment amb metadona va suposar entendre l'addicció com una malaltia "metabòlica" causada pel consum continuat d'una substància. Aquest canvi de conceptualització de l'addicció es va acompanyar d'un canvi en els objectius del tractament que van passar a ser, en primer lloc, l'estabilització del pacient i la seva rehabilitació, i deixava l'abstinència com a culminació final del procés terapèutic (Dole 1988; Kreek 2000). Aquest canvi conceptual de l'addicció com una malaltia i no com un defecte caracterial és una fita històrica que ha permès disposar del primer tractament farmacològic clarament eficaç per a aquesta malaltia.

Malgrat la seva eficàcia, el tractament de manteniment amb metadona no està exempt de problemes. D'una banda, la metadona és un agonista μ complet i la seva sobredosi pot ser mortal. A més, si s'administra per via I.V. té propietats reforçadores i és objecte d'abús i de tràfic en el mercat negre. Per assegurar que la metadona que es proporciona als pacients no és objecte de comerç clandestí, habitualment, es dispensa en forma d'unidosi ambulatòria en recursos sanitaris especialitzats. Això implica la creació de recursos específics per a la distribució i dispensació d'aquesta medicació. A més, obliga als pacients a acudir diàriament a aquests dispositius per recollir la medicació, fet que interfereix notablement amb una vida plenament normalitzada, que no deixa de ser un dels objectius principals del tractament de manteniment amb metadona (Dole et al. 1965; Dole et al. 1966; Kreek 2000). Per millorar aquests problemes s'han estudiat altres opioids com el LAAM o la buprenorfina.

El LAAM, com la metadona, és un agonista μ complet però té dos metabòlits actius amb una semivida d'eliminació de fins a 90 hores que permeten una administració a dies alterns, fet que podria millorar l'adherència al tractament i permetria normalitzar una mica més la vida dels pacients. Els estudis comparatius entre LAAM i metadona han tingut resultats contradictoris en quant a l'eficàcia, de manera que en ocasions han afavorit la metadona i en d'altres el LAAM (Clark et al. 2002; Farré et al. 2002; Longshore et al. 2005). La principal diferència entre ambdós fàrmacs ha estat la seva seguretat. L'ús de LAAM s'ha associat a problemes d'allargament del QT i arítmies ventriculars, fet que ha motivat la suspensió de la seva autorització de comercialització (European Medicines Agency, 2001; Wieneke et al. 2009). Val

a dir que també la metadona s'ha associat a un allargament de l'interval QT tot i que sembla que la mortalitat associada a aquesta arítmia és baixa (Anchersen et al. 2009; Fonseca et al. 2009).

En l'actualitat, l'única alternativa a la metadona aprovada a la UE com a TMO és la buprenorfina. Aquest fàrmac és un agonista parcial dels receptors μ fet que el converteix en un opioid diferent. En la mesura que és un agonista, els seus efectes farmacològics inclouen l'eufòria, la sedació, l'analgèsia o la depressió respiratòria i per tant, a les dosis adequades, bloqueja la síndrome d'abstinència d'opioids (SAO) i disminueix el *craving*[1] d'heroïna en pacients amb una addicció a aquesta substància. Però, com que és un agonista parcial, els seus efectes farmacològics màxims són menors i per tant té un menor potencial d'abús, una SAO més lleu i, en cas de sobredosi, un menor risc d'aturada respiratòria (Jasinski et al. 1978; Johnson et al. 2003; Tzschentke 2002). A més, en presència d'un agonista complet com l'heroïna, la buprenorfina es comporta com un antagonista, bloqueja els seus efectes euforitzants (Jasinski et al. 1978) i pot precipitar una SAO (Johnson et al. 2003). Per tant, la buprenorfina, a més de les característiques pròpies d'un tractament agonista de manteniment, es comportaria com un interdictor, és a dir, de forma similar a com ho fa el disulfiram en pacients alcohòlics. A més, és un antagonista κ (Leander 1987) i per aquest mecanisme d'acció sembla que tindria efectes antidepressius (Rothman et al. 2000).

La buprenorfina s'administra per via sublingual ja que per aquesta via la biodisponibilitat és superior que per via oral. A més, sembla que la biodisponibilitat és superior quan s'empra la presentació líquida que els comprimits (Johnson et al. 2003), tot i que hi ha algun estudi que indica que les diferències serien molt petites quan s'administra de forma continuada i, especialment, en combinació amb naloxona (Strain et al. 2004).

La buprenorfina té una semivida d'eliminació variable ($t_{½}$ = 3-40 h) i és metabolitzada a norbuprenorfina que és també activa. A més, presenta una elevada afinitat pel receptor μ del qual s'hi dissocia molt lentament. Tot plegat fa que, a dosis mitjanes-altes (> 8 mg), la durada dels seus efectes bloquejadors de la SAO sigui de fins a 72-96 hores, fet que permet una pauta d'administració cada 2-3 dies (Elkader et al. 2005).

Atenent a aquestes característiques farmacocinètiques i farmacodinàmiques, la buprenorfina s'ha investigat com a tractament de manteniment en pacients amb dependència d'heroïna. En comparació amb placebo, s'ha observat que la buprenorfina augmenta la retenció a l'estudi i disminueix el consum d'heroïna (Mattick et al. 2008). A més, entre 1 i 16 mg/d, la retenció en

[1] He emprat el terme *craving* al llarg de la memòria enlloc del terme català desig ja que, en anglès, presenta el matís de desig malaltís que es perd amb la traducció catalana.

l'estudi augmenta amb la dosi (Ling et al. 1998). Aquests estudis suggereixen que el tractament de manteniment amb buprenorfina, com el de metadona, és eficaç i que les dosis elevades ho serien més que les baixes.

Existeixen nombrosos ACAs que han comparat l'eficàcia de la buprenorfina respecte la metadona. Les dosis estudiades habitualment han oscil·lat entre 2 i 14,5 mg/d de buprenorfina i entre 30 i 100 mg/d de metadona. Les presentacions de buprenorfina emprades en aquests estudis han inclòs tant els comprimits com la presentació líquida. S'han investigat pautes amb règims fixes i flexibles. Quan s'ha comparat la buprenorfina amb la metadona en règims flexibles, el quocient de les dosis entre metadona i buprenorfina ha oscil·lat entre 5,2 i 6,6 (Mattick et al. 2008). Els primers estudis comparatius semblaven indicar que la buprenorfina té una eficàcia similar a la metadona pel que fa a la retenció en el tractament i al consum d'heroïna (Farré et al. 2002; Mattick et al. 2004). Tanmateix, les darreres evidències suggereixen que la metadona és lleugerament més eficaç que la buprenorfina amb independència del règim (dosis fixes o flexibles) o la presentació de buprenorfina (comprimits o líquid) (Mattick et al. 2008). No obstant, la buprenorfina sembla que s'acompanya d'un menor risc de sobredosi (Bell et al. 2009) i d'arítmies ventriculars (Fanoe et al. 2007; Wedam et al. 2007). A més, en alguns països, la buprenorfina, a diferència de la metadona, està classificada com a opioid amb un menor risc d'abús i per tant la seva dispensació es pot realitzar en recursos sanitaris no especialitzats, fet que permet programes de manteniment més compatibles amb una vida normal (Fatseas et al. 2007).

En resum, el TMO amb metadona, LAAM o buprenorfina disminueix el consum d'heroïna i augmenta la retenció al tractament, de manera dosi dependent. A més el TMO amb metadona sembla que s'associa a una menor criminalitat, transmissió del VIH i mortalitat. És important subratllar que aquest efecte s'aconsegueix perquè amb el TMO s'obté un bloqueig de la SAO, una disminució del *craving* d'heroïna i, probablement per un mecanisme de tolerància encreuada, un bloqueig dels efectes de l'heroïna. És per aquest triple efecte que el TMO és eficaç. De fet, el bloqueig narcòtic aïllat té una eficàcia molt limitada. Així, el tractament de manteniment amb naltrexona, malgrat que sembla disminuir el consum d'heroïna, s'acompanya de taxes d'abandonament molt elevades que fan que resulti un tractament poc útil en la pràctica clínica (Minozzi et al. 2006).

La dependència dual heroïna-cocaïna[2]

El consum de cocaïna per part de pacients amb dependència d'heroïna és un fenomen de prevalença creixent durant les darreres dècades, en paral·lel amb l'augment de la popularitat d'aquesta substància (Chambers et al. 1972; Torrens et al. 1991; Williamson et al. 2006). A la UE s'ha estimat que un 28% dels pacients dependents d'heroïna que busquen tractament per aquesta malaltia presenten, a més, un abús o dependència de cocaïna (European Monitoring Center for Drugs and Drug Addition 2009). Aquest fenomen també s'ha observat en pacients en TMO (Leri et al. 2003).

La presència d'un trastorn per dependència de cocaïna comòrbid en pacients amb addicció als opioids és un factor de mal pronòstic i s'associa a més psicopatologia (Bandettini di Poggio et al. 2006; Torrens et al. 1991), una major prevalença de trastorn antisocial de la personalitat (King et al. 2001) i a un augment del consum de droga, de conductes de risc d'infecció pel VIH i de criminalitat (Williamson et al. 2006). De forma similar, en pacients dependents d'heroïna en TMO, el consum de cocaïna s'ha associat a un empitjorament dels resultats d'aquesta intervenció pel que fa al consum d'heroïna (Marsden et al. 2009; Williamson et al. 2006), a l'abandonament del tractament (Peles et al. 2008), a un augment de les conductes de risc de transmissió del VIH (Bux et al. 1995) i a un augment de la criminalitat (Kang et al. 1993). A més, la presència de cocaïna és una troballa toxicològica freqüent en els estudis necròpsics de pacients en tractament de manteniment amb metadona (Albion et al. 2010; Shields et al. 2007). Aquestes troballes fan qüestionar si el TMO és un tractament eficaç en pacients que presenten una dependència d'heroïna amb una dependència de cocaïna comòrbida.

S'han proposat diverses explicacions farmacològiques per l'elevada prevalença de consum de cocaïna en pacients dependents d'heroïna. Leri F. et al. (Leri et al. 2003) descriuen dues modalitats de consum d'opioids i cocaïna; simultània i seqüencial. El consum simultani és aquell que es produeix quan l'opioid i la cocaïna es consumeixen alhora. Aquest consum rep el nom de *speddball*. Sembla que, especialment a dosis baixes, es produeix una sinèrgia farmacodinàmica entre les dues substàncies, de manera que els seus efectes reforçadors són més intensos quan s'administren en combinació que per separat. El consum seqüencial es produeix quan la cocaïna i l'opioid es consumeixen separadament. No queda clar si aquesta modalitat de

2 Utilitzo el concepte de dependència dual d'heroïna i cocaïna per a referir-me a l'addicció simultània a aquestes dues substàncies. Probablement sigui més acurat anomenar a aquesta situació com a dependència d'heroïna i de cocaïna. No obstant, si s'empra aquesta denominació pot semblar que es parli de dues situacions independents. Aquest malentès s'evita quan s'utilitza la fórmula dependència dual d'heroïna i cocaïna. Aquesta expressió no és original meva i, malgrat no ser habitual, es pot trobar en altres textos científics que investiguen aquesta situació.

consum es deu a uns efectes sinèrgics entre les dues substàncies, ja que els estudis que han investigat aquesta qüestió han arribat a resultats contradictoris. Una altra possibilitat és que el consum de les dues substàncies es produeixi, no per a augmentar els efectes euforitzants, sinó per pal·liar alguns efectes indesitjats. La cocaïna disminuiria la sedació que provoquen els opioids i l'heroïna l'excitació de la cocaïna. A més, s'ha observat que la SAO és menys intensa quan s'utilitzen les dues substàncies que quan només es consumeixen opiacis. Això es deuria a que, malgrat que la cocaïna augmenta la concentració sinàptica de noradrenalina, amb el consum crònic es produeix una disminució del seu alliberament com a conseqüència de canvis en la sensibilitat de l'autoreceptor adrenèrgic i, d'aquesta manera, els símptomes adrenèrgics de la SAO són menys intensos en dependents d'opioids que, a més, són consumidors crònics de cocaïna (Leri et al. 2003).

Atès que el consum de cocaïna i d'heroïna no és independent l'un de l'altre sinó que sembla produir-se com a conseqüència d'interaccions farmacodinàmiques entre ambdues substàncies, podria ser que l'eficàcia del TMO diferís en funció de les característiques farmacodinàmiques de l'opioid emprat. En aquest sentit es van dipositar grans expectatives en el TMO amb buprenorfina ja que aquesta substància, a diferència de la metadona, té accions agonistes parcials del receptor μ i, a més, és un antagonista del receptor κ.

En la mesura que la buprenorfina és un agonista parcial dels receptors μ provoca menys sedació i una SAO més lleu que la metadona. Per tant, si el consum de cocaïna es produeix per alleugerir alguns efectes indesitjats de l'heroïna, com la SAO o la sedació, és probable que, amb buprenorfina, el consum de cocaïna sigui menor que amb agonistes μ complets com la metadona. A més, pel fet de ser un agonista parcial del receptor μ, es comporta com un antagonista en presència d'un agonista complet, fet que es podria traduir en una disminució del consum de *speedball* perquè el seu ús durant el tractament amb buprenorfina precipita SAO (Cowan et al. 1977).

La potencial superioritat de la buprenorfina respecte la metadona també s'ha justificat per les seves accions sobre el receptor κ. La buprenorfina és un antagonista κ, fet que es sembla traduir-se en efectes antidepressius (Emrich et al. 1983; Rothman et al. 2000). Alguns estudis observacionals han trobat que la buprenorfina és més eficaç en pacients dependents d'heroïna que presenten una simptomatologia depressiva comòrbida (Gerra et al. 2004; Gerra et al. 2006; Kosten et al. 1990). En la mesura que els pacients amb una dependència dual d'heroïna i cocaïna presenten més simptomatologia depressiva que els dependents d'una única substància (Malow et al. 1992; Torrens et al. 1991), s'ha postulat que la buprenorfina podria ser més eficaç que la metadona per al tractament de la dependència dual d'heroïna i cocaïna.

Existeixen nombrosos estudis que han investigat la potencial utilitat de la buprenorfina per al tractament de pacients amb una dependència dual d'heroïna i cocaïna. Malauradament, els resultats no han estat consistents entre ells. Així, alguns estudis amb animals d'experimentació han mostrat que l'autoadministració de cocaïna sola o en combinació amb heroïna disminueix quan als animals se'ls administra buprenorfina (Mello et al. 1993). A més, estudis de laboratori amb humans han trobat que els efectes reforçadors de la cocaïna són menors si s'administra buprenorfina concomitantment (Mendelson et al. 1992). Estudis observacionals en pacients amb dependència d'heroïna han constatat un menor consum de cocaïna entre els pacients que reben TMO amb buprenorfina que amb metadona (Kosten et al. 1989a, Kosten et al. 1989b). Per contra, una subanàlisi d'un ACA que comparava l'eficàcia de la metadona i la buprenorfina no va observar que la buprenorfina millorés la simptomatologia depressiva respecte de la metadona (Dean et al. 2004). A més, en pacients amb dependència d'heroïna i trastorn depressiu comòrbid s'ha observat que l'administració de buprenorfina i desipramina s'acompanya d'un resultats d'eficàcia pobres (Kosten et al. 2004). Finalment, en països com França, on les dues modalitats de TMO estan implantades des de fa temps, s'ha observat que el consum de cocaïna és prevalent tant en pacients en TMO amb metadona com amb buprenorfina (Guichard et al. 2003). A més, com succeeix amb el TMO amb metadona, el consum de cocaïna té efectes negatius sobre el consum d'heroïna i la retenció al tractament en pacients en TMO amb buprenorfina (Sullivan et al. 2010). Aquestes troballes han fet rebaixar les expectatives dipositades en la buprenorfina per al tractament de la dependència dual d'heroïna i cocaïna.

En resum, el consum de cocaïna en pacients amb dependència d'heroïna és freqüent, així com també ho és entre els que reben TMO, fet que s'associa a un empitjorament dels resultats d'aquesta intervenció i que ha fet dubtar de l'eficàcia d'aquest abordatge en pacients que presenten una dependència de cocaïna comòrbida a la dependència d'heroïna. A més, existeixen dades que recolzarien una superior eficàcia de la buprenorfina respecte de la metadona, tot i que també n'hi ha que permeten defensar el contrari. Aquesta tesi ha investigat si el TMO és eficaç per al tractament de la dependència dual d'heroïna i cocaïna i ha comparat l'eficàcia de la metadona i la buprenorfina en aquests mateixos pacients.

La dependència de cocaïna

La dependència de cocaïna és una malaltia que presenta una prevalença que ha anat creixent durant les darreres dècades. A la Unió Europea, es calcula que al voltant de 13 milions de persones han consumit alguna vegada cocaïna, fet que representa el 3,9% dels ciutadans d'entre

15 i 64 anys, i és a l'Estat espanyol i al Regne Unit on s'assoleixen les xifres més elevades: 5,5% i 4,5%, respectivament (European Monitoring Center for Drugs and Drug Addition 2009). Als Estats Units, s'estima que al voltant del 15% dels ciutadans han consumit cocaïna com a mínim un cop en la seva vida i que 1,1 milions han presentat un trastorn per abús o dependència (Substance Abuse and Mental Health Services Administration 2009).

Els efectes psicòtrops aguts de la cocaïna inclouen l'estimulació locomotora, la disminució de la fatiga, l'anorèxia, la loquacitat, la millora del rendiment en la realització de tasques senzilles, l'ànim hipertímic i l'eufòria. Malgrat que la cocaïna bloqueja els recaptadors de la dopamina (DA), serotonina i, en menor mesura, de noradrenalina, i augmenta la concentració sinàptica d'aquestes monoamines (Rothman et al. 2003), sembla que els seu efectes psicoestimulants es deuen fonamentalment a les seves accions sobre la neurotransmissió DAèrgica. A aquesta conclusió s'hi ha arribat en constatar-se una correlació entre l'ocupació del transportador de dopamina (DAT) per part de la cocaïna i els seus efectes estimulants de la locomoció (Cline et al. 1992). A més, la lesió de les neurones DA de la via mesocorticolímbica bloqueja els efectes activadors de la locomoció dels psicoestimulants (Kelly et al. 1976). Sembla, també, que canvis en la neurotransmissió DA estarien implicats en els efectes reforçadors de la cocaïna. Així, per exemple, s'ha observat que la cocaïna augmenta la concentració de DA al nucli accumbens, lloc on convergeix el sistema cerebral de recompensa (Sesack et al. 2010), i que el grau d'ocupació dels receptors DA es relaciona amb la intensitat dels efectes euforitzants de la cocaïna (Kuhar et al. 1991; Volkow et al. 1997). A més, els animals knockout del DAT presenten una pràcticament nul·la autoadministració de cocaïna (Thomsen et al. 2009). Amb el consum crònic de cocaïna, s'ha observat una davallada en la disponibilitat de receptors DA que podria estar relacionada amb el fenomen de tolerància als efectes euforitzants (Volkow et al. 1990). A més, la disfunció DA té un paper cabdal en la síndrome d'abstinència, que s'esdevé quan s'interromp sobtadament el consum de cocaïna, durant la qual s'ha observat una disminució de la síntesi (Trulson et al. 1987) i alliberament de DA al nucli accumbens (Maisonneuve et al. 1995; Weiss et al. 1992).

Donat el paper central que té la neurotransmissió DA en els efectes psicoestimulants i reforçadors de la cocaïna i en el desenvolupament de la dependència d'aquesta substància, s'ha investigat la manipulació farmacològica de la neurotransmissió DA per al tractament d'aquesta malaltia. Una de les estratègies investigades ha estat el bloqueig dels receptors DA amb antipsicòtics amb l'objectiu de disminuir els efectes euforitzants i psicoestimulants de la cocaïna i, per tant, de neutralitzar els efectes reforçadors de la cocaïna. No obstant, aquesta intervenció no ha proporcionat els resultats desitjats i no ha demostrat ser més eficaç que el placebo (Amato et al. 2007). Una segona aproximació farmacològica ha estat l'agonisme DA directe amb

fàrmacs com l'amantadina, la pergolida o la bromocriptina amb l'objectiu de corregir l'estat hipodopaminèrgic que caracteritza l'abstinència de cocaïna. Els ACAs controlats amb placebo tampoc no han evidenciat uns resultats favorables (Soares et al. 2003). El fet que els agonistes DA directes ho siguin fonamentalment dels receptors D2 (Kvernmo et al. 2008) i que, per tant, no corregeixin completament el dèficit DA que caracteritza la dependència de cocaïna s'ha proposat com una possible explicació de la manca d'eficàcia d'aquests fàrmacs per a la dependència de cocaïna.

Un altra aproximació per a modificar farmacològicament la neurotransmissió DA és amb l'administració d'agonistes DA indirectes, és a dir de fàrmacs que augmenten la concentració de DA a la sinapsi, bé promovent el seu alliberament (per exemple la levodopa) o disminuint la seva eliminació (per exemple el metilfenidat). D'agonistes DA indirectes n'hi ha de dos tipus en funció de la seva capacitat d'induir efectes psicoestimulants. Existeixen pocs estudis que hagin investigat l'eficàcia dels agonistes DA indirectes sense efectes psicoestimulants i els resultats han estat poc concloents (Carroll et al. 2004; Oliveto et al. 2010; Pérez-Mañá et al. 2010). La darrera modalitat que disposem de modificar farmacològicament la neurotransmissió DA és amb psicoestimulants.

El tractament de manteniment amb psicoestimulants per a la dependència de cocaïna

Els psicoestimulants podrien ser eficaços per al tractament de la dependència de cocaïna d'una manera anàloga a la metadona per a la dependència d'heroïna. En ser agonistes del mateix sistema de neurotransmissió que la cocaïna podrien tenir efectes substitutius[3], disminuir el *craving* i la severitat de la síndrome d'abstinència de cocaïna. A més, per un mecanisme de tolerància encreuada produirien una desensibilització DA que es traduiria en una disminució dels efectes psicoestimulants i euforitzants de la cocaïna (Vocci 2007). Nombrosos estudis han investigat les propietats substitutives dels psicoestimulants i la seva capacitat d'induir tolerància encreuada amb la cocaïna.

[3] S'ha intentat evitar el terme substitutiu referit a una modalitat de tractament i s'ha preferit parlar de tractament de manteniment. Sovint s'ha considerat que l'ús del terme tractament substitutiu és inadequat ja que dóna la sensació que s'administri droga als pacients, és a dir que se "substitueixi" l'heroïna per una altra droga. A més el tractament de manteniment és més complex que la substitució d'una substància per un altre ja que, a més, implica el desenvolupament de tolerància encreuada entre el medicament administrat i la droga d'abús. Tanmateix, sí que s'accepta el terme per a referir-se al tractament substitutiu amb nicotina per a la dependència del tabac. En aquesta memòria s'ha emprat el terme substitutiu per fer referència a un efecte farmacològic, és a dir a la capacitat que té un fàrmac de substituir els efectes psicòtrops d'un altre. Una solució podria haver estat emprar la locució tractament de manteniment amb agonistes, que és molt utilitzada en publicacions científiques. Aquest terme tot i ser adequat per parlar del tractament de manteniment amb metadona, ja que aquesta és un agonista del receptor μ, és inadequat parlar de tractament de manteniment amb psicoestimulants ja que la majoria d'ells no són agonistes de cap receptor sinó bloquejadors de proteïnes transportadores.

Un paradigma de laboratori que s'empra per a estudiar els efectes substitutius dels fàrmacs és el model d'estímul discriminatori. Es defineix com a estímul discriminatori aquell esdeveniment que assenyala la disponibilitat de reforçament contingent a una resposta conductual concreta. Alguns fàrmacs poden emprar-se com a estímuls discriminatoris ja que provoquen canvis fisiològics que són percebuts pel subjecte com a estímuls interoceptius (per exemple sedació, palpitacions,...). En un experiment d'estímul discriminatori, el subjecte és entrenat per a realitzar una resposta operant concreta (per exemple prémer la palanca de la dreta) després de rebre una substància (per exemple cocaïna) per a obtenir una recompensa (per exemple menjar, aigua o diners) i una resposta diferent (per exemple prémer la palanca de l'esquerra) després de rebre placebo per a obtenir la mateixa recompensa. Un cop adquirida la capacitat per discriminar entre els efectes de la substància o del placebo es pot modificar la substància administrada. Si la nova substància té uns efectes subjectius similars als del fàrmac que el subjecte ha après a discriminar del placebo es reproduirà el comportament adquirit. Quan això es produeix es parla de substitució o generalització. La proporció de respostes generalitzades pot oscil·lar entre el 0 i el 100% i quan és d'entre el 80 i el 100% es parla de generalització completa (Overton 1991). Que un medicament presenti propietats substitutives d'una droga és una dada indirecta sobre la seva possible utilitat per al tractament de la síndrome d'abstinència i del *craving* de la droga de la qual té efectes substitutius. Un bon nombre de fàrmacs psicoestimulants han mostrat tenir propietats substitutives de la cocaïna com a estímul discriminatori, entre d'altres l'amfetamina, el metilfenidat, el mazindol, el buprópion, el dietilpropion, la catinona (Woolverton 1991), la cafeïna (Oliveto et al. 1998) o el modafinil (Gold et al. 1996). A més, l'administració de fàrmacs psicoestimulants provoca una disminució de l'administració de cocaïna en animals entrenats a autoadministrar-se aquesta substància (Negus et al. 2003a, Negus et al. 2003b, Negus et al. 2007). Aquests resultats també poden indicar l'existència d'efectes substitutius entre els fàrmacs psicoestimulants i la cocaïna.

Un cop demostrada l'existència de propietats substitutives de cocaïna, el següent pas ha estat determinar si l'administració de psicoestimulants indueix tolerància encreuada als efectes de la cocaïna i si, com a conseqüència d'aquest fenomen, es produeix una disminució dels efectes euforitzants de la mateixa. El fenomen de la tolerància encreuada entre cocaïna i altres psicoestimulants ha estat poc investigat i amb resultats poc concloents. Mentre alguns estudis han objectivat que existeix una tolerància encreuada entre la cocaïna i l'amfetamina (Woolverton et al. 1978), la metamfetamina (Peltier et al. 1996) i el metilfenidat (Leith et al. 1981) d'altres no han trobat que es produeixi aquest fenomen (Izenwasser et al. 1999; Katz et al. 1993). Diferències en la dosi, pauta, via d'administració i animal de laboratori emprat poden explicar les aparents discrepàncies en els resultats d'aquests estudis.

Els estudis que han investigat les interaccions farmacològiques que es produeixen quan s'administren conjuntament cocaïna i altres psicoestimulants han mostrat uns resultats més consistents que els dels de tolerància encreuada. S'ha observat una davallada en els efectes psicoestimulants i euforitzants de la cocaïna quan aquesta s'administra de forma sobreimposada a altres psicoestimulants com l'amfetamina (Czoty et al. 2010; Greenwald et al., 2010; Martínez et al. 2007; Rush et al. 2009), el modafinil (Dackis et al. 2003; Hart et al. 2008; Malcolm et al. 2006) la cocaïna oral (Walsh et al. 2000) i, en menor mesura, també amb el buprópion (Oliveto et al. 2001). A més, s'ha observat una davallada del *craving* de cocaïna durant el tractament amb dexamfetamina (Greenwald et al., 2010), metilfenidat (Winhusen et al. 2006) o modafinil (Hart et al. 2008). Finalment, alguns estudis han mostrat una reducció dels efectes reforçadors de la cocaïna i una davallada en l'autoadministració de cocaïna en condicions controlades de laboratori, novament, amb dexamfetamina (Greenwald et al., 2010), metilfenidat (Collins et al. 2006) o modafinil (Hart et al. 2008). Aquesta dada és destacable ja que en ocasions, medicaments com la gabapentina, que provoquen una disminució de les propietats reforçadores de la cocaïna no s'acompanyen d'una davallada de la seva autoadministració (Hart et al. 2004). Per aquest motiu, una disminució de l'autoadministració controlada de cocaïna es considera un millor predictor d'eficàcia d'un tractament sobre la dependència de cocaïna que la disminució dels seus efectes subjectius.

Alguns d'aquests estudis han inclòs determinacions de la concentració plasmàtica de cocaïna i dels seus metabòlits per establir si els canvis en els efectes cardiovasculars o psicòtrops de la cocaïna en presència d'un tractament amb psicoestimulants es deuen a interaccions farmacocinètiques. Cap d'aquests estudis ha mostrat que l'administració de psicoestimulants modifiqui la farmacocinètica de la cocaïna (Dackis et al. 2003; Hart et al. 2008; Winhusen et al. 2006) i, per tant, el canvi en els efectes psicòtrops de la cocaïna en presència d'un tractament amb psicoestimulants s'interpreten com a resultat d'una interacció farmacodinàmica.

Existeixen, però, alguns potencials perills en relació al tractament de manteniment amb psicoestimulants a pacients amb dependència de cocaïna que convé tenir presents. D'una banda és ben conegut que tant la cocaïna, com la majoria de psicoestimulants, augmenten la freqüència cardíaca i la pressió arterial (Brunton et al. 2006). Per tant, podria ser que si el pacient consumeix cocaïna durant el tractament amb psicoestimulants es pugui produir un efecte sumatori entre ambdues substàncies sobre els seus efectes hemodinàmics que es tradueixi en problemes de seguretat cardiovascular. Alguns estudis de laboratori han comparat els efectes hemodinàmics de l'administració de cocaïna a pacients que reben tractament amb psicoestimulants. Els resultats d'aquests estudis han estat poc concloents. Alguns d'ells han mostrat que els psicoestimulants atenuen alguns dels efectes hemodinàmics de la cocaïna

(Greenwald et al., 2010; Hart et al. 2008; Malcolm et al. 2006), en d'altres no s'observen canvis (Dackis et al. 2002) i en d'altres un augment (Rush et al. 2009; Walsh et al. 2000).

En resum, el tractament de manteniment amb psicoestimulants podria ser eficaç per a la dependència de cocaïna ja que nombrosos estudis de laboratori han mostrat que tenen propietats substitutives, provoquen tolerància encreuada, disminueixen els efectes reforçadors i el *craving* de cocaïna i la seva autoadministració. Aquesta tesi ha investigat si el manteniment amb psicoestimulants és eficaç per al tractament de la dependència de cocaïna. A més, atès que, com s'ha dit en l'apartat anterior, la dependència de cocaïna comòrbida és força freqüent en els pacients amb dependència d'heroïna, s'ha investigat si el tractament de manteniment doble, amb opioids i psicoestimulants, és més eficaç que el TMO.

OBJECTIUS

Objectiu general

- Determinar l'eficàcia del tractament de manteniment per a la dependència dual d'heroïna i cocaïna i per a la dependència de cocaïna.

Objectius específics

Objectius principals:

- Determinar l'eficàcia del tractament de manteniment amb opioids per a la dependència dual d'heroïna i cocaïna.
- Comparar l'eficàcia de la metadona respecte la buprenorfina per a la dependència dual d'heroïna i cocaïna.
- Determinar l'eficàcia del tractament de manteniment amb psicoestimulants per a la dependència de cocaïna.
- Comparar l'eficàcia del tractament de manteniment doble amb opioids i psicoestimulants respecte el TMO en pacients amb una dependència dual d'heroïna i cocaïna.

Objectius secundaris:

- Determinar l'eficàcia respecte del placebo dels diferents psicoestimulants investigats per a la dependència de cocaïna.

HIPÒTESIS

- El tractament de manteniment amb opioids és eficaç per a la dependència dual d'heroïna i cocaïna fet que es tradueix en un augment de l'abstinència d'heroïna i cocaïna i de la retenció en l'estudi.

- El tractament de manteniment amb psicoestimulants és eficaç per a la dependència de cocaïna, fet que es tradueix en un augment de l'abstinència de cocaïna i de la retenció en l'estudi.

- El tractament de manteniment doble amb opioids i psicoestimulants és més eficaç que el TMO en pacients amb una dependència dual d'heroïna i cocaïna fet que es tradueix en un augment de l'abstinència d'heroïna i de cocaïna i de la retenció en l'estudi.

No s'ha proposat una hipòtesis per al segon objectiu de la tesi perquè les dades existents en l'actualitat són contradictòries i no permeten formular un enunciat que es recolzi amb les evidències disponibles.

MÈTODES

Es van realitzar dos estudis. El primer tenia per objectiu investigar l'eficàcia del TMO per a la dependència dual d'heroïna i de cocaïna i comparar l'eficàcia de la metadona i la buprenorfina en aquests pacients. El segon va investigar l'eficàcia dels psicoestimulants per a la dependència de cocaïna i si el tractament de manteniment doble amb opioids i psicoestimulants era més eficaç que el TMO en pacients amb una dependència dual d'heroïna i cocaïna.

El tractament de manteniment amb opioids per a la dependència dual d'heroïna i cocaïna (estudi 1)

Es va realitzar una RSMA d'ACA. Es va fer una cerca bibliogràfica a les bases de dades MEDLINE, The Cochrane Central Register of Controlled Clinical Trials (CENTRAL) i PsychINFO. La sintaxi emprada es pot trobar a l'annex 1. A més, es van buscar referències addicionals a partir de les cites bibliogràfiques incloses en els articles obtinguts. La darrera cerca bibliogràfica es va fer el 01 de juny de 2010.

Es van incloure els ACAs de grups paral·lels que haguessin investigat l'eficàcia d'agonistes opioids o d'intervencions adjuvants al TMO per al tractament de pacients amb una dependència dual d'heroïna i de cocaïna. Es van excloure els estudis amb disseny encreuat ja que es va considerar que aquesta metodologia no era adequada per a la investigació d'intervencions per al tractament de dependències de substàncies.

Es van planejar les següents comparacions per avaluar l'eficàcia del TMO: dosi baixa de TMO vs. placebo, dosi alta de TMO vs. placebo, dosi alta de TMO vs. dosi baixa. Es va definir com a dosi baixa aquella que estava per sota de 50 mg/d de metadona, 6 mg/d de buprenorfina i 120 mg/set de LAAM. També es va comparar l'eficàcia de la metadona respecte la buprenorfina.

Només es van incloure aquelles comparacions entre dosis equivalents de metadona i de buprenorfina.

En aquesta memòria no es presenten les comparacions entre el tractament adjuvant al TMO i el placebo ja que no són un element vertebrador d'aquesta tesi. No obstant, els resultats d'aquestes comparacions es poden trobar en l'annex 1.

Les variables d'estudi van ser l'abstinència sostinguda d'heroïna i de cocaïna confirmada per mitjà de la determinació de tòxics en orina. Es va acceptar qualsevol definició de durada d'abstinència sostinguda, però en el cas que aquesta dada no fos proporcionada en la publicació, es va contactar amb els autors de l'estudi i es va demanar que ens proporcionessin l'abstinència sostinguda durant 3 setmanes. Es va seleccionar aquesta durada de l'abstinència perquè és habitualment emprada en ACAs de dependència d'heroïna o de cocaïna.

També es va investigar l'efecte d'aquestes intervencions sobre la retenció a l'estudi definida com la proporció de pacients aleatoritzats que completaven l'estudi.

De totes les variables dependents es van recollir preferentment els resultats obtinguts emprant una anàlisi per intenció de tractament.

Es va determinar el risc de biaix dels articles inclosos amb l'escala de Jadad (Jadad et al. 1996). Aquesta escala (disponible a l'annex IV) avalua la qualitat dels assaigs clínics en funció de si a la publicació es descriu l'estudi com aleatoritzat i doble cec, si aquestes dos processos s'han realitzat correctament i si s'hi descriuen els abandonaments i retirades. La seva puntuació oscil·la entre 0 i 5, i es considera que una puntuació per sota de 3 és indicativa que l'estudi té un risc elevat de presentar uns resultats esbiaixats.

Es va calcular el RR, la RAR i el NNT i els seus corresponents IC95% per cada estudi, i es varen combinar els seus resultats per mitjà del mètode d'efectes aleatoris de l'invers de la variança. Atès que la RAR i el NNT són molt sensibles a la durada de l'estudi, es va homogeneïtzar el número d'esdeveniments observats en un mateix període de temps per a tots els estudis. Es va decidir que aquest període de temps era de 12 setmanes. D'aquesta manera si un ACA tenia una durada de 24 setmanes i s'observaven 10 esdeveniments en un grup d'estudi, a l'hora de calcular la RAR i el NNT s'introduïen la part proporcional a 12 setmanes, en aquest cas, 5 esdeveniments. Els estudis amb diversos grups de tractament actiu i un únic grup control i que per tant proporcionen múltiples comparacions que estan correlacionades, es van incloure en la metanàlisi com una única comparació després de combinar els resultats dels grups que rebien

el tractament actiu (Higgins et al. 2009). De manera que aquests estudis s'incloïen en la metanàlisi com una única comparació.

L'heterogeneïtat estadística es va quantificar amb el paràmetre I^2, que és una mesura de la proporció de la variabilitat entre els resultats dels estudis inclosos. Es va calcular la significació estadística d'aquesta heterogeneïtat amb la prova de la χ^2. El risc de biaix de publicació es va determinar amb la prova d'Egger (Higgins et al. 2009). Es va fer una anàlisi de sensibilitat incloent-hi només aquells estudis que segons l'escala de Jadad presentaven un baix risc de biaix.

El tractament de manteniment amb psicoestimulants per a la dependència de cocaïna

Es varen realitzar dues RSMAs (Castells et al. 2007 i Castells et al. 2010 que es poden trobar als Annexes 2 i 3, respectivament) en les que s'hi varen incloure ACAs que van comparar l'eficàcia del tractament amb psicoestimulants respecte de placebo per a la dependència de cocaïna. Es descriuen els mètodes i els resultats principals de la segona RSMA (Annex 3) ja que empra uns criteris d'inclusió menys restrictius, conté una cerca bibliogràfica més extensa, inclou una anàlisi del risc de biaix dels ACAs més acurada, utilitza una metodologia estadística més adequada i conté una anàlisi de subgrups més exhaustiva. Es presenten els resultats després d'haver actualitzat la cerca bibliogràfica amb data de 01 de juny de 2010 i haver reanalitzat les dades amb la inclusió d'un estudi (Anderson et al. 2010) de recent publicació que no es va incloure en cap de les dues publicacions realitzades.

Es varen incloure els ACAs de grups paral·lels que van comparar l'eficàcia d'un psicoestimulant respecte al placebo en pacients amb dependència de cocaïna. Com que no existeix cap grup farmacològic que reculli tots els medicaments amb efecte psicoestimulant es va realitzar un cerca de tots els possibles fàrmacs amb aquest efecte en els grups farmacològics de la classificació ATC (Organització Mundial de la Salut 2010) i de l'American Hospital Formulary Service (American Hospital Formulary Service 2009) que, *a priori*, podrien contenir algun medicament que presentés aquest efecte. Aquests grups varen ser el N06BA (Simpaticomimètics d'acció central), A08AA (Fàrmacs amb acció central per al tractament de l'obesitat), N06BC (Derivats xantínics), N06BX (Altres psicoestimulants i nootròpics), N07BA (Fàrmacs emprats per al tractament de la dependència de nicotina) i R03DA (Xantines) de la classificació ATC; i el 12:92 (Fàrmacs autonòmics miscel·lànics), 28:16.04.92 (Antidepressius, miscel·lànics), 28:20.04 (Amfetamines), 28:20.92 (Fàrmacs anorexígens i estimulants respiratoris i cerebrals, miscel·lanis) i 86:16 (Relaxants de la musculatura llisa respiratòria) de la

classificació AHFS. També es va revisar el llistat de medicaments de l'agència mundial antidòping i altres fonts d'informació en farmacologia i psicofarmacologia (British Medical Association and the Royal Pharmaceutical Society of Great Britain 2010; Brunton et al. 2006; Schatzberg et al. 2009; Sweetman 2009). Finalment, també es van incloure fàrmacs que, com la selegilina, donen lloc a metabòlits amb efecte psicoestimulant. Del llistat de fàrmacs potencialment psicoestimulants, se'n van seleccionar només aquells pels quals existís, com a mínim, un estudi que demostrés que té un efecte psicoestimulant (taula 1). Es va definir com a efecte psicoestimulant a un augment de l'activitat del SNC que es tradueix en l'augment de la vigília i de l'activitat locomotora i anorèxia en animals o voluntaris sans (Boutrel et al. 2004; King et al. 2005; Kosman et al. 1968).

amfetamina, acefil·lina piperazina, adrafinil, amfepramona, aminorex, aminofil·lina, bamifil·lina, benzfetamina, bufil·lina, buprópion*, cafeïna, catina, catinona, clobenzorex, cocaïna, dexamfetamina*, dexmetilfenidat, dietilpropion, diprofil·lina, doxofil·lina, difil·lina, efedrina, etamifil·lina, etilamfetamina, fencamfamina, fenetilina, fenozolona, lisdexamfetamina, mazindol*, mefenorex, mesocarb, metamfetamina, metilendioximetamfetamina, metilfenidat*, modafinil*, nicotina, norpseudoefedrina, pemolina, fentermina, pipradrol, prolintà, propentofil·lina, proxifil·lina, radafaxina, selegilina*, sidnocarb, teobromina, teofil·lina, teofil·linat de colina

Taula 1: Psicoestimulants inclosos en la cerca bibliogràfica.
* indica els psicoestimulants per als quals s'hi va identificar algun ACA controlat amb placebo.

A fi d'identificar el major nombre possible d'estudis es va realitzar una cerca bibliogràfica a les bases de dades MEDLINE, CENTRAL, EMBASE i PsychINFO. A més, es van buscar ACAs registrats a les bases de dades clinicaltrial.gov, clinicalstudies.org i centerwatch.com. Es varen revisar les referències bibliogràfiques dels articles inclosos i es va contactar amb experts en la matèria per identificar estudis que haguessin passat desapercebuts amb la cerca de les bases de dades bibliogràfiques (als Annexes 1, 2, 3 i 4 de l'article inclòs a l'annex 3 hi consta la sintaxi emprada en les cerques de cada una de les bases de dades bibliogràfiques).

Es va comparar l'eficàcia dels psicoestimulants respecte del placebo, així com la de cada un dels fàrmacs individualment. A més, es va comparar l'eficàcia de tractament de manteniment doble

amb opioids i psicoestimulants respecte del TMO i placebo en pacients amb dependència dual d'heroïna i cocaïna.

Les variables principals de l'estudi varen ser l'abstinència sostinguda de cocaïna, confirmada per mitjà de la determinació de tòxics en orina, i la retenció en l'estudi. En estudis que van incloure pacients amb una dependència dual de cocaïna i heroïna, també es va recollir l'abstinència sostinguda d'heroïna. També en aquest estudi es va acceptar qualsevol definició de durada d'abstinència sostinguda, però en el cas que aquesta dada no fos proporcionada en la publicació es va contactar amb els autors de l'estudi i se'ls va sol·licitar l'abstinència sostinguda durant 3 setmanes.

Es va determinar el risc de biaix dels ACAs inclosos per mitjà de l'escala Cochrane. Aquesta escala avalua si els processos d'aleatorització, d'ocultació de la seqüència d'aleatorització, l'emmascarament doble cec i l'abordatge de les dades perdudes s'ha realitzat correctament. A més, inclou una cinquena categoria que contempla la possibilitat d'altres biaixos com, per exemple, l'efecte *carry-over* en ACAs encreuats. Tres d'aquestes dimensions, aleatorització, ocultació de la seqüència d'aleatorització i altres biaixos s'avaluen de manera independent per cada estudi inclòs, mentre que les dues dimensions restants, doble cec i gestió de les dades perdudes, s'avaluen de manera independent per a les variables objectives, com l'abstinència de droga, i per variables subjectives, com el *craving* de droga. A l'annex 5 s'inclou l'escala de la Cochrane.

Es va calcular el RR, la RAR i el NNT i els seus corresponents IC95%, i els resultats obtinguts per als diferents estudis es van combinar de manera ponderada emprant el model d'efectes fixes o aleatoris de Mantel-Haenszel en funció de l'absència o presència d'heterogeneïtat estadística, respectivament (Higgins et al. 2009). Es va calcular la RAR i el NNT després d'ajustar el número d'esdeveniments observats a un període de 12 setmanes. Els estudis amb diversos grups de tractament actiu i un únic grup control i que per tant proporcionen múltiples comparacions que estan correlacionades es van incloure en la metanàlisi com una única comparació després de combinar els resultats dels grups que rebien el tractament actiu. Així mateix, es van combinar els resultats dels grups comuns en els estudis amb un disseny factorial, de manera que si un ACA va estudiar l'eficàcia d'un psicoestimulant respecte del placebo i a més la d'una segona intervenció respecte d'un control, per exemple una teràpia cognitivo-conductual respecte el reforç amb contingències, es van combinar els resultats del grup que va rebre psicoestimulants i teràpia cognitivo-conductual amb els que van rebre psicoestimulants i reforç amb contingències, i aquest grup es va comparar amb el que va resultar de combinar els grups que van rebre placebo i una o altra psicoteràpia (Higgins et al. 2009).

L'heterogeneïtat estadística es va quantificar amb el paràmetre I^2 i es va determinar la seva significació estadística amb la prova de la χ^2. El risc de biaix de publicació es va determinar amb la prova de l'embut (Higgins et al. 2009).

Es van fer dues anàlisis de subgrups. La primera per a determinar l'eficàcia individual de cada un dels psicoestimulants agrupant els estudis inclosos segons el fàrmac estudiat. La segona subanàlisi va comparar l'eficàcia del tractament de manteniment doble amb opioids i psicoestimulants respecte del TMO sol en pacients amb dependència dual d'heroïna i cocaïna. Per fer-ho es va repetir l'anàlisi agrupant els estudis en funció de si la presència d'una dependència d'heroïna comòrbida era o no un criteri d'inclusió.

Es va empra el programa Review Manager (Review Manager (RevMan) 2008) per a l'anàlisi estadística de les dades.

RESULTATS

El tractament de manteniment amb opioids per a la dependència dual d'heroïna i cocaïna (estudi 1)

Sis estudis que van incloure 828 pacients van estudiar l'eficàcia del TMO en pacients amb una dependència dual d'heroïna i cocaïna. L'actualització de la cerca bibliogràfica no ha permès identificar cap nou ACA que compleixi els criteris d'inclusió d'aquesta RSMA. Els opioids investigats van ser la metadona, el LAAM i la buprenorfina. Cap d'ells no va ser comparat amb placebo. En absència d'estudis comparatius amb placebo es va determinar l'eficàcia del TMO de manera indirecta a partir de la comparació entre dosis altes i baixes.

Tres estudis (456 pacients) van comparar l'eficàcia de dosis altes i baixes de TMO (Montoya et al. 2004; Oliveto et al. 2005; Schottenfeld et al. 1997). Dos d'aquests estudis (Oliveto et al. 2005; Schottenfeld et al. 1997) tenien un disseny factorial, de manera que en resultaven 5 comparacions. Tots 3 estudis presentaven un baix risc de biaix segons l'escala de Jadad. Tanmateix, és probable que aquests estudis presentin un cert biaix de desgast atès que la retenció en l'estudi va ser força baixa i en aquestes circumstàncies cap mètode d'abordatge de dades perdudes garanteix uns resultats amb un baix risc de biaix. A més, no és descartable que s'hagués produït un trencament de l'emmascarament de la intervenció d'estudi ja que els efectes psicòtrops dels opiacis són força intensos, de manera que és probable que molts pacients i investigadors identifiquessin la dosi de TMO administrada. Ara bé, atès que les variables d'estudi són objectives, és improbable que d'aquest trencament del cec en resultés un esbiaixament dels resultats.

Els 3 estudis varen ser realitzats als EUA. Els pacients eren majoritàriament homes (65%), amb una edat de 34,4 anys de mitjana i una durada del consum d'heroïna i de cocaïna de 10,5 i 8,9 anys, respectivament. La freqüència de consum d'heroïna i de cocaïna el mes previ a la participació a l'estudi era de 28,7 i 11,7 dies/mes, respectivament.

Aquests 3 ACAs van comparar dosis baixes i altes de 3 opioids diferents: metadona (Schottenfeld et al. 1997), LAAM (Oliveto et al. 2005) i buprenorfina (Montoya et al. 2004; Schottenfeld et al. 1997). A la taula 2 es mostren les comparacions disponibles entre les dosis baixes i altes de TMO. A més de la intervenció d'estudi, en els 3 ACA, tots els pacients van rebre intervencions psicosocials concomitants i, en un d'ells (Oliveto et al. 2005), que tenia un disseny factorial, la meitat dels pacients va rebre una tercera intervenció en forma de reforç amb contingències. La durada del tractament va ser variable; de 12 setmanes en un estudi (Oliveto et al. 2005), de 13 setmanes en un altre (Montoya et al. 2004), i del doble en l'estudi restant (Schottenfeld et al. 1997). En tots tres estudis es va definir com a abstinència sostinguda d'heroïna i de cocaïna aquella amb una durada de com a mínim 3 setmanes.

	Opioid	**Dosi baixa**	**Dosi alta**
Montoya 2004	Buprenorfina	2 mg/d	8 mg/d o 16 mg/d o 16 mg/2d[4]
Oliveto 2005	LAAM	30, 30, 39 mg (DL, DX, DV)	100, 100, 130 mg DL, DX, DV
Schottenfield 1997a	Metadona	20 mg/d	65 mg/d
Schottenfield 1997b	Buprenorfina	4 mg/d	12 mg/d

Taula 2: Dosis d'opiod administrades en la comparació entre dosis baixes i altes de TMO. Abreviatures: DL: dilluns, DX: dimecres, DV: divendres

A la figura 1 s'hi mostren els resultats de la comparació entre les dosis altes i baixes de TMO respecte de l'abstinència d'heroïna, de cocaïna i de la retenció en l'estudi. Es va observar que l'abstinència d'heroïna era superior en el grup de pacients que van rebre dosis altes de TMO. En canvi, no es van trobar diferències estadísticament significatives pel que fa a l'abstinència de cocaïna. Es va fer una anàlisi *post hoc* per determinar si existien diferències entre les dosis altes i baixes de TMO sobre l'abstinència de cocaïna en funció del tipus d'opioid i tampoc es van trobar diferències. La retenció en l'estudi va ser superior entre els pacients que van rebre dosis altes de TMO, tot i així, va ser baixa en ambdues intervencions. Cap de les anàlisis realitzades va presentar resultats estadísticament heterogenis.

[4] Aquest estudi (Montoya et al. 2004) comparava 4 intervencions (Buprenorfina 2 mg/d, 8 mg/d, 16 mg/d i 16 mg/2d). En aquesta RSMA, els 3 darrers grups es van combinar i es van comparar amb el primer.

Pel que fa al benefici absolut de l'administració de les dosis altes de TMO respecte de les dosis baixes, la RAR d'assolir una abstinència sostinguda d'heroïna en 3 mesos de tractament i el NNT van ser de 0,13 [IC95% de 0,05 a 0,21] i de 7,7 [IC95% de 4,8 a 20,0], respectivament (I^2 = 22%). No es va calcular la RAR ni el NNT per l'abstinència sostinguda de cocaïna ja que no es van observar diferències estadísticament significatives per aquesta variable entre les dosis altes i baixes de TMO. La RAR de mantenir-se en TMO durant 3 mesos de tractament i el NNT van ser de 0,08 [IC95% de -0,02 a 0.17] i de 12,5 [IC95% de 5,9 a NA], respectivament (I^2 = 0%).

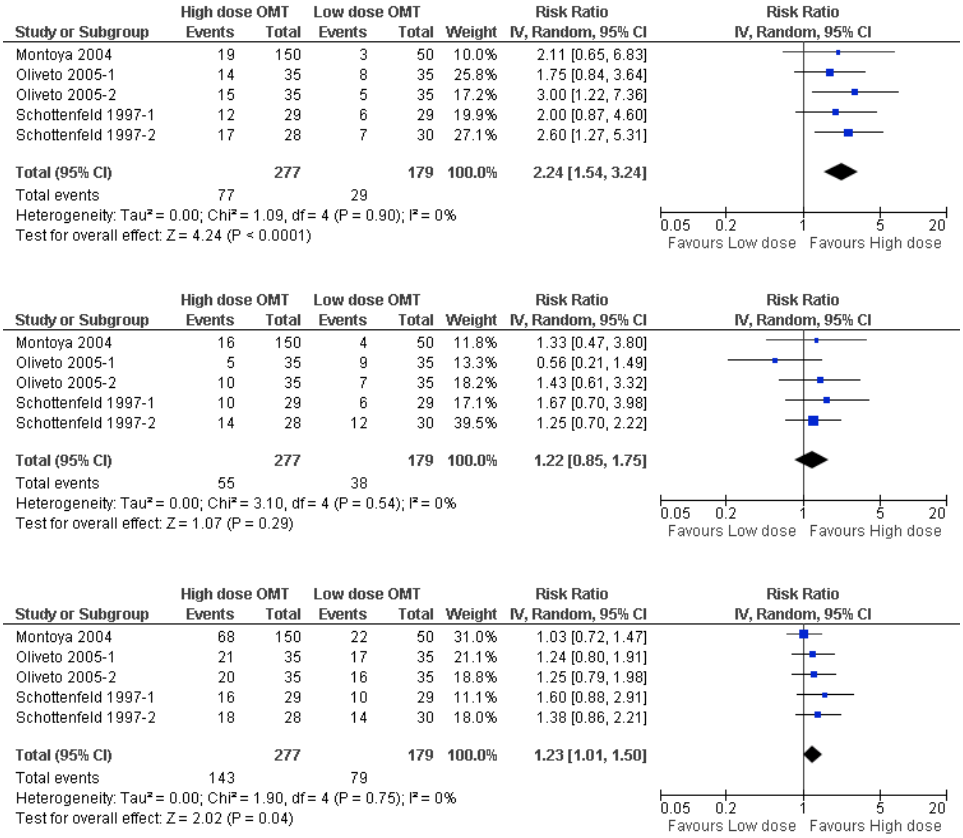


Figura 1: Eficàcia de les dosis altes de TMO respecte les dosis baixes sobre l'abstinència sostinguda d'heroïna (dalt), l'abstinència sostinguda de cocaïna (mig) i la retenció a l'estudi (baix), en pacients amb dependència d'heroïna i cocaïna.

Quatre ACAs van comparar l'eficàcia de la buprenorfina respecte la metadona. Es va disposar de dades en un format que permetia la seva metanàlisi en tres dels ACAs identificats (N = 329) (Schottenfeld et al. 1997; Schottenfeld et al. 2005; Strain et al. 1994). Dos d'aquests ACAs

(Schottenfeld et al. 1997; Schottenfeld et al. 2005) tenien un disseny factorial, de manera que en resultaven 5 comparacions entre metadona i buprenorfina. Tots 3 ACAs presentaven un baix risc de baix segons l'escala de Jadad. No obstant, és probable que s'hagi produït un cert baix de desgast com a conseqüència de la baixa retenció en l'estudi.

També aquí, els 3 ACAs inclosos en la metanàlisis varen ser realitzats als EUA. La proporció d'homes va ser del 68% i la mitjana d'edat de 34,3 anys. La durada del consum d'heroïna era de 8,5 anys i la de cocaïna de 6,7. La freqüència de consum d'heroïna i de cocaïna el mes previ a la participació a l'estudi era de 28,9 i 10,0 dies/mes, respectivament. La durada de l'abstinència de droga va ser de 3 setmanes en tots els estudis inclosos.

La presentació de metadona i buprenorfina administrada als 3 ACAs inclosos a la metanàlisi va ser la solució oral i la solució sublingual, respectivament. Per a mantenir el cec de la medicació es va realitzar un procediment de doble simulació, de manera que tots els pacients van rebre metadona o placebo P.O. i buprenorfina o placebo SL. A la taula 3 s'hi descriu la dosi de metadona administrada, el règim i el quocient entre les dosis de metadona i buprenorfina de cada comparació que va oscil·lar entre 5,0 i 5,9. A més de la intervenció d'estudi, en els 3 ACA tots els pacients van rebre intervencions psicosocials concomitants, i en un d'ells (Schottenfeld et al. 2005), que tenia un disseny factorial, la meitat dels pacients va rebre una tercera intervenció en forma de reforç amb contingències. La durada del tractament va ser de 24 setmanes en dos estudis (Schottenfeld et al. 1997; Schottenfeld et al. 2005) i de 16 setmanes en l'altre (Strain et al. 1994).

	Règim	**Dosi de Metadona (mg/d)**	**Dosi de Buprenorfina (mg/d)**	**Quocient**
Schottenfeld 1997a	fix	20	4	5,0
Schottenfeld 1997b	fix	65	12	5,4
Schottenfeld 2005	flexible	80	15	5,3
Strain 1994	flexible	66,6	11,2	5,9

Taula 3: Règim, dosi de metadona, dosi de buprenorfina i quocient de dosis dels ACAs inclosos en la comparació entre la metadona i la buprenorfina.

Es va observar que la proporció de pacients que aconseguien una abstinència sostinguda d'heroïna i de cocaïna i que completaven l'estudi era superior entre els que van rebre metadona (figura 2). Tanmateix, convé destacar que la retenció a l'estudi va ser baixa amb independència de la dosi estudiada. Es va observar una moderada heterogeneïtat en la metanàlisi de la variable l'abstinència d'heroïna. La RAR entre el grup tractat amb metadona i el tractat amb buprenorfina respecte de l'abstinència sostinguda d'heroïna, de cocaïna i de la retenció en tractament a les 12 setmanes va ser de 0,08 [IC95% de -0,1 a 0,16], 0,09 [IC95% de 0,01 a 0,17] i 0,07 [IC95% de -0,03 a 0,16]. Per la seva part, el NNT va ser, respectivament, de 12,5 [IC95% de 6,25 a NA], 11,1 [IC95% de 5,88 a 100] i 14,3 [IC95% de 6,25 a NA].

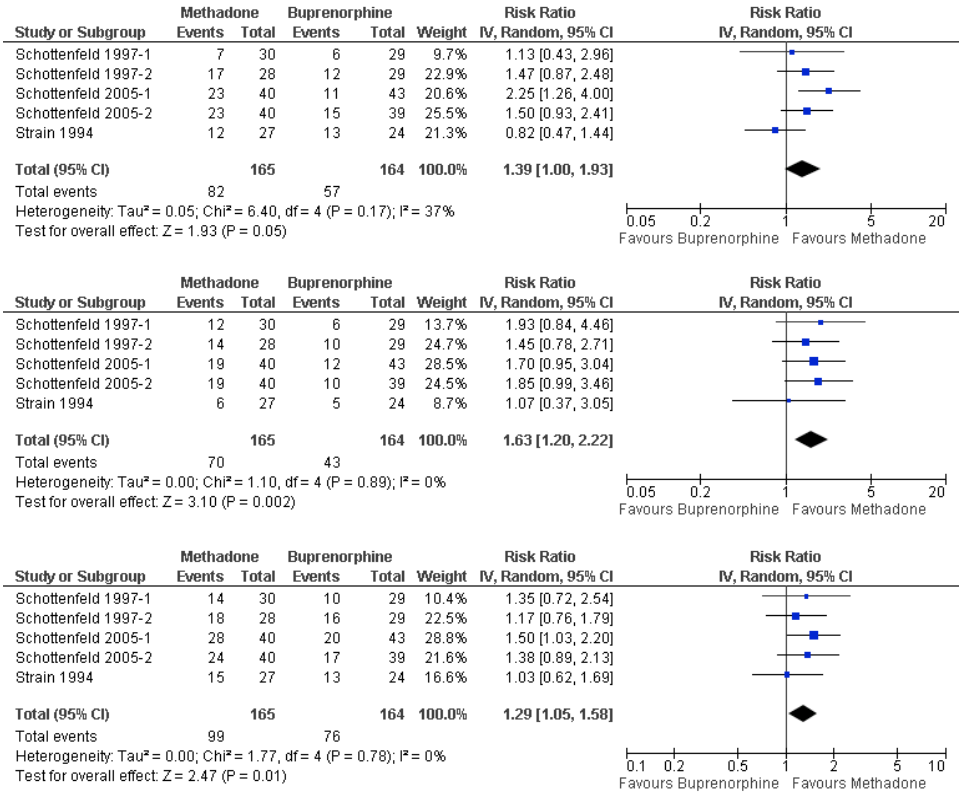


Figura 2: Eficàcia de la buprenorfina respecte la metadona sobre l'abstinència sostinguda d'heroïna (dalt), l'abstinència sostinguda de cocaïna (mig) i la retenció a l'estudi (baix), en pacients amb dependència d'heroïna i cocaïna. L'estudi de Schottenfeld et al. 1997 va comparar dosis baixes i dosis altes de TMO i l'estudi de Schottenfeld et al. 2005 va comparar dosis altes de TMO amb i sense teràpia de contingències.

No es va fer l'anàlisi de sensibilitat excloent els estudis que presentaven un alt risc de biaix segons l'escala de Jadad ja que cap estudi complia aquest criteri.

La prova d'Egger va mostrar que no hi havia una correlació estadísticament significativa entre l'efecte observat i la grandària de la mostra, fet que suggereix que l'existència de biaix de publicació en els estudis que han investigat l'eficàcia del TMO per a la dependència d'heroïna i cocaïna és improbable (figura 9 del material suplementari de l'annex 1).

El tractament de manteniment amb psicoestimulants per a la dependència de cocaïna

Disset ACAs van complir els criteris d'inclusió. A la secció "*Characteristics of studies*" de l'article inclòs en l'annex 3, pàgines 42 – 73, s'hi pot trobar una descripció detallada de cada un dels estudis inclosos.

L'avaluació del risc de biaix dels ACAs inclosos en aquesta RSMA es presenta de forma resumida a la figura 3 i a la taula 4. Pocs estudis van descriure amb prou detall el mètode emprat per a generar i ocultar la seqüència d'aleatorització, de manera que es va considerar que el risc de biaix relacionat amb aquestes dimensions era "por clar" per a la majoria d'ACAs inclosos. El psicoestimulants són intervencions que presenten uns intensos efectes subjectius, de manera que és molt difícil el seu emmascarament quan es comparen amb placebo. Tanmateix, es va considerar que el probable trencament del doble cec dels ACAs inclosos no esbiaixaria els resultats ja que les variables d'estudi d'aquesta metanàlisi són objectives, com l'abstinència de cocaïna o heroïna avaluada amb urinoanàlisi o la retenció en l'estudi i, per tant poc influïbles pel desemmascarament de la intervenció d'estudi. Per contra, es va considerar que la majoria d'estudis presentaven un elevat risc de biaix en relació a l'abordatge de les dades perdudes ja que, atesa la baixa retenció en l'estudi, era improbable que cap mètode de gestió de dades perdudes pogués corregir el biaix generat per l'elevada proporció de pacients que van abandonar l'estudi abans de la seva finalització formal. El risc de biaix atribuïble a "altres causes" va ser considerat inexistent per a la majoria dels ACA, amb l'excepció de 4 estudis que presentaven importants problemes de desequilibri en les característiques basals dels pacients inclosos o que van presentar canvis en la intervenció de l'estudi quan l'ACA ja havia començat. En resum, pel que fa a les variables proporció de abstinència sostinguda de cocaïna, cap dels ACAs inclosos estava lliure de biaix en totes les dimensions de l'escala Cochrane, i només dos, pel que fa a la variable retenció en l'estudi.

Figura 3: Esquerra: Proporció d'estudis amb un risc de biaix alt (vermell), poc clar (verd clar) i baix (verd fosc) per a cada un dels ítems de l'instrument de la Cochrane. Dreta: Resultats de l'avaluació del risc de biaix, alt (vermell), poc clar (verd clar) i baix (verd fosc), de cada un dels estudis inclosos.

La dimensió que avalua l'adequació de la metodologia emprada per a gestionar les dades perdudes (*incomplete outcome data*) s'ha aplicat només a la variable abstinència sostinguda de cocaïna.

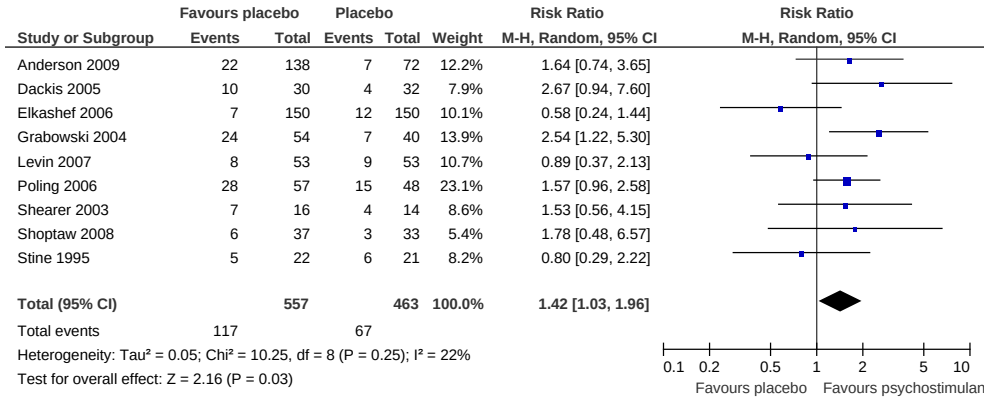
	Abstinència sostinguda de cocaïna	Retenció en l'estudi
Anderson 2009	No	No
Dackis 2005	No	No
Elkashef 2006	No	No
Grabowski 1997	No	No
Grabowski 2001	No	No
Grabowski 2004	No	No
Levin 2007	No	No
Margolin 1995 b	No	No
Margolin 1995 m	No	No
Margolin 1997	No	No
Mooney 2009	No	No
Perry 2004	No	No
Poling 2006	No	Sí
Schubiner 2002	No	No
Shearer 2003	No	Sí
Shoptaw 2008	No	No
Stine 1995	No	No

Taula 4: Estudis que presenten un baix risc de biaix en totes les dimensions de l'escala Cochrane que afecten a les dues variables metanalitzades en aquesta RSMA.

Aquests 17 estudis van incloure un total de 1.555 pacients, la majoria dels quals eren homes (74,4%), nordamericans (98%) i amb una mitjana d'edat de 38,1 anys. La proporció de pacients de raça caucàsica i afroamericana va ser similar, 41,1% i 46,0%, respectivament. Els pacients consumien cocaïna des de feia 12,5 anys i la mitjana de dies de consum de cocaïna el darrer mes va ser de 19,9 dies. Un 42% dels pacients presentaven una dependència d'heroïna comòrbida.

Es van estudiar 7 psicoestimulants diferents: buprópion, dexamfetamina, mazindol, metilfenidat, metamfetamina, modafinil i selegilina. En tots els estudis es va proporcionar algun tipus de psicoteràpia, essent la teràpia cognitivo-conductual i el consell sobre drogues les més freqüentment administrades. Els ACAs inclosos tenien una durada mitjana de 13 setmanes (rang: 6 – 24 setmanes).

La proporció de pacients que van assolir una abstinència sostinguda de cocaïna va ser més gran entre els pacients que van rebre tractament amb psicoestimulants que amb placebo (figura 4). Aquesta anàlisi va presentar una heterogeneïtat moderada. No es varen observar diferències en quant a la retenció entre les intervencions estudiades. La proporció de pacients que van assolir una abstinència sostinguda de cocaïna durant 12 setmanes de tractament va ser d'un 6% més elevada entre els que van rebre psicoestimulants que entre els que van rebre placebo (RAR = 0,06 [IC95% de -0,01 a 0,12], fet que es tradueix en un NNT de 16,7 [IC95% de 8,3 a NA]).



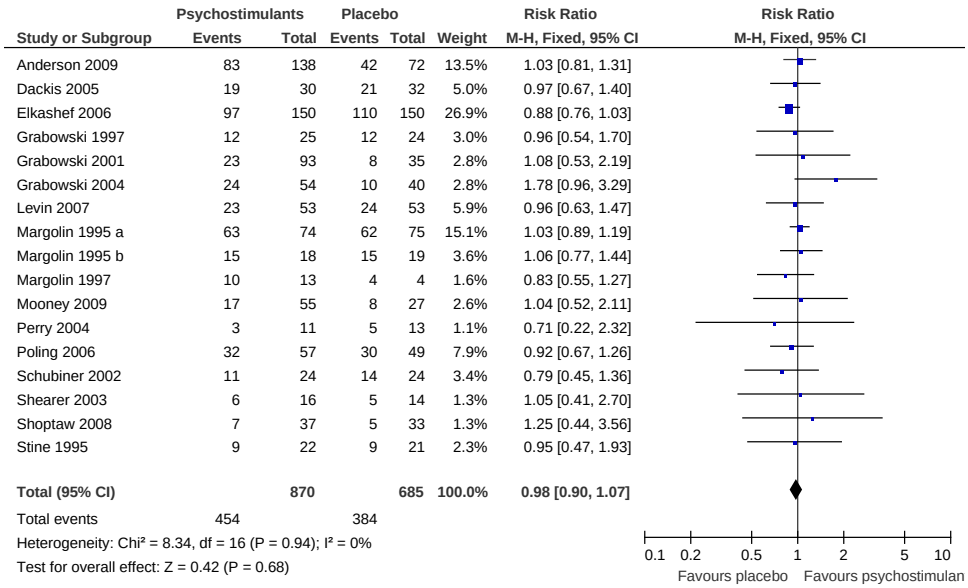


Figura 4: Eficàcia dels psicoestimulants respecte del placebo sobre l'abstinència sostinguda de cocaïna (dalt) i la retenció a l'estudi (baix) en pacients amb dependència de cocaïna.

A la taula 5 s'hi mostren els resultats de l'anàlisi de subgrups. Quan es va comparar l'eficàcia individual de cada un dels psicoestimulants estudiats es va observar que el buprópion, la dexamfetamina i el modafinil eren més eficaços que el placebo respecte de l'abstinència sostinguda de cocaïna, tot i que no ho eren respecte de la retenció. La proporció de pacients que van assolir una abstinència sostinguda de cocaïna durant 12 setmanes de tractament va ser d'un 8%, un 13% i d'un 17% més elevada, respectivament, amb buprópion, dexamfetamina i modafinil que amb placebo, tot i que aquesta diferència només va assolir la significació estadística en el cas de la dexamfetamina (RAR: buprópion = 0,08 [IC95% de -0,02 a 0,18], dexamfetamina 0,13 [IC95% de 0,01 a 0,26] i modafinil 0,17 [IC95% de -0,08 a 0,41]) fet que representa un NNT amb buprópion, dexamfetamina i modafinil de 12,5 [IC95% de 5,6 a NA], 7,7 [3,8 a 100] i 5,9 [2,4 a NA], respectivament. Pel que fa a la resta de psicoestimulants estudiats, cap d'ells va mostrar ser eficaç sobre cap de les variables estudiades.

	Abstinència sostinguda de cocaïna RR [IC95%]	**Retenció en l'estudi RR [IC95%]**
Tipus de psicoestimulant		
Buprópion	1,61 [de 1,01 a 2,56]	1,00 [de 0,87 a 1,16]
Dexamfetamina	2,12 [de 1,18 a 3,84]	1,36 [de 0,90 a 2,05]
Mazindol	0,80 [de 0,29 a 2,22]	0,94 [de 0,71 a 1,24]
Metamfetamina	ND	1,04 [de 0,52 a 2,11]
Metilfenidat	0,89 [de 0,37 a 2,13]	0,91 [de 0,68 a 1,22]
Modafinil	1,96 [de 1,04 a 3,71]	1,01 [de 0,83 a 1,24]
Selegilina	0,58 [de 0,24 a 1,44]	0,88 [de 0,76 a 1,03]
Presència d'una dependència d'heroïna comòrbida		
Sí	1,85 [de 1,18 a 2,90]	1,02 [de 0,88 a 1,18]
No	1,21 [de 0,82 a 1,79]	0,93 [de 0,84 a 1,04]
Risc de biaix respecte de totes les dimensions		
Baix	NA	0,94 [de 0,69 a 1,27]
Alt/Poc clar	1,42 [de 1,03 a 1,96]	0,99 [de 0,90 a 1,08]

Taula 5: Anàlisi de subgrups segons el tipus de psicoestimulant, la presència d'una dependència d'heroïna comòrbida com a criteri d'inclusió i el risc de biaix.

Es va estudiar la influència de la dependència comòrbida d'heroïna sobre l'efecte dels psicoestimulants. Es va observar que els psicoestimulants, administrats en combinació amb TMO, augmentaven la probabilitat d'aconseguir una abstinència sostinguda tant de cocaïna (RR = 1,85 [IC95% de 1,18 a 2,90] com d'heroïna (RR = 1,77 [IC95% de 1,31 a 2,39]). La retenció a l'estudi va ser força més elevada que entre els estudis on la dependència comòrbida de cocaïna no era un criteri d'inclusió. No obstant, tampoc en aquest subgrup de pacients, els psicoestimulants van augmentar la retenció en l'estudi respecte del placebo. La proporció de pacients que van assolir una abstinència sostinguda de cocaïna i d'heroïna durant 12 setmanes de tractament va ser, respectivament, d'un 11% i d'un 13% més elevada amb psicoestimulants que amb placebo (RAR: abstinència sostinguda de cocaïna = 0,11 [IC95% de 0,01 a 0,22] i abstinència sostinguda d'heroïna = 0,13 [IC95% de 0,01 a 0,24]) fet que representa un NNT de 9,1 [IC95% de 4,5 a 100] i de 7,7 [4,2 a 100]. Per contra, l'administració de psicoestimulants no va mostrar una millora de l'abstinència de cocaïna o de la retenció en l'estudi quan s'agrupaven els ACAs pels quals la dependència d'heroïna no era un criteri d'inclusió.

En quant a la influència del risc de biaix, indicar, en primer lloc, que el rendiment d'aquesta anàlisi va ser força baix ja que, per la variable abstinència sostinguda de cocaïna, cap dels estudis inclosos va presentar un baix risc de biaix en totes les dimensions de l'escala Cochrane i per tant no es va poder comparar si hi havia diferències en el resultat d'aquesta variable en funció del risc de biaix dels ACAs inclosos. A més, per la variable retenció en l'estudi, només dos ACAs van presentar un baix risc de biaix en totes les dimensions de l'escala Cochrane. No es van observar diferències estadísticament significatives en l'efecte de la intervenció d'estudi sobre la retenció entre els ACAs amb un baix i un alt/poc clar risc de biaix. L'anàlisi de la influència del risc de biaix de cada una de les dimensions de l'escala Cochrane es pot trobar en l'annex 3, comparacions 7 – 11, pàgines 79 – 84.

Es va analitzar el risc de biaix de publicació per mitjà de la prova de l'embut que va mostrar una distribució simètrica dels estudis que suggereix que aquest tipus de biaix és improbable que s'hagi produït en aquesta RSMA (figures 31 i 32, pàgines 33 i 34, de l'annex 3).

DISCUSSIÓ

S'ha emprat la metodologia metanalítica per a investigar l'eficàcia del tractament de manteniment amb opioids i amb psicoestimulants per a la dependència dual d'heroïna i cocaïna i per a la dependència de cocaïna. A la taula 6 s'hi mostra un resum dels resultats obtinguts.

Eficàcia del TMO per a la dependència dual d'heroïna i cocaïna

Nombrosos estudis han posat de manifest que el TMO és eficaç per al tractament de la dependència d'heroïna fet que l'ha convertit en una de les principals estratègies terapèutiques per al tractament d'aquest trastorn (Kleber et al. 2007). No obstant, l'eficàcia del TMO davalla considerablement en pacients que consumeixen cocaïna, de manera que, en comparació amb els pacients que no en consumeixen, els que sí que ho fan presenten un major consum d'heroïna (Marsden et al. 2009; Williamson et al. 2006), una taxa d'abandonament del TMO més elevada (Peles et al. 2008) i un augment de les conductes de risc de transmissió del VIH (Bux et al. 1995) i de la criminalitat (Kang et al. 1993). Tot plegat ha fet qüestionar l'eficàcia del TMO per a aquests pacients.

Aquesta RSMA mostra que el TMO és parcialment eficaç en pacients addictes a l'heroïna i que presenten una dependència comòrbida de cocaïna. Les dosis altes de TMO augmenten en un 124% de promig la probabilitat d'aconseguir una abstinència sostinguda d'heroïna i en un 23% de completar l'estudi respecte de les dosis baixes. Tanmateix, no s'observen diferències estadísitcament significatives pel que fa al consum de cocaïna. Aquests resultats són comparables amb els observats en d'altres estudis on la dependència de cocaïna comòrbida no és un criteri d'inclusió i on també les dosis altes de TMO han mostrat ser més eficaces que les dosis baixes respecte de l'abstinència d'heroïna i de la retenció en l'estudi (Faggiano et al. 2003). No obstant, aquest mateix estudi, a diferència d'aquesta RSMA, troba que les dosis altes s'associen a un augment de l'abstinència sostinguda de cocaïna. Ara bé, els resultats de l'estudi de Faggiano s'obtenen de combinar 2 ACAs (Johnson et al. 2000; Schottenfeld et al. 1997) i són

completament dependents dels resultats individuals d'un d'ells (Johnson et al. 2000) en el que la dependència de cocaïna comòrbida no era un criteri d'inclusió. Tot plegat es tradueix en uns resultats força indirectes ja que no queda clar en quins pacients davalla el consum de cocaïna; si és a expenses dels pacients consumidors ocasionals, dels abusadors o dels dependents de cocaïna. A més, els resultats s'obtenen a partir d'un reduït nombre de participants (n=168) i d'esdeveniments (n=55) i per tant són menys precisos que els que es presenten aquí (n participants = 456, n esdeveniments = 93).

Comparació **Variable**	**RR [95%IC], I^2**	**RAR**	**NNT**
TMO dosi baixa vs. alta			
Abstinència d'heroïna	2,24 [de 1,54 a 3,24], 0%	0,13	7,7
Abstinència de cocaïna	1,22 [de 0,85 a 1,75], 0%	-	-
Retenció en el tractament	1,23 [de 1,01 a 1,50], 0%	0,08	12,5
Metadona vs. Buprenorfina			
Abstinència d'heroïna	1,39 [de 1,00 a 1,93], 37%	0,08	12,5
Abstinència de cocaïna	1,63 [de 1,20 a 2,22], 0%	0,09	11,1
Retenció en el tractament	1,29 [de 1,05 a 1,58], 0%	0,07	14,3
Psicoestimulants vs. Pbo			
Abstinència de cocaïna	1,42 [de 1,03 a 1,96] , 22%	0,06	16,7
Retenció en el tractament	0,98 [de 0,90 a 1,07], 0%	-	-
TMO +Psicoestimulants vs. TMO + Pbo			
Abstinència de cocaïna	1,85 [de 1,18 a 2,90], 13%	0,11	9,1
Abstinència d'heroïna	1,77 [de 1,31 a 2,39], 0%	0,13	7,7
Retenció en el tractament	1,02 [de 0,88 a 1,18], 19%	-	-
Psicoestimulants vs. Pbo en estudis on la dependència d'heroïna no és un criteri d'inclusió	1,21 [de 0,82 a 1,79], 13%	-	-
Abstinència de cocaïna	0,93 [de 0,84 a 1,04], 0%	-	-
Retenció en el tractament			
Buprópion vs. Pbo			
Abstinència de cocaïna	1,61 [de 1,01 a 2,56], 0%	0,08	12,5
Retenció en el tractament	1,00 [de 0,87 a 1,16], 0%	-	-
Dexamfetamina vs. Pbo			
Abstinència de cocaïna	2,12 [de 1,18 a 3,84], 0%	0,13	7,7
Retenció en el tractament	1,36 [de 0,90 a 2,05], 0%	-	-
Modafnil vs. Pbo			
Abstinència de cocaïna	1,96 [de 1,04 a 3,71], 0%	0,17	5,9
Retenció en el tractament	1,01 [de 0,83 a 1,24], 0%	-	-

Taula 6: Resultats de les comparacions realitzades en aquestes RSMAs sobre les variables abstinència de cocaïna i d'heroïna i retenció en l'estudi. Només es presenta la RAR i el NNT d'aquells resultats que mostren un RR estadísticament significatiu.

Les dosis altes de TMO augmenten en un 23% la probabilitat de completar l'estudi respecte de les dosis baixes en pacients amb dependència dual d'heroïna i cocaïna. Demostrar un augment de la retenció en el tractament en estudis que investiguen l'eficàcia d'intervencions per a la dependència d'heroïna, amb o sense una dependència de cocaïna comòrbida, té un importància cabdal ja que en estudis observacionals s'ha constatat que l'abandonament dels programes de manteniment amb opioids s'associa a un augment de la mortalitat (Bell et al. 2009; Caplehorn et al. 1996; Davoli et al. 2008; Degenhardt et al. 2009; Peles et al. 2010). Per aquest motiu la retenció s'ha considerat com una variable subrogada d'efectivitat en els ACAs que investiguen l'eficàcia del TMO (Amato et al. 2005). Ara bé, convé destacar que no existeixen dades específiques de l'impacte de l'abandonament del TMO en pacients amb dependència dual d'heroïna i cocaïna.

La significació clínica de la millora de la retenció és discutible, especialment perquè el límit inferior de l'IC95% es troba molt proper al valor 1,0. No obstant, és important ressaltar que l'efecte observat és el que resulta de comparar dosis altes de TMO amb dosis baixes i no pas amb placebo. Si tenim present aquest fet i que, en pacients amb dependència d'heroïna sense una dependència de cocaïna comòrbida s'ha observat que les dosis baixes de metadona (20 mg/d) augmenten la retenció en l'estudi en comparació amb el placebo (RR = 1,98 [1,20 – 3,24]) (Strain et al. 1993), és d'esperar que l'efecte de dosis altes respecte al placebo sobre la retenció hauria estat superior a l'observat en aquesta RSMA.

La superioritat de les dosis altes de TMO respecte de les dosis baixes no ho és només en termes relatius sinó que l'administració de dosis altes de TMO beneficien a un nombre elevat de pacients, tal i com ho indiquen els NNTs de les variables abstinència d'heroïna i de retenció en l'estudi que són força baixos, especialment si tenim present que el comparador no és placebo sinó un tractament actiu.

Eficàcia de la buprenorfina respecte la metadona per a la dependència dual d'heroïna i cocaïna

Existeixen importants interaccions entre els opioids i la cocaïna que explicarien que el consum concomitant d'ambdues substàncies sigui tant prevalent (Leri et al. 2003). Alguns estudis de laboratori, juntament amb estudis clínics (Kosten et al. 1989b, Leri et al. 2003), han suggerit que els pacients amb una dependència dual d'heroïna i cocaïna es beneficiarien més del TMO amb agonistes opioids parcials com la buprenorfina que amb agonistes complets com la metadona.

Els resultats d'aquesta RSMA recolzen la hipòtesi contrària, és a dir que és més eficaç el TMO amb metadona que amb buprenorfina en pacients dependents d'heroïna que presenten una dependència de cocaïna comòrbida. La proporció de pacients que aconsegueixen una abstinència sostinguda d'heroïna, de cocaïna i que completen l'estudi és, respectivament, un 39%, un 63% i un 29%, de promig, més elevat amb metadona que amb buprenorfina. A més, el NNT per aquestes 3 variables és raonablement baix, de manera que el nombre de pacients que es beneficien del TMO amb metadona respecte de la buprenorfina és elevat. Aquests resultats són especialment destacables ja que s'obtenen de comparar dues intervencions que han mostrat ser eficaces com a tractament de manteniment en pacients dependents d'heroïna.

Els resultats respecte de l'abstinència d'heroïna i de la retenció en l'estudi van en la mateixa direcció als observats en pacients amb dependència d'heroïna (Mattick et al. 2008). La superioritat de la metadona respecte la buprenorfina pot ser deguda a les seves diferències farmacodinàmiques. En la mesura que la metadona és un agonista μ complet i la buprenorfina un agonista parcial, l'efecte farmacològic màxim de la metadona és superior al de la buprenorfina i, per tant, és probable que la metadona disminueixi més que la buprenorfina els símptomes de la SAO i el *craving* d'heroïna i que això es tradueixi en una major proporció de pacients que aconsegueixen una abstinència sostinguda d'heroïna. Una altra explicació podria ser que les dosis de buprenorfina hagin estat baixes en relació a les de metadona. Aquest raonament podria ser vàlid en el cas dels ACAs on la medicació d'estudi s'administra amb un règim fix i en els que la buprenorfina podria haver estat infradosificada. No obstant, en aquesta RSMA s'inclouen també estudis on l'administració és amb un règim flexible i en els que, per tant, la dosi administrada no és determinada *a priori*, sinó que és la que el clínic jutja més adequada en relació a la seva eficàcia i tolerabilitat. A més, resulta que la relació entre la dosi de buprenorfina i la de metadona en aquests estudis és similar a la dels estudis amb règim flexible, de manera que es pot descartar que la major eficàcia de la metadona respecte de la buprenorfina es degui a una infradosificació relativa de la buprenorfina.

Una proporció més gran de pacients amb TMO amb metadona aconsegueixen una abstinència sostinguda de cocaïna que amb buprenorfina. No hi ha una explicació clara d'aquesta troballa. Podria ser que, atès que la metadona és més eficaç que la buprenorfina respecte del consum d'heroïna, els pacients en manteniment amb metadona sovintegin menys els ambients on es trafica i es consumeix heroïna i que, per tant, tinguin un menor accés a altres drogues com la cocaïna, fet que es traduiria en un menor consum d'aquesta substància. Cal reconèixer que la plausibilitat d'aquesta explicació es troba contradita pel fet que, de ser certa, aleshores també s'hauria d'haver trobat un augment de l'abstinència de cocaïna amb dosis elevades de TMO respecte de les dosis baixes, ja que les primeres s'associen a un menor consum d'heroïna. No

obstant, no s'ha trobat que existissin diferències entre les dosis de TMO elevades i les baixes pel que fa a l'abstinència de cocaïna o, si més no, aquestes diferències no eren estadísticament significatives.

Els resultats d'aquesta RSMA respecte de l'impacte del TMO sobre el consum de cocaïna són aparentment contradictoris ja que per una banda no s'ha trobat una relació entre la dosi de TMO i l'abstinència de cocaïna, resultat que indicaria que el TMO no té efecte sobre el consum de cocaïna, i per l'altra s'ha observat un augment de l'abstinència de cocaïna amb el TMO amb metadona respecte al TMO amb buprenorfina. L'explicació més plausible a aquests resultats és estadística, és a dir que l'efecte del TMO sobre el consum de cocaïna és petit i que calen més estudis i més pacients per disposar del poder estadístic suficient per demostrar un efecte dosi-resposta del TMO sobre l'abstinència de cocaïna. Recolzaria aquesta explicació el fet que, malgrat no ser estadísticament significatiu, l'estimador central de l'efecte indica un augment de l'abstinència de cocaïna amb dosis altes de TMO (RR = 1,22). A més, alguns ACAs que han investigat l'eficàcia del TMO respecte al placebo en pacients amb una dependència d'heroïna i que acceptaven d'incloure-hi consumidors de cocaïna, malgrat que la dependència de cocaïna comòrbida no era un criteri d'inclusió, i que, per tant, no complien els criteris d'inclusió d'aquesta RSMA, també han objectivat una reducció del consum de cocaïna (Johnson et al. 1995; Johnson et al. 2000). Finalment, estudis amb un disseny observacional també han posat de manifest una davallada en el consum de cocaïna amb el TMO (Borg et al. 1999). Amb aquestes dades es podria pensar que hi ha prou evidències per considerar que el TMO té un impacte positiu sobre l'abstinència de cocaïna i, per tant, quedaria tancada la discussió sobre aquesta qüestió.

No obstant, també podria ser que el TMO no augmentés l'abstinència de cocaïna en pacients amb una dependència dual d'heroïna i cocaïna. Recolzarien aquesta conclusió els resultats d'aquesta RSMA, que ha combinat les dades de tots els estudis publicats que han comparat diferents dosis de TMO en pacients amb dependència dual de cocaïna, i que no ha trobat que dosis més altes de TMO s'acompanyin d'augments de l'abstinència de cocaïna estadísticament significatius en la seva anàlisi principal ni en les secundàries disponibles a l'annex 1. En aquest cas, l'única explicació al fet que l'abstinència de cocaïna sigui superior amb el TMO amb metadona que amb la buprenorfina seria farmacodinàmica. Podria ser que la buprenorfina, però no la metadona, tingués accions farmacològiques sobre, per exemple un receptor, i que l'efecte d'aquesta acció fos un augment del *craving* i del consum de cocaïna. Si, a més, l'afinitat per aquest receptor fos clarament superior a la del receptor μ, es podria entendre que quan es comparen dosis baixes amb dosis altes de buprenorfina no s'observin diferències respecte del consum de cocaïna, ja que, inclús a les dosis baixes, l'efecte sobre aquest receptor seria màxim

i, per tant, augments de dosis, que sí que representarien un augment dels efectes derivats de l'agonisme del receptor μ, no es traduirien en un augment dels efectes sobre aquest receptor. La metadona, que no tindria accions sobre aquest receptor, no augmentaria el *craving* ni el consum de cocaïna. Aquestes diferències farmacodinàmiques explicarien que, tal i com mostra aquesta RSMA, no es trobin diferències d'abstinència de cocaïna entre les dosis altes i les baixes de TMO però que el consum de cocaïna sigui menor amb el TMO amb metadona que amb buprenorfina. Una explicació complementària a aquesta seria que la metadona, però no la buprenorfina, té accions sobre un receptor que es tradueixen en una davallada del *craving* de cocaïna, i per tant en un augment de l'abstinència de cocaïna però com que l'afinitat sobre aquest receptor és molt elevada, inclús a dosis baixes s'obté l'efecte màxim i, per tant, augments posteriors de la dosi no implicarien un major augment de l'abstinència de cocaïna però sí d'heroïna. Convé insistir, que aquesta possibilitat és remota i altament especulativa i que el més probable és que, tal i com s'ha comentat anteriorment, amb un major nombre de pacients i d'esdeveniments es pugui demostrar un efecte sobre l'abstinència de cocaïna de les dosis altes de TMO respecte les dosis baixes. En aquestes circumstàncies sempre és bo tenir present l'aforisme metodològic "la no evidència de diferències no és evidència d'igualtat".

Els resultats d'aquesta RSMA en relació a la major abstinència de cocaïna amb metadona que amb buprenorfina serien difícilment reconciliables amb els dels estudis de Mello (Mello et al. 1993) que mostren que l'autoadministració de cocaïna és menor en pacients que reben buprenorfina que metadona. Aquests estudis es van realitzar en un context de laboratori on l'accés a la droga està limitat per l'experiment. En aquest context, els efectes del TMO sobre el consum de cocaïna s'estudien aïlladament dels del consum d'heroïna. No obstant, sembla que el consum d'ambdues substàncies no és independent, i en la mesura que la metadona és més eficaç que la buprenorfina sobre el consum d'heroïna, no és estrany que també augmenti l'abstinència d'una altra substància el consum de la qual està relacionat amb el de l'heroïna.

La superioritat de la metadona respecte la buprenorfina en quant a la retenció en l'estudi és un resultat consistent amb el d'altres RSMAs que han investigat l'eficàcia de la buprenorfina i la metadona en pacients dependents d'heroïna (Mattick et al. 2009). Hi ha diverses explicacions possibles a aquesta troballa. La major retenció en l'estudi amb metadona que amb buprenorfina expressa una major satisfacció dels pacients amb la primera ja que aquesta també s'associa a uns millors resultats sobre el consum d'heroïna i de cocaïna. A més, com que la buprenorfina és un agonista parcial es comporta com un antagonista en el cas que es combini amb heroïna (Cowan et al. 1977), fet que pot empènyer alguns pacients a abandonar el tractament amb buprenorfina. Finalment, en el cas que un pacient vulgui interrompre el TMO, ho tindrà més fàcil si rep

buprenorfina ja que la SAO de la buprenorfina és menys intensa que la de la metadona (Kleber et al. 2007; Orman et al. 2009).

Tal i com s'ha indicat anteriorment, nombrosos estudis observacionals suggereixen que l'abandonament del TMO s'associa a un augment de la mortalitat (Bell et al. 2009; Brugal et al. 2005; Caplehorn et al. 1996; Davoli et al. 2008; Peles 2010) i, per tant, és destacable la troballa que el tractament amb metadona s'acompanya d'una retenció més elevada que amb buprenorfina i, per tant, és esperable una menor mortalitat amb metadona que amb buprenorfina. Tanmateix, en els últims anys han aparegut un conjunt d'estudis observacionals que han comparat la retenció i la mortalitat de pacients amb dependència d'heroïna en TMO amb metadona o buprenorfina (Bell et al. 2009a, Burns et al. 2009; Degenhardt et al. 2009) i que han mostrat que malgrat que la retenció és superior amb metadona, tant durant la inducció com al llarg del tractament (Bell et al. 2009a, Burns et al. 2009), en contra de l'esperable, no s'observen diferències de mortalitat i, si en algun moment del tractament n'hi ha, aquestes diferències afavoreixen la buprenorfina, de manera que la mortalitat durant la inducció del TMO és menor amb buprenorfina que amb metadona (Degenhardt et al. 2009). Aquesta paradoxa s'explica per l'existència de diferències en les característiques basals dels pacients. En general, els pacients que reben metadona són més greus que els que reben buprenorfina (Bell et al. 2009a). Aquesta diferència en la selecció del tractament queda pal·lesa pel fet que la mortalitat dels pacients en TMO amb metadona va augmentar quan es va introduir la buprenorfina fet que suggereix que aquesta s'administrava a pacients menys greus (Degenhardt et al. 2009).

Eficàcia dels psicoestimulants per a la dependència de cocaïna

El tractament de manteniment amb psicoestimulants augmenta d'un 42% (entre un 3% i un 96%) la proporció de pacients que assoleixen una abstinència sostinguda de cocaïna respecte del placebo. No obstant el nombre de pacients que es beneficien d'aquest tractament és modest tal i com indica el NNT calculat. Cal tractar entre 16 i 17 pacients durant 12 setmanes per a que un pacient addicional aconsegueixi una abstinència sostinguda de cocaïna, respecte del placebo.

L'augment de l'abstinència de cocaïna amb el tractament de manteniment amb psicoestimulants és un resultat consistent amb el que s'observa quan aquest mateix abordatge s'empra per al tractament d'altres dependències. Així, el TMO ha demostrat que disminueix el consum d'heroïna respecte de placebo (Faggiano et al. 2003; Farré et al. 2002; Mattick et al. 2009). Així mateix, el tractament substitutiu amb nicotina també ha demostrat que augmenta l'abstinència

de tabac (Stead et al. 2008). La consistència entre aquests resultats proporciona un plus de versemblança a les troballes d'aquesta metanàlisi.

El resultat respecte de l'eficàcia sobre l'abstinència de cocaïna s'ha obtingut de combinar 9 de 17 estudis publicats. La resta d'estudis no es van incloure perquè no proporcionaven els resultats de manera adequada per a ser analitzats amb la metodologia planejada. Podria ser que si els estudis no inclosos tinguessin uns resultats negatius es neutralitzaria l'efecte observat. Alguns d'aquests estudis proporcionen els resultats de manera contínua, és a dir com a mitjana d'urinoanàlisi negatius al llarg de l'estudi. Existeix una metodologia metanalítica que permet la combinació de resultats expressats de forma dicotòmica amb els expressats de forma contínua. Recentment, hem emprat aquesta metodologia en una RSMA sobre l'eficàcia dels agonistes DA per a la dependència de cocaïna i de metamfetamina (Pérez-Mañá et al. 2010). Aquest estudi tenia una subanàlisi que avaluava l'eficàcia dels psicoestimulants per a la dependència de cocaïna. La metodologia anteriorment indicada va permetre la inclusió de 4 estudis més en la metanàlisi i els resultats han estat similars als presentats aquí, de manera que no sembla que els resultats obtinguts es deguin a un biaix de selecció.

Hi ha dues troballes d'aquesta RSMA que qüestionen la possible eficàcia del tractament de manteniment amb psicoestimulants. D'una banda, no s'ha trobat que aquest tractament augmenti la retenció en l'estudi, fet que sí que s'observa de manera recurrent en les RSMAs del TMO (Faggiano et al. 2003; Farré et al. 2002; Mattick et al. 2009). A més, és probable que els resultats obtinguts respecte de l'abstinència de cocaïna siguin esbiaixats. Així, no s'ha trobat que, segons l'escala Cochrane, cap dels ACAs inclosos en aquesta RSMA estigui lliure de biaix pel que fa a la variable abstinència de cocaïna. S'han identificat nombroses causes potencials de biaix, com ara incerteses respecte de l'aleatorització i de l'ocultació de la seqüència d'aleatorització. No obstant, la principal causa de biaix potencial en els ACAs inclosos prové de la baixa retenció observada en aquests estudis que fa que no es disposi dels resultats de les urinoanàlisi a partir del moment que el pacient ha abandonat o ha estat retirat de l'estudi i que s'hagin hagut d'imputar per permetre una anàlisi estadística per intenció de tractament.

En aquest punt, convé indicar que l'anàlisi de la influència del risc de biaix avaluat amb l'escala de la Cochrane s'ha fet d'una manera diferent en aquesta monografia que en l'article inclòs en l'annex 3. Aquí s'ha optat per avaluar el risc de biaix de cada ACA tenint present totes les dimensions, de manera que un estudi es considerava lliure de biaix si puntuava com a tal en totes les dimensions de l'escala. En canvi el *Cochrane Collaborative Drugs and Alcohol Review Group* (CCDAG) estableix que s'ha d'avaluar la influència de cada ítem de forma individual. Fer-ho de la manera com recomana el CCDAG dificulta la interpretació dels resultats ja que els

estudis inclosos sovint presenten més d'una font de biaix de manera que mai queden ben classificats en una única categoria i per tant les comparacions dels resultats entre els ACAs que presenten o no el biaix que avalua una categoria concreta queden confoses per la influència d'altres biaixos. L'única manera d'estudiar la influència individual de cada biaix seria per mitjà d'una metaregressió múltiple, però per fer-ho caldria un nombre molt superior d'estudis. Mentre això no sigui possible, l'única alternativa possible de quantificar la influència dels biaixos és com s'ha fet aquí, aglutinant els resultats en un estimador únic.

No hi ha una explicació clara al fet que el tractament de manteniment tingui uns resultats molt favorables quan es tracta de la dependència d'heroïna i, en canvi, siguin discutibles pel que fa a la dependència de cocaïna. Una possible explicació seria de tipus farmacològic. En el desenvolupament del tractament de manteniment amb agonistes per a la dependència d'heroïna es va fer una aposta ferma i decidida per la metadona. Un cop demostrat que el TMO amb metadona era eficaç s'han investigat altres agonistes opioids com la buprenorfina, el LAAM, la morfina i, des de fa una mica més d'una dècada, l'heroïna, i en la majoria dels estudis s'ha emprat la metadona com a comparador. Per contra, la recerca de fàrmacs amb efecte substitutiu per a la dependència de cocaïna s'ha realitzat de forma més heterogènia, fet que s'ha traduït en un nombre de psicoestimulants investigats força elevat en comparació amb el d'ACA i de pacients inclosos en aquests estudis. Probablement, el fet que la majoria de psicoestimulants no estiguin classificats com a tals (Castells et al. 2007) hagi contribuït a que s'hagin investigat nombrosos medicaments amb efectes similars. A més, les dosis investigades es corresponen, en la majoria de casos, a les emprades en altres indicacions i, probablement, no siguin les més adequades per al tractament de la dependència de cocaïna amb un abordatge de tractament de manteniment. Així, la dosis estudiada de buprópion és la indicada per a la deshabituació del tabac, la de la dexamfetamina o el metilfenidat per al tractament del TDAH, la del modafinil per a la narcolèpsia i la de la selegilina per a la de la malaltia de Parkinson. Probablement, calguin dosis més elevades per aconseguir una tolerància encreuada amb la cocaïna, disminuir els seus efectes euforitzants i obtenir una eficàcia més convincent per a la dependència de cocaïna. Una explicació al fet que les dosis emprades siguin relativament baixes és que tant el consum de cocaïna (Satel et al. 1991a) com el tractament amb psicoestimulants poden provocar símptomes psicòtics (Gross-Tsur et al. 2004; Mosholder et al. 2009), sembla ser que per un mecanisme d'hipersensibilització dopaminèrgica (Yui et al. 1999). Per tant, hi ha una certa prevenció a l'hora d'administrar dosis elevades de fàrmacs amb efecte psicoestimulant a pacients que consumeixen cocaïna des de fa anys, ja que es podrien provocar símptomes psicòtics o agreujar-los (Hahn et al. 2007).

Una altra possible explicació per la baixa eficàcia del tractament amb psicoestimulants és de tipus neurobiològic. Per bé que l'alteració de la neurotransmissió dopaminèrgica és cabdal per entendre els efectes psicoestimulants de la cocaïna i la dependència d'aquesta substància, el consum de cocaïna també modifica la neurotransmissió serotoninèrgica i en menor mesura també la noradrenèrgica (Rothman et al. 2003) que no quedarien completament corregides amb molts dels psicoestimulants estudiats. Això és especialment cert amb fàrmacs com el buprópion, el mazindol, el metilfenidat o el modafinil que, com la cocaïna, bloquegen el recaptador de la DA, però estan mancats d'accions sobre la neurotransmissió serotoninèrgica (Minzenberg et al. 2008; Tatsumi et al. 1997).

Finalment, hi hauria també una explicació clínica. La dependència d'heroïna es caracteritza per una síndrome d'abstinència greu que fa que sigui molt difícil d'interrompre el consum d'heroïna. Amb el TMO, la SAO queda molt atenuada i per tant desapareix una de les principals motivacions per al consum d'heroïna. Per contra, la síndrome d'abstinència de cocaïna és relativament lleu, de manera que el principal problema de la dependència de cocaïna no és la interrupció del consum sinó mantenir-se abstinent (Satel et al. 1991b). Per aquest motiu, un abordatge farmacològic orientat a la prevenció de recaigudes podria ser més apropiat per al tractament de pacients amb dependència de cocaïna. El fenomen de la recaiguda és complex i, des del punt de vista biològic, sembla que els neurotransmissors i hormones implicades serien, entre d'altres, la DA (Shalev et al. 2002), el glutamat (Cornish et al. 1999; Cornish et al. 2000; Cornish et al. 2001; Kalivas et al. 2005), el CRF i l'ACTH (Koob et al. 2007; Piazza et al. 1998) i la serotonina (Filip et al. 2005; Porrino et al. 1989; Rothman et al. 2003). Els psicoestimulants no actuen directament a tots aquests nivells i per tant serien un tractament de prevenció de recaigudes incomplet, fet que podria explicar que la seva eficàcia sigui modesta. Una excepció podria ser el modafinil el qual sembla tenir accions sobre la neurotransmissió glutamatèrgica (Minzenberg et al. 2008) que li podria conferir un potencial avantage respecte la resta de psicoestimulants. Malauradament, no existeixen estudis comparatius entre els diferents psicoestimulants per confirmar aquesta hipòtesi.

Set fàrmacs amb efecte psicoestimulant han estat investigats per al tractament de la dependència de cocaïna. De tots els psicoestimulants estudiats, només el buprópion, la dexamfetamina i el modafinil presenten uns resultats positius. Malgrat que el mecanisme d'acció dels fàrmacs inclosos no és idèntic, sembla poc probable que les diferències farmacodinàmiques expliquin les diferències d'eficàcia observades. És probable que aquestes diferències es deguin a que les dosis estudiades dels diferents fàrmacs no són equipotents. L'exemple més clar en aquest sentit seria la selegilina que per ella mateixa no té efectes psicoestimulants però sí dos dels seus metabòlits, la levoamfetamina i levometamfetamina. No obstant, les dosis de selegilina administrades no

produïrien quantitats suficients de levoamfetamina i levometamfetamina per a tenir efectes psicoestimulants i substitutius de cocaïna (Yasar et al. 1996; Yasar 2006). Una explicació alternativa podria ser que les diferències d'eficàcia entre els diferents psicoestimulants estudiats es deguin a diferències en les característiques dels pacients inclosos. Així, per exemple la dexamfetamina o el buprópion sovint s'han estudiat en pacients amb dependència d'heroïna comòrbida, que sembla ser una covariable que s'associa a una millor resposta als psicoestimulants.

Eficàcia del tractament de manteniment doble amb opioids i psicoestimulants respecte el TMO en pacients amb una dependència dual d'heroïna i cocaïna

En anteriors apartats s'ha mostrat que el TMO, especialment amb metadona, disminueix el consum d'heroïna i cocaïna en pacients dependents d'ambdues substàncies. A més, el tractament de manteniment amb psicoestimulants a pacients dependents de cocaïna augmenta l'abstinència de cocaïna respecte del placebo. El següent pas ha estat investigar si el tractament de manteniment doble amb opioids i psicoestimulants és més eficaç que el TMO. S'ha trobat que afegir-hi un psicoestimulant al TMO augmenta en un 85% el nombre de pacients que aconsegueixen una abstinència sostinguda de cocaïna respecte del TMO i que la població que es beneficia d'aquesta intervenció és considerable, tal i com es desprèn d'un NNT de 9. A més, els psicoestimulants potencien l'efecte del TMO sobre el consum d'heroïna ja que l'abstinència d'heroïna és superior entre els pacients que reben tractament de manteniment doble que entre els que reben TMO. Hi ha dues possibles explicacions per aquest resultat. D'una banda, i de manera anàloga al que es comentava en relació a les diferències entre la metadona i la buprenorfina sobre l'abstinència de cocaïna, si els pacients que reben psicoestimulants consumeixen menys cocaïna que els que reben placebo, és probable que sovintegin menys els llocs on es trafica i es consumeix cocaïna i, per tant, probablement també heroïna; és a dir, hi hauria una disminució en l'exposició a situacions que afavoririen el consum d'heroïna. Aquesta disminució del consum d'heroïna no s'acompanya de síndrome d'abstinència perquè tots els pacients estan rebent TMO. Una segona explicació és que aquells pacients que consumeixen l'heroïna simultàniament amb la cocaïna (speedball) o que utilitzen l'heroïna per a mitigar els efectes excitadors de la cocaïna, en la mesura que el tractament amb psicoestimulants augmenta l'abstinència de cocaïna, no és estrany que secundàriament també ho faci la d'heroïna.

Un resultat força sorprenent és que quan s'exclouen els ACAs on la dependència d'heroïna comòrbida és un criteri d'inclusió no s'observa que el tractament amb psicoestimulants

disminueixi el consum de cocaïna. Probablement, la causa d'aquest resultat negatiu és l'absència d'un poder estadístic suficient. De fet, quan s'empra una metodologia estadística que permet combinar resultats de variables qualitatives i quantitatives i que, per tant, fa possible que augmenti el nombre d'ACAs inclosos en la metanàlisi s'observa que el tractament amb psicoestimulants augmenta l'abstinència de cocaïna, inclús quan s'exclouen els ACAs on la dependència d'heroïna comòrbida és un criteri d'inclusió (Pérez-Mañá et al. 2010). Una altra explicació és la notable diferència de retenció en l'estudi que hi ha entre els ACAs on la dependència d'heroïna comòrbida és un criteri d'inclusió i els ACAs on no ho és. Així, la retenció en l'estudi és superior en els ACAs que inclouen pacients amb una dependència comòrbida d'heroïna i, per tant, també ho és la qualitat de les dades ja que hi ha una menor proporció de dades perdudes. Que la retenció en l'estudi sigui més elevada en pacients amb una dependència dual d'heroïna i cocaïna es pot deure a que aquests pacients estan rebent TMO, que és una intervenció que ha mostrat ser eficaç per al tractament de la dependència d'heroïna i que fidelitza el pacient al recurs sanitari. A més, com que la metadona, en els pacients inclosos en aquests ACA, s'administra diàriament i de forma presencial, s'aprofita l'assistència del pacient per proporcionar-li la medicació d'estudi per al tractament de la dependència de cocaïna, fet que, presumiblement, es tradueix en una adherència al tractament d'estudi superior que en els ACAs on la dependència d'heroïna no és un criteri d'inclusió i en els que, habitualment, el pacient s'emporta la medicació d'estudi a casa, de manera que no es pot assegurar si l'adherència terapèutica és l'adequada.

Convé subratllar que els resultats de l'eficàcia dels psicoestimulants en pacients amb o sense dependència d'heroïna comòrbida s'obtenen d'anàlisis de subgrups. La interpretació dels resultats d'aquestes subanàlisis s'ha de fer amb precaució atès el reduït nombre d'ACAs disponibles en relació a l'elevat nombre de subanàlisis realitzades i a l'elevada correlació entre les variables independents emprades per estratificar l'anàlisi. Així, per exemple, la presència d'una dependència comòrbida d'heroïna s'associa a una major eficàcia dels psicoestimulants. No obstant, com s'ha comentat anteriorment, els psicoestimulants que s'han investigat en aquest tipus de pacients són el buprópion i la dexamfetamina, que també s'han associat a resultats més favorables. Per tant, podria ser que ambdues variables, tipus de psicoestimulant i presència d'una dependència d'heroïna comòrbida, s'estiguin confonent mútuament. Caldria fer una metaregressió multivariant per poder determinar si existeix una influència independent d'aquestes dues variables, però per fer-ho caldria disposar d'un nombre considerable d'ACA.

Evidències sobre l'eficàcia del tractament de manteniment per a la dependència dual d'heroïna i cocaïna i la dependència de cocaïna

Fa uns 50 anys, Dole i Nyswander varen proposar d'administrar dosis altes de metadona per al tractament de l'addicció d'heroïna (Dole et al. 1966). Nombrosos estudis han demostrat que el TMO amb metadona i amb d'altres opioids és eficaç ja que redueix el consum d'heroïna, augmenta la retenció en el tractament i disminueix la transmissió del VIH, les activitats delictives i la mortalitat, de manera que avui en dia el TMO està considerat un dels tractaments d'elecció per a la dependència d'heroïna (Kleber et al. 2007). En les darreres dècades s'ha presenciat un augment del consum de cocaïna que sovint es produeix concomitantment amb el d'heroïna. L'ús de cocaïna per part de pacients en TMO s'ha relacionat amb una pèrdua d'eficàcia d'aquesta intervenció. Això ha fet plantejar-se si el TMO amb metadona era eficaç per a la dependència dual d'heroïna i cocaïna i si el TMO amb buprenorfina era més eficaç que amb metadona. Paral·lelament s'han investigat nombroses intervencions farmacològiques adreçades al tractament de la dependència de cocaïna. Una de les possibles estratègies és el tractament de manteniment amb psicoestimulants de forma anàloga al TMO per a la dependència d'heroïna.

Aquest treball recull 2 estudis, en els que, emprant la metodologia de la revisió sistemàtica i de la metanàlisi, s'ha investigat l'eficàcia del TMO en pacients amb dependència dual d'heroïna i cocaïna, de la seva combinació amb altres intervencions farmacològiques i la del tractament de manteniment amb psicoestimulants per a la dependència de cocaïna. Aquesta sèrie de RSMAs han mostrat que el TMO sembla eficaç per a la dependència dual d'heroïna i cocaïna ja que augmenta l'abstinència d'heroïna i la retenció en l'estudi, que el TMO amb metadona és més eficaç que amb buprenorfina ja que s'acompanya d'un augment de l'abstinència d'heroïna i de cocaïna i de la retenció en l'estudi, que el tractament de manteniment amb psicoestimulants és eficaç per a la dependència de cocaïna ja que augmenta l'abstinència de cocaïna, especialment quan s'utilitza buprópion, dextroamfetamina i modafinil, i que el tractament de manteniment doble amb opioids i psicoestimulants és més eficaç que el TMO en pacients amb una dependència dual d'heroïna i cocaïna ja que augmenta l'abstinència de cocaïna i d'heroïna. Aquests resultats proporcionen una dada més a favor del manteniment amb fàrmacs amb efectes substitutius per al tractament de la dependència de substàncies.

Ara bé la confiança en els resultats obtinguts en aquestes RSMAs és en general modesta degut a la possible presència de biaixos, resultats heterogenis, un elevat grau d'indirectesa d'algunes troballes i la imprecisió d'alguns efectes observats.

Possibles biaixos

Els resultats d'aquestes RSMAs poden estar esbiaixats perquè els propis ACAs inclosos tenen biaixos (Egger et al. 2001) o per la presència d'un biaix específic de les RSMAs que és el biaix de publicació (Egger et al. 1998). En quant als ACAs inclosos, existeixen diverses fonts potencials de biaix. D'una banda, el biaix que es produeix quan l'assignació del tractament no és aleatòria. Només una assignació veritablement aleatòria garanteix que els grups d'estudi siguin semblants en quant a les variables pronòstiques de la malaltia i a les que poden influir en la resposta del tractament. Per tant, en un assaig clínic que no és aleatoritzat és força probable que els grups d'estudi siguin diferents en quant a les seves característiques basals, fet que pot esbiaixar els resultats obtinguts.

Existeixen dubtes de si tots els estudis inclosos en aquestes RSMAs eren realment aleatoritzats. Aquests dubtes provenen del fet que en molts casos no es proporciona informació en la publicació de l'estudi sobre la manera com s'ha generat la seqüència d'aleatorització. No n'hi ha prou d'indicar que es tracta d'un estudi aleatoritzat ja que s'ha vist que en ocasions es consideren aleatoris mètodes d'assignació del tractament que realment no ho són, com ara els que basen l'assignació de la intervenció d'estudi en la terminació del document d'identitat o en la xifra de la data de naixement. Per estar segurs que l'assignació és verdaderament aleatòria, les guies de publicació dels ACAs recomanen que s'indiqui com s'ha generat la seqüència d'aleatorització (Schulz et al. 2010). La majoria d'estudis inclosos en aquestes RSMAs no especifiquen el mètode d'aleatorització i per tant no hi ha certesa suficient per assegurar que no estan esbiaixats com a conseqüència d'un mètode d'assignació del tractament inadequat.

Una ocultació inadequada de la seqüència d'aleatorització també pot provocar un biaix de selecció. No n'hi ha prou amb que l'assignació sigui aleatòria, cal, a més, que la seqüència mateixa sigui desconeguda per part dels investigadors i que, per tant, aquests no puguin preveure el tractament assignat als pacients, de manera que no puguin condicionar la inclusió del pacients en funció del tractament que rebran. Les guies de publicació d'ACA recomanen que es proporcioni aquesta informació per a poder valorar el risc de biaix associat a una inadequada ocultació de la seqüència d'aleatorització (Schulz et al. 2010). La majoria d'estudis inclosos en aquestes RSMAs no especifiquen el mètode d'ocultació de la seqüència d'aleatorització i per tant no hi ha certesa suficient per assegurar que no presenten uns resultats esbiaixats per aquest motiu.

En aquest punt, és important destacar que les dues escales emprades per avaluar el risc de biaix, l'escala de Jadad i l'escala de la Cochrane, són força diferents en quant a l'avaluació de risc associat a la generació i ocultació de la seqüència d'aleatorització. Així, l'escala de Jadad fa un gran èmfasi en que a la publicació s'indiqui explícitament que l'estudi és aleatoritzat i que la seqüència d'aleatorització ha estat ocultada. Mentre que l'escala de la Cochrane hi posa l'accent a la descripció i adequació d'aquests dos processos. De manera que un estudi pot puntuar com lliure de biaix segons l'escala de Jadad i que tingui un risc de biaix elevat segons la de la Cochrane.

S'ha de reconèixer que, malgrat que la majoria d'ACAs inclosos en aquestes RSMAs no proporcionen informació sobre com s'ha generat la seqüència d'aleatorització ni de com s'ha ocultat la mateixa, és força improbable que aquests processos s'hagin realitzat de forma inadequada, i el fet que en l'article no es proporcioni informació al respecte es deu fonamentalment a les limitacions d'extensió del mateix que imposen les revistes científiques. Els errors en la generació i en l'ocultació de la seqüència d'aleatorització eren freqüents fa unes dècades, abans de la realització dels estudis inclosos en aquestes RSMAs. A més, tots els ACAs inclosos han estat subvencionats per institucions públiques, fonamentalment per l'NIH, i sembla improbable que en les memòries presentades no s'inclogués aquesta informació i, en canvi, el projecte hagués obtingut el finançament sol·licitat.

Una altra possible biaix és el que es produeix pel desemmascarament de la intervenció rebuda com a conseqüència dels efectes subjectius de la medicació estudiada. La majoria dels fàrmacs estudiats en aquestes RSMAs tenen uns intensos efectes psicòtrops que poden permetre reconèixer la medicació que s'està estudiant. Això es pot haver produït en els ACAs que han comparat dosis altes i baixes de TMO o psicoestimulants i placebo. El trencament del doble cec pot provocar un biaix de realització i de detecció com a conseqüència d'una atenció clínica i una avaluació dels resultats diferents en funció de la intervenció administrada. No obstant, quan les variables d'estudi són objectives, com és el cas de les variables estudiades en aquestes RSMAs, abstinència d'heroïna o cocaïna avaluades per mitjà d'urinoanàlisi i la retenció en l'estudi, sembla que l'absència d'emmascarament de la intervenció d'estudi és poc probable que generi biaixos (Schulz et al. 2002). Per contra, quan les variables són subjectives, per exemple la gravetat de la simptomatologia depressiva en estudis d'eficàcia d'antidepressius, el trencament del doble cec sí que pot esbiaixar els resultats. La possible presència d'aquest biaix ha generat incerteses sobre l'eficàcia dels psicoestimulants en altres indicacions en les quals són habitualment emprats com el trastorn per dèficit d'atenció amb hiperactivitat (Castells et al. 2011).

Més important que tots els anteriors, és el biaix de desgast que es pot haver produït per la baixa retenció en l'estudi observada en la majoria d'ACA. El biaix de desgast es produeix perquè els pacients que abandonen l'estudi no són representatius del conjunt de pacients inclosos i és d'esperar que aquests pacients presentin un pitjor pronòstic que els que completen l'estudi. A més, és també molt probable que els motius que duen a l'abandonament de l'estudi siguin diferents entre les intervencions avaluades. Així, en les comparacions respecte el placebo, és probable que els pacients que abandonen l'estudi per manca d'eficàcia es concentrin entre els que reben placebo mentre que els que ho fan per intolerància a la medicació d'estudi siguin aquells que reben el tractament actiu. Aquest biaix és encara més marcat quan existeixen diferències en la proporció d'abandonaments entre els grups d'estudi, com és el cas de les comparacions entre dosis altes i baixes de TMO i entre metadona i buprenorfina. A fi de minimitzar la influència d'aquest biaix es recomana la utilització d'una anàlisi estadística per intenció de tractament. No obstant, aquesta aproximació sovint obliga a imputar resultats i no sembla que cap mètode d'imputació sigui adequat quan la retenció en l'estudi és baixa, com és el cas de la majoria d'ACAs inclosos en aquestes RSMAs.

Existeixen diversos dissenys d'ACA que permeten reduir la influència del biaix de desgast. Una possibilitat és augmentant la retenció en l'estudi. Això es pot aconseguir reduint la durada de l'estudi o limitant la inclusió a pacients que estiguin abstinents de cocaïna durant un període de temps abans de la inclusió en l'estudi (Bisaga et al. 2005; Konstenius et al. 2010). Qualsevol d'aquestes dues opcions té com a contrapartida una davallada de la validesa externa de l'estudi. Una altra possibilitat és emprar variables d'estudi que no puguin presentar biaix de desgast. En aquest sentit, la variable retenció en l'estudi compliria aquesta característica essent, a més, una variable crítica en estudis de dependència a substàncies ja que l'abandonament de l'estudi s'associa amb un resultat clínic negatiu, en aquest cas, a recaiguda en el consum de droga (Simpson et al. 1999).

Les escales de risc de biaix de la Cochrane i de Jadad també presenten importants diferències en quant al paper de la retenció en l'estudi sobre el biaix dels resultats dels ACA. Mentre l'escala de Jadad només té en compte si s'han descrit els abandonaments i retirades de l'estudi, la de la Cochrane obliga a indicar si aquests poden haver esbiaixat els resultats del mateix. Com a conseqüència d'aquestes diferències, un ACA que presenta una baixa retenció en l'estudi però que descriu de forma detallada els abandonaments no puntuarà negativament en l'escala de Jadad i sí que ho farà en la de la Cochrane.

El biaix de publicació és específic de les RSMAs i es produeix perquè la probabilitat que un ACA es publiqui és més elevada quan els seus resultats són positius. S'ha estudiat la

probabilitat que els resultats de les RSMAs incloses presentessin aquest biaix i no s'ha trobat cap evidència al respecte. El fet que cap dels ACAs inclosos estigués finançat per la indústria farmacèutica pot explicar que s'hagin publicat malgrat que la majoria d'estudis hagin presentat resultats negatius. Ara bé, el nombre d'estudis inclosos en la majoria de comparacions és baix, fet que disminueix la sensibilitat per detectar la presència de biaix de publicació (Sterne et al. 2001).

Heterogeneïtat i inconsistència

La inconsistència dels resultats genera desconfiança en les troballes de qualsevol estudi. En una RSMA, la inconsistència pot tenir dos orígens. En primer lloc, es pot produir quan l'efecte observat de la intervenció estudiada és diferent entre els diferents ACAs inclosos. La inconsistència interna en un metanàlisi es tradueix en un resultat agregat que presenta heterogeneïtat estadística i que es posa de manifest per un valor de I^2 més gran que zero. Quan el valor d'aquest paràmetre estadístic és superior al 50-60%, es considera que l'heterogeneïtat és gran (Higgins et al. 2003; Higgins et al. 2009). Cap de les anàlisis realitzades en aquestes RSMAs ha presentat un resultat amb una heterogeneïtat elevada, fet que és especialment destacat atès l'elevat nombre d'anàlisis realitzades. Tot i així, cal tenir present que la sensibilitat de les proves estadístiques emprades per a quantificar l'heterogeneïtat és baixa quan es combinen pocs estudis, com és el cas d'algunes comparacions d'aquesta RSMA.

La segona font d'inconsistència és la que es produeix quan els resultats de l'estudi són incoherents amb el coneixement previ i les hipòtesis plantejades. En aquest sentit, els resultats obtinguts presenten una notable consistència externa. S'ha trobat que les dosis altes de TMO són més eficaces que les dosis baixes i la metadona més que la buprenorfina en pacients dependents duals d'heroïna i cocaïna, que és un resultat similar a l'observat en pacients dependents d'heroïna (Faggiano et al. 2003; Farré et al. 2002; Mattick et al. 2008; Mattick et al. 2009). A més, s'ha trobat que el tractament de manteniment amb psicoestimulants en pacients dependents de cocaïna augmenta l'abstinència d'aquesta substància. Aquest resultat és consistent amb l'obtingut amb altres tractaments substitutius (Faggiano et al. 2003; Farré et al. 2002; Longo et al. 2010; Mattick et al. 2009; Stead et al. 2008). Finalment, que el tractament de manteniment doble amb opioids i psicoestimulants sigui més eficaç que el TMO sol en pacients amb una dependència dual d'heroïna i cocaïna és congruent amb les troballes anteriors.

L'elevada consistència dels resultats d'aquestes RSMAs és una de les seves principals fortaleses i una important font de confiança en els resultats obtinguts.

Indirectesa dels resultats

Una de les situacions que redueix més la qualitat de les evidències generades per una RSMA es produeix quan els resultats obtinguts són indirectes. Hi ha diverses fonts d'indirectesa. La primera es produeix perquè no existeixen les comparacions desitjades. Aquesta situació es produeix en aquesta RSMA quan s'ha investigat si el TMO és eficaç per la dependència dual d'heroïna i cocaïna. La comparació ideal era respecte placebo però no es va identificar cap ACA que inclogués aquest comparador. Per tant, aquesta l'avaluació de l'eficàcia del TMO es va generar a partir de la comparació entre dosis altes i dosis baixes de TMO. El fet d'observar que les dosis altes de TMO són més eficaces que les dosis baixes indica de manera indirecta que el TMO és eficaç en aquesta indicació.

Una segona causa d'indirectesa prové de la combinació dels resultats d'intervencions amb diferències substancials. Aquesta situació es produeix en nombroses ocasions, per exemple, en les comparacions entre dosis altes i baixes de TMO o entre els psicoestimulants i el placebo. Ambdues intervencions contenen fàrmacs amb mecanismes d'acció diferents. Per tant, la troballa que els psicoestimulants són eficaços per a la dependència de cocaïna és de difícil traducció en una recomanació específica ja que hi ha molts medicaments que presenten efectes psicoestimulants. A més, hi ha medicaments individuals com la dexamfetamina que s'han estudiat a dosis diferents, entre 15 i 60 mg/d, i els resultats d'aquesta RSMA no indiquen a quina dosi és eficaç aquest fàrmac. Això és especialment important perquè la dosi és un factor clau en el TMO (Farré et al. 2002; Mattick et al. 2008) i en els efectes farmacològics i terapèutics dels psicoestimulants (Castells et al. 2011; Solanto 1998). Disposar d'una taula de dosis equipotents entre els diferents psicoestimulants permetria incloure la dosis com a covariable en una metanàlisi, de manera similar a les metanàlisis que inclouen múltiples antipsicòtics i en les que s'ajusta la seva dosi en forma d'equivalents de clorpromazina o d'olanzapina (Gardner et al. 2010; Lehman et al. 2004; Leucht et al. 2009). Malauradament, aquesta dada no existeix per als psicoestimulants.

La darrera font d'indirectesa prové de la baixa validesa externa dels ACAs inclosos. La majoria d'ells s'han realitzat als Estats Units i cap d'ells a l'Estat espanyol o a la Unió Europea, fet que es tradueix en una extrapolació indirecta al nostre àmbit dels resultats obtinguts en països amb pacients i sistemes sanitaris que presenten característiques força diferents als nostres. A més, és probable que els pacients inclosos presentin una malaltia de menor gravetat que la dels pacients que s'atenen en la pràctica clínica diària. Això podria explicar que en els ACAs que avaluen

l'eficàcia del TMO, el grup de pacients que reben dosis "altes" de TMO, en realitat s'estabilitzen amb dosis que en la pràctica clínica habitual serien dosis mitges.

Precisió dels resultats

El número de pacients estudiats i d'esdeveniments observats és baix per a la majoria de variables i comparacions investigades, fet que es tradueix en uns efectes que tenen uns IC95% molt amples. Aquesta imprecisió en la mesura de l'efecte disminueix considerablement la qualitat de l'evidència dels resultats obtinguts. Així, per exemple l'augment de la retenció quan s'administren dosis altes de TMO en pacients amb dependència dual d'heroïna i cocaïna oscil·la entre un insignificant 1% i un considerable 50%. Una situació similar es produeix quan es compara l'eficàcia dels psicoestimulants respecte el placebo sobre l'abstinència de cocaïna que presenta un RR d' 1,44 però que es mou entre l'1,05 i el 1,97.

En resum, la confiança que generen els resultats d'aquestes RSMAs és, en general, modesta, fonamentalment degut a l'existència de biaixos per la dificultat d'emmascarar intervencions amb efectes psicòtrops intensos i per la baixa retenció de la majoria d'ACAs inclosos fet que obliga a la imputació de moltes dades. Així mateix, molts dels resultats tenen un grau d'indirectesa elevat i són poc precisos degut al reduït nombre de pacients inclosos i d'esdeveniments observats.

Rellevància de les variables estudiades

Amb independència de la confiança que generen els resultats d'aquestes RSMAs, queda el dubte de si les variables estudiades, abstinència d'heroïna i cocaïna i retenció en l'estudi, són les més adequades per a establir l'eficàcia d'una intervenció per al tractament d'un trastorn per dependència d'heroïna o cocaïna. El dubte prové del fet que l'abstinència de cocaïna o heroïna és una variable subrogada ja que amb aquesta prova s'avalua el consum de droga, que és un dels aspectes que caracteritza la dependència de substàncies, però no l'únic. Variables amb un major significat clínic, com la remissió de la dependència, o variables relacionades amb les conseqüències negatives del consum de substàncies com la criminalitat, la situació laboral, la transmissió d'infeccions pel VIH o VHC o la mortalitat serien més informatives de l'eficàcia d'una intervenció per al tractament de la dependència de substàncies. Ara bé, per poder demostrar que una intervenció és eficaç respecte d'aquestes variables caldria realitzar un ACA

amb un nombre molt superior de pacients i amb un seguiment molt llarg, fet que complicaria molt la seva realització.

Un altre aspecte que convé ressaltar en quant a la validesa de la variable abstinència de droga mesurada per mitjà d'urinoanàlisis està relacionat amb els falsos positius que genera aquesta mesura. Així, si un pacient dependent d'heroïna disminueix el consum de droga de 4 a 1 cop al dia continuarà presentant tots els urinoanàlisis positius, per tant aquest pacient es classificarà com una absència de resposta terapèutica. Una manera d'augmentar l'especificitat és operativitzant aquesta variable com s'ha fet aquí; comparant la proporció de pacients que assoleixen 3 setmanes consecutives d'abstinència de droga. Queda el dubte, però, de si una abstinència sostinguda de 3 setmanes és clínicament informativa de l'eficàcia d'una intervenció per al tractament d'una dependència de substàncies atesa la naturalesa crònica d'aquest trastorn. En aquest sentit seria raonable exigir que la variable d'eficàcia fos l'abstinència sostinguda durant un període més llarg de temps, de manera semblant a com es fa en els estudis que avaluen intervencions per a la dependència de tabac en els quals la durada de l'abstinència oscil·la entre 3 i 12 mesos (Gonzales et al. 2006; Hurt et al. 1997; Jorenby et al. 2006; Moore et al. 2009). Malauradament, no sembla possible plantejar uns objectius similars per al tractament de la dependència de cocaïna, heroïna o alcohol ja que només per a la dependència del tabac s'obtenen abstinències prolongades en una proporció prou elevada de pacients. Per a la resta de dependències cal plantejar-se objectius menys ambiciosos i més realistes com ara la disminució del consum de droga o l'assoliment de períodes breus d'abstinència.

La retenció en l'estudi és probablement una variable més informativa de l'eficàcia. A diferència de l'abstinència de droga, la retenció en l'estudi proporciona una idea de la relació benefici risc. Una millora de la retenció indica que la intervenció presenta una eficàcia que compensa els possibles efectes indesitjats o inconveniències que pugui ocasionar. A més, tal i com s'ha comentat anteriorment, aquesta variable no s'afecta pel biaix de desgast, mentre que sí que ho fa l'abstinència de droga. Per aquests dos motius, probablement, la retenció en l'estudi hauria de ser la variable principal de qualsevol ACA que investigui l'eficàcia d'una intervenció per al tractament de les dependències de cocaïna o d'heroïna i, per aquest mateix motiu, l'absència de millora en la retenció amb el tractament amb psicoestimulants genera incerteses en quant a l'eficàcia real d'aquesta intervenció.

CONCLUSIONS

- El TMO sembla eficaç per al tractament de la dependència dual d'heroïna i cocaïna, com ho demostra el fet que l'abstinència d'heroïna i la retenció en l'estudi són més elevades amb dosis altes de TMO que amb dosis baixes.

- Calen més estudis per aclarir si el TMO augmenta l'abstinència de cocaïna en pacients amb una dependència dual d'heroïna i cocaïna.

- El TMO amb metadona s'acompanya d'una abstinència d'heroïna i de cocaïna i d'una retenció en l'estudi més elevades que amb buprenorfina.

- El tractament de manteniment amb psicoestimulants a pacients amb dependència de cocaïna, en comparació amb placebo, augmenta l'abstinència de cocaïna però no millora la retenció en l'estudi.

- El tractament de manteniment doble amb psicoestimulants i opioids a pacients amb dependència dual d'heroïna i cocaïna augmenta l'abstinència d'ambdues substàncies respecte del TMO.

- El buprópion, la dexamfetamina i el modafinil són els únics psicoestimulants que, individualment, han mostrat augmentar l'abstinència de cocaïna en pacients dependents d'aquesta substància.

- La qualitat de les evidències que generen els resultats d'aquestes RSMAs és, en general, modesta, fonamentalment degut a l'existència de biaixos per la dificultat d'emmascarar intervencions farmacològiques amb efectes psicòtrops intensos i per la baixa retenció en l'estudi observada en la majoria d'ACAs inclosos. Així mateix, molts dels resultats tenen un grau d'indirectesa elevat i són poc precisos degut al baix nombre de pacients inclosos i d'esdeveniments observats.

- La retenció en l'estudi és la variable que proporciona més informació sobre l'eficàcia de les intervencions investigades en pacients amb dependència de substàncies ja que no s'afecta pel biaix de desgast, que és omnipresent en estudis que inclouen aquest tipus de pacients, i perquè proporciona una idea general de la relació benefici-risc de les intervencions estudiades.

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ANNEX I

Castells X, Kosten TR, Capellà D, Vidal X, Colom J, Casas M. Efficacy of opiate maintenance therapy and adjunctive interventions for opioid dependence with comorbid cocaine use disorders: A systematic review and meta-analysis of controlled clinical trials. *Am J Drug Alcohol Abuse* 2009;35:339-49.

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Efficacy of Opiate Maintenance Therapy and Adjunctive Interventions for Opioid Dependence with Comorbid Cocaine Use Disorders: A Systematic Review and Meta-Analysis of Controlled Clinical Trials

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***Aims*: To determine the efficacy of Opiate Maintenance Therapy (OMT) and adjunctive interventions for dual heroin and cocaine dependence by means of a meta-analysis. *Method*: We searched for and retrieved randomized controlled clinical trials. We used RevMan 5.0 with random effects modeling for statistical analysis and for comparisons of relative risk, effect sizes, and confidence intervals. Subsequent moderator variables and sensitivity analyses were performed. *Results*: Thirty-seven studies, which have enrolled 3,029 patients, have been included in this meta-analysis. High doses of OMT were more efficacious than lower ones in the achievement of sustained heroin abstinence (RR = 2.24 [1.54, 3.24], $p < .0001$) but had no effect on cocaine abstinence. At equivalent doses, methadone was more efficacious than buprenorphine on cocaine abstinence (RR = 1.63 [1.20, 2.22], $p = .002$) and also appeared to be superior on heroin abstinence (RR = 1.39 [1.00, 1.93], $p = .05$). Several pharmacological and psychological potentiation strategies have been investigated. An improvement on sustained cocaine abstinence was achieved with indirect dopaminergic agonists (RR = 1.44 [1.05, 1.98], $p = .03$) and with contingency management (CM) focusing on cocaine abstinence (RR = 3.11 [1.80, 5.35], $p < .0001$). *Conclusions*: Dual opioid and cocaine dependence can be effectively treated with OMT in combination with adjunctive interventions. Higher OMT doses are preferable to lower ones and methadone to buprenorphine. OMT can be enhanced with indirect dopaminergic drugs and with CM focusing on cocaine abstinence.**

Keywords Buprenorphine, cocaine, heroin, meta-analysis, methadone

INTRODUCTION

Heroin dependence can be effectively treated with oral opiates like methadone or buprenorphine (1). Opioid maintenance treatment (OMT) has increased treatment retention (2) and has reduced heroin use (3), crime (3, 4), HIV risk behaviors (3), and mortality (5). However, cocaine use is present in about a half of patients receiving OMT (6–11). Cocaine use has been associated with poorer OMT outcomes on heroin use (12), engagement in criminal activities, psychosocial functioning (13), and HIV risk behaviors (9, 14). Thus, addressing cocaine use

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among opioid dependent patients has become a priority in order to improve the efficacy of OMT.

Two strategies for treating cocaine use in patients receiving OMT could be to optimize OMT and to add adjunctive treatments. Since opioid and cocaine interactions can affect their reinforcing properties (15), OMT optimizing strategies have addressed the type of opiate agonist (methadone vs. buprenorphine) and its dose (1). The second approach of using adjunctive interventions has not clearly shown any efficacious agent (16). The efficacy of both OMT and adjunctive interventions merits a meta-analysis of the different studies to identify any consistently efficacious intervention.

METHOD

Search Strategy

A systematic review and meta-analysis was carried out by searching bibliographic databases, including PubMed, The Cochrane Central Register of Controlled Trials (CENTRAL) and Psychinfo and hand-searching the reference list of retrieved studies.

To be included in this meta-analysis, studies had to be randomized controlled clinical trials with parallel groups, which assessed the efficacy of an OMT strategy or adjunctive interventions for opiate dependent patients with a comorbid cocaine use disorder. Studies had to be available before September 2007. For studies assessing the efficacy of OMT, studies comparing OMT against either placebo or another OMT intervention were included. For clinical trials assessing OMT adjunctive interventions, only those with an inactive control group were included. Laboratory studies as well as those published as abstracts were excluded. There were no restrictions regarding publication year or language. Search syntax is described in table 1 online.

Data Extraction

The following data was collected: study design, patients' features, intervention description, drug use outcomes and study retention. Intention to treat (ITT) data was preferred to per protocol (PP) ones.

Study quality was assessed by means of the Jadad scale (17). This scale is based on the description of subject withdrawals from the study and on the description and appropriateness of randomization and double blinding. Its score ranges from 0 to 5, and a score below 3 indicates poor quality. Because psychological interventions cannot be double blinded, the items of the Jadad scale pertaining to study blinding were not applied and the study quality indicating poor quality was set at 2.

Data Synthesis and Statistical Analysis

The primary outcomes were the proportion of patients achieving sustained heroin abstinence and the proportion achieving sustained cocaine abstinence. Sustained abstinence was defined as continuous heroin or cocaine abstinence determined by means of urine screens. The definition of sustained abstinence differed across the studies regarding the number of weeks of drug abstinence. We did not use any a priori definition of abstinence length; however, when this variable was not reported, the authors were contacted, and the proportion of participants achieving a sustained heroin or cocaine abstinence during 3 weeks was requested. Secondary outcomes were heroin and cocaine use, defined as the number of drug free urinanalysis (UA) over the course of the intervention period, and study retention, defined as the proportion of randomized patients that completed the intervention protocol. Study outcomes that were not reported in the article were requested to the contact author.

Data on the efficacy of OMT and adjunctive interventions were analyzed separately. To determine the efficacy of OMT, the following comparisons were planned: high dose OMT vs. placebo, low dose vs. placebo, and high dose vs. low dose. Low dose of OMT was defined as that below 50 mg/d for methadone, 6 mg/d for buprenorphine, and 120 mg/week for Levo-Alpha-Acetymethadol (LAAM). To determine which opiate was the most efficacious, the available head-to-head comparisons at equivalent doses were pooled together. Thus, for instance, only comparisons of high dose methadone vs. high dose buprenorphine, and low dose methadone vs. low dose buprenorphine were included. By proceeding that way, a dose adjusted pooled effect of the efficacy of one opiate over another one was obtained.

OMT pharmacological adjunctive interventions were combined based on the predominant neurotransmitter effects. For instance, studies assessing the efficacy of bupropion, desipramine, and fluoxetine were not pooled together in a so-called "antidepressant" group, but were combined with other drugs sharing the same pharmacological actions on the dopaminergic, serotoninergic, and noradrenergic systems.

Cochrane collaboration recommendations were used for the inclusion of studies with multiple intervention groups (18). When several independent comparisons were available, they were included as independent studies. In studies with multiple and correlated interventions, e.g., studies with one control and multiple experimental ones, experimental groups were combined into a single group and included in the meta-analysis as one comparison.

RevMan 5.0 (19) was used to perform the statistical analysis. Relative risk (RR) and standardized mean difference (SMD) were calculated for dichotomous (achievement of sustained heroin and cocaine abstinence and study retention) and continuous outcomes (heroin and cocaine use across the study), respectively. Hedges' method was used for calculating SMD with individual study weights calculated as the inverse of the variance (20). Weighted averages and 95% confidence intervals (CI) were calculated by means of a random effects model. Between-study statistical heterogeneity was assessed using the I^2 and χ^2 tests for heterogeneity (20). The possibility of publication bias was assessed by means of the Egger test (21) using the Epidat software (22). The Egger test consists on a regression

of the standardized effect estimates (RR or SMD) against their precision (inverse of the variance). A Y-intercept deviation from zero is suggestive of publication bias.

We performed an analysis of moderator variables in two steps. 1) We stratified for type of cocaine use disorder separating studies that included patients with both cocaine dependence and abuse from those with cocaine dependence alone. 2) We separately analysed studies where participants were already on OMT at baseline from those including heroin users who were induced on to OMT during the course of the study. A sensitivity analysis was carried out by repeating the analysis after removing the clinical trials with low quality according to the Jadad score. We determined whether the findings were unduly influenced by a single comparison by extracting each comparison once and repeating the analysis.

RESULTS

We included 37 articles (see Fig. 1 online for a description of the progress of the articles selection through the stages of this meta-analysis) (23–59) which enrolled 3,029 patients. Additional data was requested for 34 studies, and we succeeded in obtaining nonpublished data in 17 (50%). Table 2 online summarizes the study features of the included articles. It is notable that all studies were conducted in the United States and were funded by national institutions, commonly National Institute on Drug and Alcohol Abuse (NIDA).

Patients were mostly middle aged (range of mean age = 32.0–42.6), men (63%), and about a half (55%) were Caucasian. All patients were heroin dependent and most (93%) had a comorbid cocaine dependence, and 7% were cocaine abusers. (This data was obtained by averaging the baseline demographics of 34, 36, 32, 37, and 32 studies reporting this data, respectively.) Psychiatric diagnoses were performed using the DSM III criteria (1 study), DSM III-R (20 studies), and DSM-IV (14). Two studies did not report the diagnostic criteria that were used (41, 57).

Efficacy of OMT for Dual Heroin–Cocaine Abusers

Six studies (44–46, 54, 55, 59) assessed the efficacy of OMT in 828 patients. No study compared the efficacy of OMT against placebo, and thus, the efficacy of OMT could not be directly estimated. However, three studies included high vs. low OMT comparisons (44, 46, 54), allowing indirect inference of OMT efficacy from a dose response analysis. Three opiates at high vs. low doses have been investigated: methadone, buprenorphine, and LAAM.

Figure 1 shows the efficacy of high vs. low dose OMT on sustained heroin (top) and cocaine (bottom) abstinence. Higher doses were more efficacious than lower ones in achieving sustained heroin abstinence (RR = 2.24 [1.54, 3.24], $p < .0001$), but no differences were found on sustained cocaine abstinence. The secondary outcomes yielded similar findings. Higher doses were associated with increased heroin-free UA (*SMD* = .40 [.17, .64], $p = .0009$) (Fig. 2 online) but no effect was found for cocaine-free UA. In addition, higher OMT doses were associated with higher retention (RR = 1.23 [1.01, 1.49], $p = .04$).

Four studies (45, 54, 55, 59) compared the efficacy of equivalent doses of methadone and buprenorphine. Three studies (54, 55, 59) reported data on sustained drug abstinence and study retention, and 2 (55, 59) on heroin and cocaine use. The methadone to buprenorphine dose ratio ranged from 5.0 to 5.8. Buprenorphine was administered as an oral solution in these studies. At equivalent doses (Fig. 2), methadone was more efficacious than buprenorphine in the achievement of sustained cocaine abstinence (RR = 1.63 [1.20, 2.22], $p = .002$) and of heroin abstinence but at a trend level of significance (RR = 1.39 [1.00, 1.93], $p = .05$). Furthermore, methadone was associated with an increased cocaine-free UA (*SMD* = .37 [.10, .65], $p = .007$) and retention (RR = 1.29 [1.05, 1.58], $p = .01$) (Fig. 3 online). Heroin use was lower with methadone but did not reach statistical significance (*SMD* = 0.35 [−.16, .87], $p = .18$).

Efficacy of Adjunctive Interventions to OMT for Dual Heroin–Cocaine Abusers

Thirty-four studies investigated the efficacy of adjunctive pharmacological interventions, psychological interventions, and acupuncture.

Twenty studies have investigated the efficacy of 14 drugs as adjunctive interventions to OMT. Pharmacological modulation of the dopamine (DA) system has been the most common approach. Three types of dopaminergic modulation have been studied: direct agonism using amantadine (33, 36, 37) or bromocriptine (34), indirect agonism using bupropion (40, 50), dexamphetamine (32), disulfiram (28, 47), or mazindol (41, 42), and antagonism using risperidone (32). Indirect noradrenergic agonism using desipramine to block the noradrenaline (NA) reuptake transporter has also been widely studied (23, 36, 37, 39, 45). Other pharmacological strategies such as serotonin reuptake inhibition using fluoxetine (31), GABAergic agonism using tiagabine (29, 30) or gabapentin (30), cortisol inhibition (38), nicotine antagonism (52), and magnesium (43) have been infrequently studied. Clinical trials that have investigated these adjunctive pharmacological interventions predominantly focused on their efficacy over cocaine use and their efficacy over heroin use was infrequently reported. Study retention was the only available data for meta-analysis of ketoconazole and mecamylamine.

Results on sustained cocaine abstinence and cocaine use for those interventions with more than one study are displayed in Figs. 3 and 4. (The results of those interventions for which only one single study was available can be found in the online Figs. 6 and 7. Results on sustained heroin abstinence, heroin use, and study retention can be found in the online Figs. 4, 5, and 8).

Direct DA agonism and DA antagonism did not appear to be efficacious (Figs. 3, 4, 6, and 7 online). Conversely, indirect DA agonism increased the likelihood of achieving sustained cocaine abstinence (Fig. 3) (RR = 1.44 [1.05, 1.98], $p = .03$) and

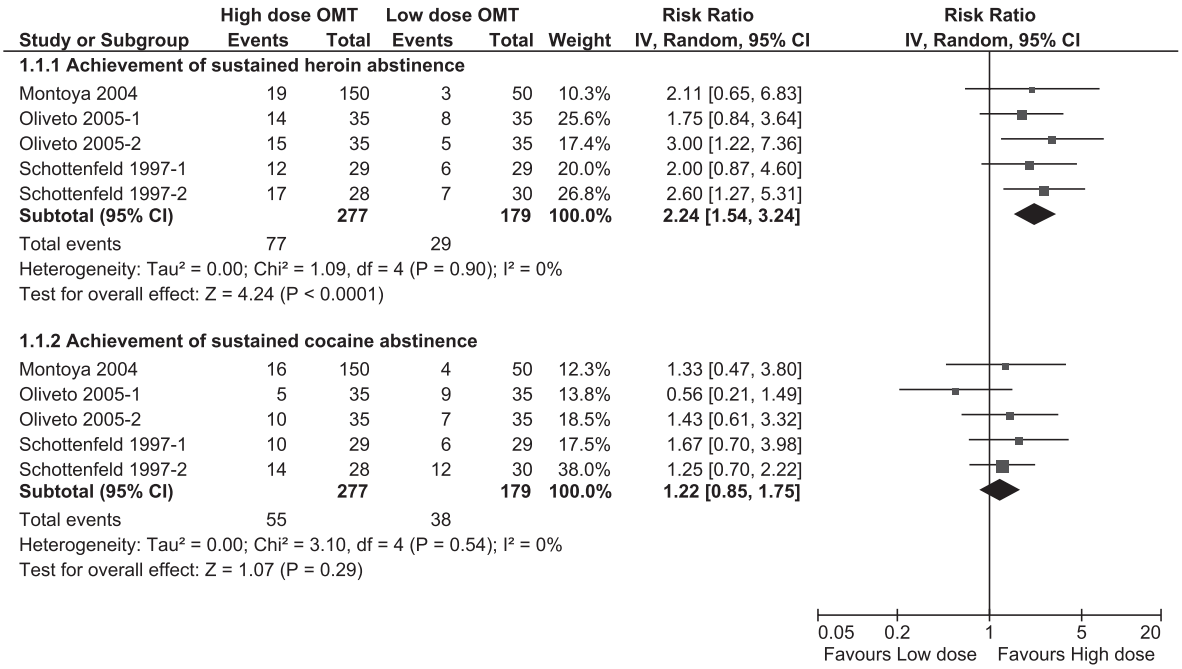

FIG. 1. High versus Low dose OMT on sustained heroin (top) and cocaine (bottom) abstinence. Abbreviations: IV = Inverse Variance, OMT = Opioid Maintenance Treatment.

cocaine-free UA (Fig. 4) (*SMD* = .28 [.04, .51], $p = .02$). Indirect DA agonists had no effect on sustained heroin abstinence, heroin-free UA or study retention. However, results on sustained heroin abstinence were heterogeneous ($I^2 = 75\%$, $p = .01$). This heterogeneity seemed to be explained by one single study (28) that used buprenorphine as the maintenance opiate, whereas the remaining clinical trials used methadone. When this study was removed, the result was homogeneous and showed

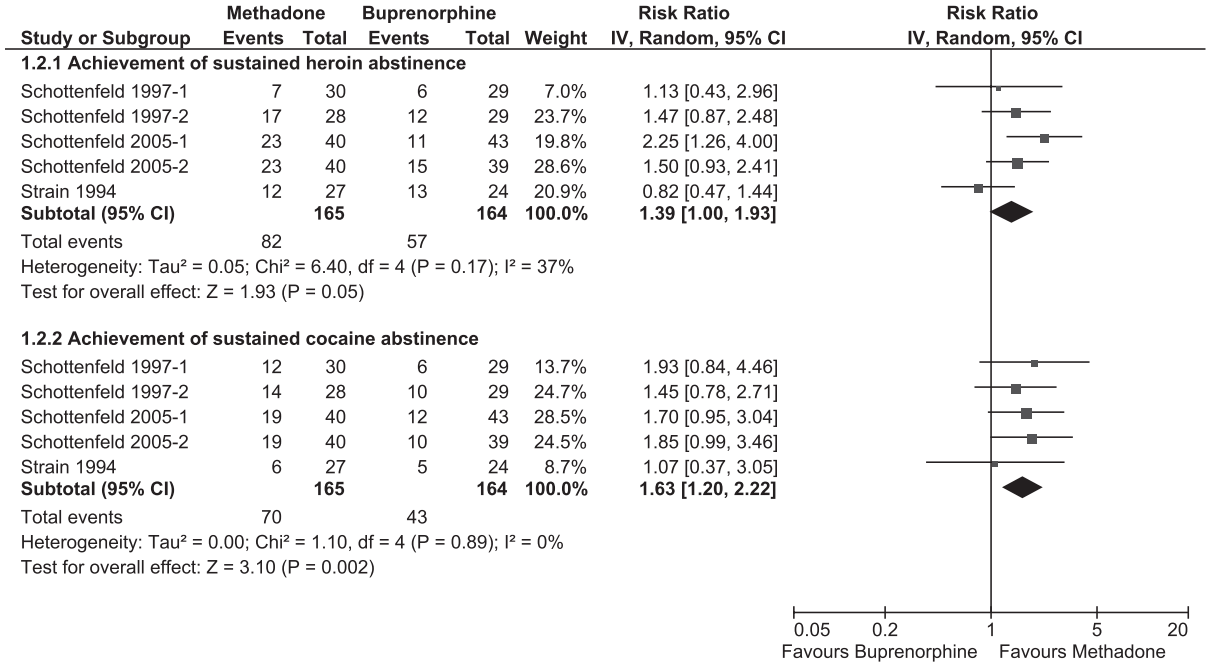

FIG. 2. Methadone versus Buprenorphine on sustained heroin (top) and cocaine (bottom) abstinence. Abbreviations: IV = Inverse Variance.

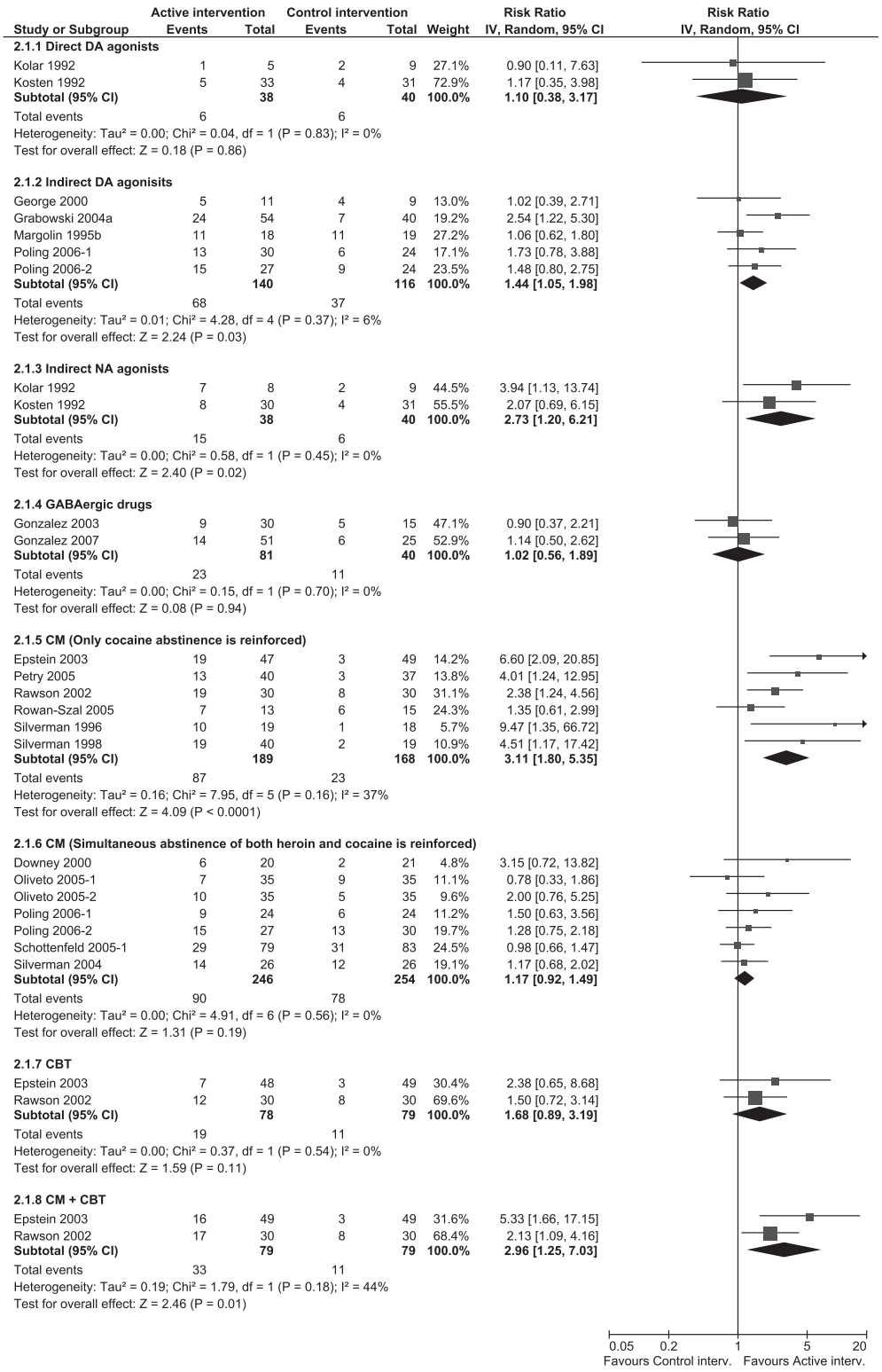

FIG. 3. Efficacy of adjunctive interventions on sustained cocaine abstinence. Abbreviations: CBT = Cognitive Behavioral Treatment, CM = Contingency Management, DA = dopamine, IV = Inverse Variance, NA = Noradrenaline.

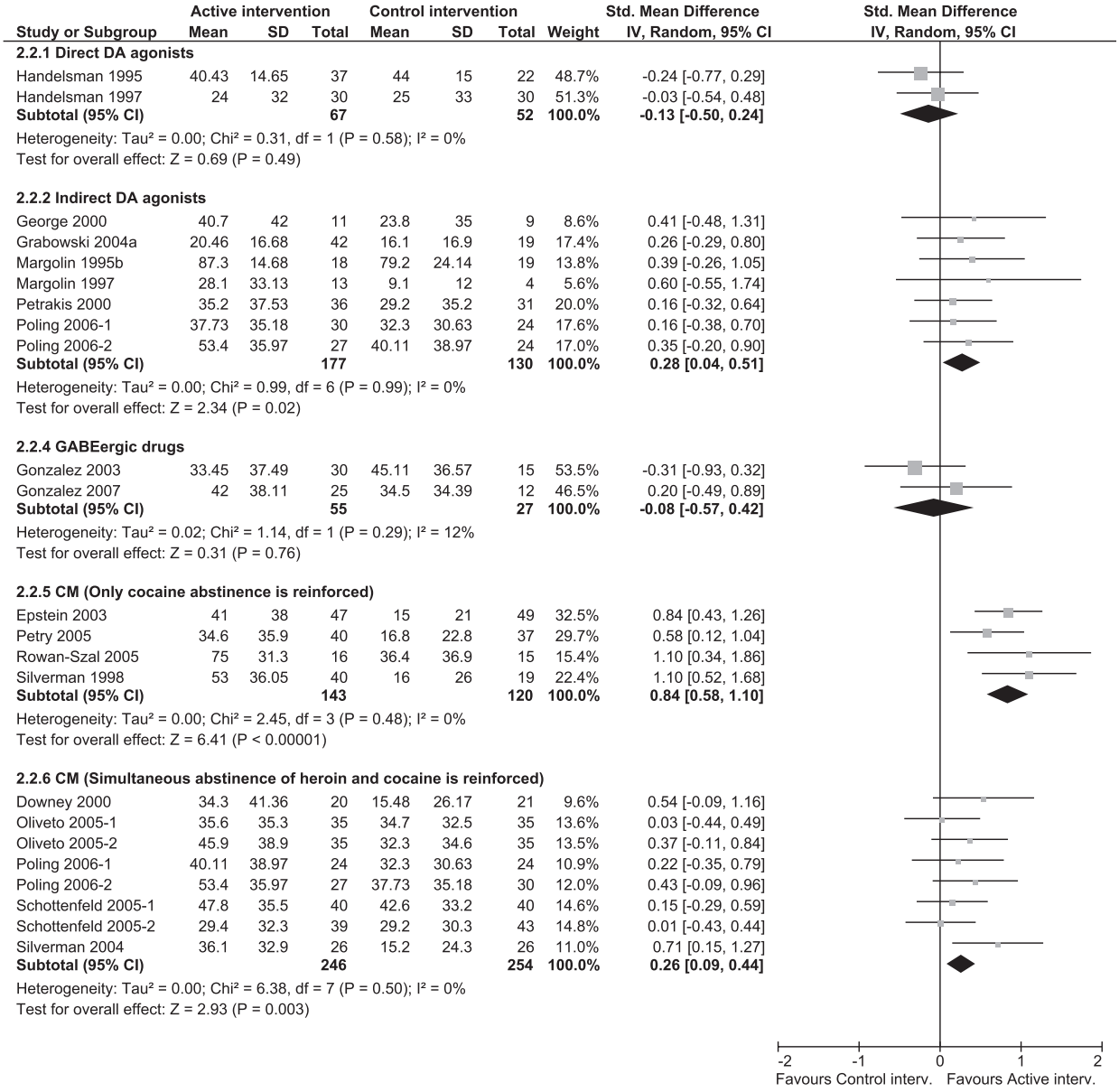

FIG. 4. Efficacy of adjunctive interventions on cocaine-free UA. Abbreviations: CM = Contingency Management, DA = Dopamine, NA = Noradrenaline, UA = urinalysis.

that indirect DA agonists improved the efficacy of methadone on sustained heroin abstinence (RR = 1.72 [1.16, 2.56], $p = .008$).

Indirect NA agonism using desipramine was the second most studied pharmacological adjunctive intervention. However, no data was available for sustained heroin abstinence, heroin use or cocaine use. Only two out of 5 studies reported data on sustained cocaine abstinence and indicated that desipramine was more efficacious than placebo (RR = 2.73 [1.20, 6.21], $p = .02$). No differences were found on study retention.

The remaining pharmacological interventions showed no beneficial effect over placebo on any study outcome, and GABAergic agonists were associated with lower study retention (RR = .84 [.72, .97], $p = .02$).

Fourteen studies determined the efficacy of psychological interventions. Because of the nature of these interventions, none had a double-blind design. The behavioral intervention of contingency management (CM) (26, 27, 46, 48–51, 53, 55–58) has been the most studied. Cognitive behavioral therapy (CBT) (27, 51), cognitive interventions (53), and the combination of psychological interventions with other treatments have also been investigated (27, 50, 53).

The CM has been designed typically to reinforce either cocaine abstinence alone (27, 49, 51, 53, 56, 57) or simultaneous

heroin and cocaine abstinence (26, 46, 50, 55, 58). Other CM strategies have been infrequently studied, such as targeting either heroin or cocaine abstinence (48) or providing a separate reinforcement for heroin and cocaine abstinence (58). Regarding the type of reinforcer, vouchers have been the most widely used ones (26, 27, 35, 39, 46, 49–51, 53, 55–58). Other abstinence reinforcers have been prizes (48), methadone take-homes (58), and opportunities to work for pay (35).

The efficacy of CM was largely dependent upon the type of behavior being reinforced (Fig. 3). Using CM to reinforce only cocaine abstinence was more effective than the control intervention to achieve sustained cocaine abstinence (3.11 [1.80, 5.35], $p < .0001$), cocaine-free UA (*SMD* = .84 [.58, 1.10], $p < .00001$), and heroin-free UA (*SMD* = .36 [.09, .64], $p = .01$), but this intervention did not achieve sustained heroin abstinence (1.39 [0.82, 2.36] $p = .22$). On the other hand, reinforcement for simultaneous heroin and cocaine abstinence was not effective for achieving cocaine abstinence or sustained heroin and had only a small benefit on cocaine use (*SMD* = .26 [.09, .44], $p = .003$).

CBT achieved higher sustained cocaine abstinence than control intervention, but it was not statistically significant (RR = 1.68 [.89, 3.19], $p = .11$). When CBT was provided in combination with CM the effect over cocaine abstinence was large (RR = 2.96 [1.25, 7.03], $p = .01$). No psychological intervention was statistically significant different from placebo on study retention.

Acupuncture was assessed in two studies (24, 25). Neither one reported data on sustained drug abstinence. One study reported data on cocaine use and 2 on retention, showing no statistically significant effect on either variable.

Moderator Variables, Sensitivity, and Publication Bias Analyses

The influence of moderator variables and study quality on the main study findings are shown as online supplementary material (Table 3 online). The influence of the type of cocaine use disorder could not be determined for the comparison of methadone vs. buprenorphine because all the meta-analyzed studies included patients with cocaine abuse or dependence.

The moderator variable analyses showed that the type of cocaine use disorder had no influence on the intervention efficacy. Nevertheless, the efficacy of CM to reinforce cocaine abstinence and of indirect DA agonists on the achievement of sustained cocaine abstinence appeared to be lower among patients who were on OMT at study inclusion, but these differences did not reach statistical significance.

The meta-analysis results after the exclusion of low quality clinical trials according to the Jadad scale did not significantly change. The Egger test was not suggestive of publication bias for any meta-analyzed intervention since no Y-intercept deviated significantly from zero (Figs. 9 and 10 online). Excluding each study once from the meta-analysis showed that no single study was decisive for the main study findings.

DISCUSSION

This meta-analysis showed that dual opioid–cocaine dependence can be effectively treated with OMT in combination with adjunctive interventions. Higher doses of OMT were more efficacious than lower ones in achieving sustained heroin abstinence, decreasing heroin use and increasing study retention. At equivalent doses, methadone was more efficacious than buprenorphine in achieving sustained cocaine abstinence and in increasing treatment retention and appeared to be more efficacious on sustained heroin abstinence. Adjunctive pharmacological treatment with indirect DA agonists was efficacious in the achievement of sustained cocaine abstinence and decreasing cocaine use. Indirect NA agonism with desipramine can also be efficacious. Adjunctive CM to reinforce cocaine free urines also had a significant effect in achieving cocaine abstinence, decreasing cocaine use and improving heroin abstinence. Combining CBT with CM appears promising for helping patients to attain sustained cocaine abstinence.

OMT for Dual Heroin–Cocaine Abusers

High OMT doses were associated with a 124% increase in the likelihood of achieving sustained heroin abstinence for dual heroin–cocaine dependence and, at an equivalent dose, sustained heroin abstinence was higher with methadone than with buprenorphine at a trend level of significance. While another meta-analysis (60) recently found no difference between buprenorphine and methadone on heroin use, their comparison was not limited to dual heroin–cocaine dependence. These apparently discrepant findings must be interpreted in light of the existing functional interactions between opioids and cocaine (5) that make dual opioid–cocaine dependence more than merely the sum of two addictions. Therefore, OMT guidelines should make specific recommendations for dual opioid–cocaine dependence.

This study did not find a statistically significant dose response relationship between OMT and cocaine abstinence. Since opioid maintenance medications do not directly target cocaine induced neurobiological changes, the effect of OMT on cocaine could be smaller than that on heroin use. In order to demonstrate such a smaller effect, larger samples than the available ones, a larger difference in opiate dose between the study groups or, fundamentally, a placebo-controlled trial would be required.

Full mu opiate agonism with methadone was more efficacious than a partial agonism with buprenorphine to attain sustained cocaine abstinence. This difference from human and animal laboratory studies, that suggest buprenorphine might be superior for cocaine abuse, might reflect the artificial environment of a laboratory setting (61). In laboratory studies, participants are maintained with an opiate and have no contact with heroin,

while in the clinical setting patients often obtain both cocaine and heroin from the same person and place. Thus, a medication's greater ability to reduce heroin abuse will also drive a greater reduction in cocaine use, and methadone is better than buprenorphine at reducing heroin.

High dose methadone was more efficacious than low dose methadone or any dose of buprenorphine in retaining patients. This better efficacy of methadone can be explained by the limitations of buprenorphine. Since buprenorphine is a partial mu agonist, patients with high levels of opiate dependence will not get sufficient agonist activity to reduce their craving for illicit opiates leading patients to quit treatment. Buprenorphine also has a less severe withdrawal (62), and thus it is easier to discontinue.

This meta-analysis showed that methadone was more efficacious than buprenorphine for dual dependent patients. However, buprenorphine is safer and less often diverted allowing for a more flexible administration regime (1, 71), and it is preferred for OMT in some countries (71). In addition, our findings may not fully apply to patients receiving buprenorphine in primary care settings. At first, the bioavailability of buprenorphine is related to its dose presentation (72), and in the RCCTs comparing this opioid with methadone, buprenorphine has been administered as an oral solution, whereas tablets are used nowadays in clinical practice for buprenorphine maintenance. Secondly, the methadone and buprenorphine doses used in clinical practice are frequently higher than those studied in the RCCTs and comparisons might differ if higher OMT doses were studied. Finally, all the RCCT have been conducted in opioid treatment program facilities, which differ substantially from primary care clinics where buprenorphine is the opioid of choice (73).

Adjunctive Interventions to OMT for Dual Heroin–Cocaine Abusers

Although a great variety of adjunctive medications have been added to OMT for dual opioid–cocaine abusers, only indirect DA agonists have shown efficacy as OMT add-on medications. Since no drug is currently approved for the treatment of cocaine dependence, it is hard to conclude that any particular one combined with OMT would be superior. However, the group of indirect DA agonists include a variety of different mechanisms of action that share all increase DA in the synapse. This DA increase appears important because chronic cocaine use leads to a striatal and cortical DA deficit, which may contribute to cocaine craving and relapse (63). Indirect DA agonists may renormalize DA homeostasis in the cocaine addicted brain by increasing DA input (disulfiram (64) and dexamphetamine (65)) or inhibiting DA removal (bupropion, dexamphetamine, mazindol) (66). Direct DA agonists may not be efficacious because instead of increasing physiological DA in the synapse they replace it.

Although improved GABAergic drugs are being tested (74, 75), this meta-analysis did not show the currently studied drugs to be efficacious, and they were associated with a lower retention rate than placebo, which could indicate that, in the absence of efficacy, side effects predominate.

Behavioral interventions appeared efficacious and CBT promising. CM targeting cocaine use showed larger improvements. An explanation could be that abstinence appears easier to attain from cocaine alone than both heroin and cocaine, and thus, it is also more likely to obtain abstinence reinforcement and modify drug use behavior. However, direct comparisons between both CM strategies should be carried out to test this hypothesis. The finding that CM was efficacious is consistent with previous studies (67, 68). Our analyses also found 3-fold greater improvements in achieving sustained abstinence and in increasing cocaine-free urines by targeting cocaine alone rather than both heroin and cocaine. This difference is larger than expected from previous studies conducted on methadone maintained patients with any other comorbid dependence (68).

The analysis of moderator variables showed that the adjunctive interventions of indirect DA agonists and CM targeting cocaine use were more efficacious in dual dependent patients, if they were simultaneously started on OMT, and these interventions rather than introducing these interventions in patients already stabilized on OMT. However, direct comparisons of these two populations of patients are needed to confirm this finding.

Meta-Analytic Procedures

This appears to be the first meta-analysis using sustained heroin or cocaine abstinence rather than any drug use or study retention as the main outcome. Achieving sustained abstinence represents a meaningful improvement. Besides, because it is a dichotomous variable, data extraction errors are unlikely (69), and the effect is calculated as Relative Risk, which is easier to interpret than SMD. Furthermore, the combination of data from different studies is not limited by whether data have a normal distribution, and it always allows for an ITT analysis.

Reporting bias can jeopardize the findings of any meta-analysis. However, since public institutions funded all studies, and many of them had negative outcomes, publication bias seems unlikely. Furthermore, no language restrictions existed to avoid the bias that results from including only studies published in English (70). In addition, the Egger graphs did not suggest publication bias. Outcome-reporting bias was limited by obtaining data from the contact author. Nevertheless, for desipramine data on sustained cocaine abstinence were obtained from only 2 out of 5 studies, thus, an overestimation of the efficacy of this intervention as a consequence of this bias cannot be ruled out. In addition, the results on sustained cocaine abstinence could not be compared with that on cocaine free UA because no study reported this data. Thus, results with desipramine should be interpreted with caution.

Studies assessing the efficacy of psychological interventions were not double blinded. Nevertheless, we used objective

outcomes, thus, it is unlikely that having included single blind studies has yielded biased results.

Though the results of this meta-analysis did not change after the exclusion of studies with low quality, the items of the Jadad scale pertaining to study blinding were not applied for psychological interventions, and thereby, we may have overscored the quality of these studies.

All 38 studies were performed in the U.S., mainly in North-East States, and adjunctive interventions predominantly involved methadone OMT. Clinical trials in other areas of the world should be performed, and adjunctive interventions should be carried out in buprenorphine maintained patients. Future research also could study the combination of indirect DA agonists with CM to reinforce cocaine abstinence. Although one study (50) shows synergism between bupropion and CM for both heroin and cocaine abstinence, CM targeting only cocaine abstinence rather than both heroin and cocaine abstinence should show larger effects.

CONCLUSION

In conclusion, this meta-analysis shows that OMT is efficacious for dual heroin–cocaine dependence, although higher OMT doses are preferable to lower ones and methadone to buprenorphine. Indirect DA agonists and CM, particularly when reinforcing only cocaine abstinence, can improve cocaine outcomes in cocaine abusers on OMT.

Declaration of Interest

Dr. Xavier Castells has participated as speaker in conferences organized by Janssen-Cilag.

Prof. Thomas Kosten's conflict of interests: speakers bureau of Cephalon, Forrest, and Reckitt Benkizer, as consultant for Novartis, Celtic, Alkermes, Synosia, Catalyst, Lannacher, Gerson Lerman, and stock in Pfizer and Johnson and Johnson.

Prof. Miguel Casas has received lecture and consulting fees from Janssen-Cilag and Laboratorios Rubió, and research funding from Janssen-Cilag.

Dr. Dolors Capellà, Dr. Xavier Vidal, and Dr. Joan Colom report no competing interests.

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PubMed:

(methadone OR buprenorphine OR Levo-acetyl* OR LAAM OR heroin OR opioid OR opioids OR opiates OR opiate) AND (cocaine OR crack) AND (abstinen* OR dependen* OR addict* OR withdraw* OR *use OR abus*)

Limits: Randomized Controlled Trial

CENTRAL:

(methadone OR buprenorphine OR levo-acetyl* OR LAAM OR heroin) AND (cocaine OR crack)

Psychinfo:

(methadone OR buprenorphine OR levo-acetyl* OR LAAM OR heroin) AND (cocaine OR crack)

Limits: clinical trials

TABLE 1 online: Search syntax that has been used for PubMed, CENTRAL and Psychinfo.

Reference	Participants	Methods	Interventions	Jadad score[a]
Arndt et al., 1992 (23)	N = 79 Methadone maintained cocaine abusers.	Two group double blind RCCT. Follow up length: 12 weeks.	Desipramine 300 mg/d Placebo Participants were randomized to desipramine or placebo with a 2:1 ratio. Additional interventions: methadone maintenance (45 mg/d) and twice monthly individual counselling.	3
Avants et al., 1995 (24)	N = 40 Methadone maintained cocaine dependent patients.	Two group RCCT. Follow up length: 6 weeks	Acupuncture: needles were inserted in the following areas: sympathetic, lung, shen men and he gu – LI 4. Control group: auricular needles were inserted approximately 2 mm from active points. Patients were treated for 5 days per week (Mon through Fri) for 6 weeks. Participants were randomized to acupuncture or control intervention. Additional interventions: Methadone 72.6 (SD = 18.7) mg/d.	0
Avants et al., 2000 (25)	N = 82 Methadone maintained cocaine dependent patients.	Three group RCCT. Follow up length: 8 weeks	Acupuncture: needles were inserted into the cartilage of the following 4 auricular regions: sympathetic, lung, liver and shen men. Auricular Needle-Insertion Control Condition: needles were inserted subcutaneously into the helix of the auricles bilaterally at 3 zones not commonly used for the treatment of any disorder. Relaxation Control Condition: videos depicting relaxation strategies, as well as relaxing visual imagery and music. In all 3 interventions, treatment was administered for 40 minutes each weekday (Monday through Friday) for 8 weeks. Participants were randomized to acupuncture, auricular needle insertion control or relaxation control interventions. Additional interventions: Methadone 78 (SD = 17) mg/d	2
Downey et al., 2000 (26) *	N = 41 Heroin dependent cocaine users.	Two groups RCCT. Follow up length: 17 weeks (buprenorphine induction phase: weeks 1-5, study phase: buprenorphine + study intervention: weeks 6-17).	CM: targeted drugs were heroin, cocaine, OH, amphetamines, barbiturates and phencyclidine. Participants received vouchers of escalating value for polydrug abstinence. Control CM condition: Subjects were linked to a participant randomized to CM and received the same vouchers but independently of the UA results. Participants were randomized to CM or control intervention. Additional interventions: Buprenorphine + Naloxone (4:1 ratio) and CBT. Buprenorphine dose ranged from 16-16-24 mg to 32-32-48 mg (Mon-Wed-Fri)	2
Epstein et al., 2003 (27) *	N = 93 Heroin dependent cocaine users.	Four groups RCCT Follow up length: baseline phase 5 weeks, intervention phase 12 weeks, maintenance phase 12 weeks	CM: escalating incentives were given for providing cocaine free urines. Control CM: Non-contingent vouchers were given on a totally unpredictable schedule. CBT Control CBT: social support. Participants were randomized to CM + control CBT, CBT + control CM, CM + CBT, control CBT + control CM.	2

			Additional interventions: all participants received methadone (50 – 80 mg/d) and weekly individual counselling.	
George et al., 2000 (28)	N = 20 Heroin and cocaine dependent patients. OH dependence was an exclusion criterion.	Two groups RCCT. Follow up length: 13 weeks. Subjects were induced on buprenorphine on week 1 and randomized to disulfiram or placebo on week 2.	Disulfiram 250 mg/d. Placebo. Participants were randomized to disulfiram or placebo. Additional interventions: Buprenorphine 24 mg/d and 1-hour weekly counselling sessions.	2
González et al., 2003 (29) *	N = 45 Heroin and cocaine dependent patients.	Three groups RCCT. Follow up length: 12 weeks: 2-week methadone induction with a subsequent 10-week follow up.	Tiagabine 12 mg/d Tiagabine 24 mg/d Placebo Participants were randomized to high dose or low dose tiagabine or placebo. Additional interventions: methadone (63.6 mg/d (range: 40-90 mg/d)) and 1 h weekly group counselling session counseling sessions.	4
González et al., 2007 (30) *	N = 76 Heroin dependent cocaine users.	Three group RCCT. Follow up length: 10 weeks.	Tiagabine 24 mg/d. Gabapentin 2400 mg/d. Placebo Participants were randomized to tiagabine, gabapentin or placebo. Additional interventions: All participants were placed on methadone (50-105 mg/d) and received 1 hour weekly CBT.	4
Grabowski et al., 1995 (31) *	N = 21 Methadone maintained cocaine dependent patients. MDD was an exclusion criterion.	Two groups RCCT. Follow up length: 10 weeks: 2 weeks dose run up and stabilization + 8 weeks follow up.	Fluoxetine 20 mg/d Placebo Additional interventions: all participants received methadone 70.9 (SD = 7.51) mg/d, 1 h/week behavioural psychotherapy and CM of double incentive according to which methadone dose was increased or lowered depending on the presence of non-methadone opioids in urine screens.	4
Grabowski et al., 2004a (32) Ŧ*	N = 94 Heroin and cocaine dependent patients.	Three groups RCCT. Follow up length: 26 weeks: 10 stabilization days + 168 follow up days	Dexamphetamine 15-30 mg/d b.i.d. Dexamphetamine 30-60 mg/d/d b.i.d. Placebo Participants were randomized to high or low dose dexamphetamine or placebo. Additional interventions: methadone (73 mg/d) and cognitive behaviourally based psychosocial therapy (1h/week).	4
Grabowski et al., 2004b (32) Ŧ*	N = 96 Heroin and cocaine dependent patients.	Three groups RCCT. Follow up length: 26 weeks: 10 stabilization days + 168 follow up days.	Risperidone 2 mg/d Risperidone 4 mg/d Placebo Participants were randomized to high or low dose risperidone or placebo.	4

			Additional interventions: methadone (70 mg/d) and cognitive behaviourally based psychosocial therapy (1h/week).	
Handelsman et al. 1995 (33)	N = 67 Methadone maintained cocaine dependent men.	Three groups RCCT. Follow up length: 9 weeks	Amantadine 200 mg/d. Amantadine 400 mg/d. Placebo Participants were randomized to high or low dose amantadine or placebo. Additional interventions: Methadone 63-69 mg/d.	3
Handelsman et al., 1997 (34)	N = 60 Methadone maintained men with a comorbid cocaine dependence or abuse.	Two groups RCCT. Follow up length: 5 weeks.	Bromocriptine 1.25 – 2.5 mg/d. Placebo Participants were randomized to bromocriptine or placebo. Additional interventions: Methadone (73.1) mg/d and CBT.	3
Knealing et al., 2006 (35)	N = 47 Methadone maintained cocaine abusers. Other inclusion criteria: unemployed crack users, with at least one child aging 18 or below and meeting criteria for Maryland welfare assistance.	Two groups RCCT. Follow up length: 9 months. An additional assessment was performed at 6-month post intervention.	CM: Therapeutic workplace + vouchers contingent on heroin and cocaine UA, OH use and training outcomes. Participants were randomized to therapeutic CM or standard treatment. Additional interventions: methadone, case management (assisting patient in day care, employment counseling, job skills training and placement services if requested) and HIV counseling.	2
Kolar et al., 1992 (36)	N = 24 Methadone cocaine dependent maintained patients. MDD: NR	Three groups parallel RCCT. Follow up length: 12 weeks	Amantadine 200 mg/d Desipramine 200 mg/d. Placebo Participants were randomized to amantadine, desipramine or placebo. Additional interventions: methadone (61.1 mg) and weekly group and individual counselling.	3
Kosten et al., 1992 (37)	N = 94 Methadone maintained cocaine dependent patients. MDD was neither an inclusion nor an exclusion criterion.	Three groups double blind RCCT. Follow up length: 12 weeks	Amantadine 300 mg/d Desipramine 150 mg/d Placebo Participants were randomized to amantadine, desipramine or placebo. Additional interventions: methadone (57 mg/d) and once a week group relapse prevention psychotherapy.	4
Kosten et al., 2002 (38)	N = 39 Heroin dependent cocaine	Two groups RCCT. Follow up length: 12 weeks.	Ketoconazole (600-900 mg/d) + hydrocortisone (20 mg/d). Placebo	3

	users.		Participants were randomized to ketoconazole or placebo. Additional interventions: methadone (62.5 mg/d) and weekly group and monthly individual therapy sessions.	
Kosten et al., 2003 (39)	N = 160 Heroin and cocaine dependent patients. MDD was not an inclusion not an exclusion criterion.	Design: Four groups RCCT. Follow up length: 12 weeks.	Desipramine 150 mg/d Placebo CM: vouchers (up to 738 $) targeting both heroin and cocaine use and linked to attending to therapy sessions. Control: vouchers for sample submission. Participants were randomized to desipramine + CM, desipramine + control, placebo + CM or placebo + control. Additional interventions. All participants received Buprenorphine 15,8 mg/d, once weekly CBT and participated in weekly group prevention therapy and weekly individual psychotherapy.	3
Margolin et al., 1995a (40)	N = 149 Methadone maintained cocaine dependent patients. MDD was an exclusion criterion.	Two group multicenter (3 sites) RCCT. Follow up length: 12 weeks.	Bupropion 200-300 mg/d t.i.d. Placebo Participants were randomized to bupropion or Placebo. Additional interventions: methadone maintenance and group or individual psychotherapy for patients on MMT.	3
Margolin et al., 1995b (41)	N = 37 Methadone maintained patients with comorbid cocaine dependence who were abstinent from cocaine use for at least 2 weeks.	Design: Two groups RCCT. Follow up length: 12 weeks.	Mazindol 1 mg/d Placebo Participants were randomized to mazindol or placebo. Additional interventions: methadone (70.5 mg/d) and psychosocial therapy integrated by case management, behavioural contingency (methadone dose was lowered in case of submitting BE positive/missed urine samples) and group psychotherapy.	2
Margolin et al., 1997 (42)	N = 17 Methadone maintained cocaine dependent patients.	Three groups double blind RCCT Follow up length: 12 weeks	Mazindol 1 mg/d Mazindol 8 mg/d Placebo Participants were randomized to high or low dose of mazindol or placebo. Additional interventions: Methadone 78 (SD = 18) mg/d and weekly group counselling sessions.	3
Margolin et al., 2003 (43)	N = 17 Methadone maintained cocaine abusers who used illegal opiates.	Two groups double blind RCCT Follow up length: 12 weeks	Mg L-Aspartate: 732 mg/d (tid) Participants were randomized to Mg L-Aspartate or Placebo. Additional interventions: Methadone (85-100 mg/d) and weekly 30 minutes length individual counselling sessions.	2
Montoya et al., 2004 (44) *	N = 200 Heroin and cocaine dependent patients.	Two groups double blind RCCT Follow up length: 13 weeks: induction phase: 5 days, maintenance phase: 65 days, withdrawal phase 20 days.	Buprenorphine 2 mg/d Buprenorphine 8 mg/d Buprenorphine 16 mg/d Buprenorphine 16 mg/2d	4

			Participants were randomized to 1 out of 4 buprenorphine regimes. Additional interventions: individual weekly counselling based on interpersonal psychotherapy.	
Oliveto et al., 1999 (45)	N = 180 Heroin dependent cocaine users. MDD was neither an inclusion nor an exclusion criterion.	Four groups RCCT. Follow up length: 13 weeks.	Buprenorphine: 12 mg/d Methadone: 65 mg/d Desipramine: 150 mg/d. Participants were randomized to buprenorphine + desipramine, buprenorphine + placebo, methadone + desipramine or methadone + placebo. Additional interventions: weekly group relapse prevention and monthly individual therapy sessions.	4
Oliveto et al., 2005 (46) *	N = 140 Heroin and cocaine dependent patients.	Four groups RCCT Follow up length: 12 weeks. Induction phase: high dose LAAM = 32 days, low dose LAAM = 5 days	LAAM high dose: (100, 100, 130 mg on Mon, Wed, Fri) LAAM low dose: (30, 30, 39 mg on Mon, Wed, Fri) CM: vouchers (up to 738 $) targeting both heroin and cocaine use. Control: vouchers according to a yoked schedule. Participants were randomized to the following groups: low-dose LAAM + CM; low-dose LAAM + control; high-dose LAAM + CM; high-dose LAAM + Control. LAAM dose was decreased in case of positive OH breath test. Additional interventions: weekly individual and weekly group counselling sessions.	3/2
Petrakis et al., 2000 (47) *	N = 67 Methadone maintained cocaine dependent patients. Alcohol abuse was neither an inclusion nor an exclusion criterion.	Two group RCCT. Follow up length: 12 weeks	Disulfiram 250 mg/d. Participants were randomized to Disulfiram or Placebo. Additional treatments: Methadone (88.6 mg/d), weekly individual or group counseling and behavioral contract according to which methadone was decreased if continued drug use, missing appointments or non-compliance with rules of the methadone clinic.	4
Petry and Martin 2002 (48) *	N = 42 Methadone maintained patients with a comorbid cocaine abusers or dependence.	Two groups RCCT. Follow up length: 24 weeks (12 study intervention weeks + 12 post-intervention follow up weeks)	CM: lottery based contingent intervention consisting on prizes targeting cocaine or opioid abstinence. Control: standard additional intervention. Participants were randomized to CM or standard intervention Additional interventions: all participants received methadone (69-70 mg/d) and monthly individual counselling.	2
Petry et al., 2005 (49) *	N = 77 Methadone maintained cocaine dependent patients.	Two groups RCCT. Follow up length: study intervention lasted 12 weeks. Post intervention assessments were performed through weeks 12 to 24.	CM: lottery based CM. Subjects had an escalating number draws from the bowl for attending group sessions (up to 78 draws) or providing cocaine negative UA (up to 270 draws). Control group: 1 draw for each sample submitted. Participants were randomized to CM or control intervention. Additional interventions: all participants received methadone (74.8 mg/d), weekly group therapy and monthly individual counselling.	2
Poling et al., 2006	N = 106	Four groups RCCT.	Bupropion 300 mg/d. Placebo	4/2

(50) *	Heroin dependent cocaine users. MDD was neither an inclusion nor an exclusion criterion.	Follow up length: 25 weeks.	CM: vouchers for free cocaine and heroin screens (max: 934 $). CM control: non-contingent vouchers (max 250 $). Participants were randomized to bupropion + CM, bupropion + CM control, placebo + CM or placebo + CM control. Additional interventions: All participants were placed on methadone (60-120 mg/d) and received counselling sessions and individual CBT.	
Rawson et al., 2002 (51)	N = 120 Methadone maintained cocaine dependent patients.	Four groups RCCT. Follow up length: 52 weeks. Intervention lasted 16 weeks. Additional follow up visits until week 52.	CM: vouchers dependent on cocaine abstinence (max: 1277.5 $). CBT: 48 group sessions concurrent with participation in methadone treatment. Control group: a $25 gift certificate at each follow up interview irrespective of drug use. Participants were randomized to CM, CBT, CM + CBT or control. Additional interventions: all patients received methadone (78-83 mg/d). All study participants were awarded with a monthly $40 fee reduction.	2
Reid et al., 2005 (52)	N = 35 Opioid and cocaine dependent patients maintained with either LAAM or Methadone.	Two groups RCCT. Follow up length: 24 weeks. 8 weeks placebo run-in phase followed by a 16 weeks intervention phase.	Mecamylamine 3-6 mg/d Control group received a placebo containing Nicotine 1 mg. Participants were randomized to Mecamylamine or Placebo. Additional interventions: methadone (88,6 mg/d) or LAAM (88,1 mg/d) and individual or group counselling. Participants could earn up to 290 USD for participating throughout the study.	3
Rowan-Szal et al., 2005 (53) *	N = 61 Methadone maintained cocaine users.	Four groups RCCT Follow up length: 5 weeks of baseline phase, 8 weeks of intervention and 8 weeks of post-intervention follow-up. Statistical analysis: PP.	Cognitive intervention: 8 specific cocaine counselling sessions including motivational interviewing and acquisition of cognitive strategies to face drug related problems. CM: Vouchers, up to 25 $, could be earned for target behaviours: attending to general drug abuse counselling interventions, providing cocaine free urine screens and completing tasks related to treatment goals. Participants were randomized to Cognitive intervention + CM, cognitive intervention alone, CM alone or standard treatment. Additional interventions: all participants received methadone (75 mg/d), case management and Individual counselling on drug abuse.	1
Schottenfeld et al., 1997 (54)	N = 116 Heroin dependent patients with a comorbid cocaine dependence or abuse.	Four groups double blind RCCT. Follow up length: 24 weeks (2 weeks of induction phase + 22 weeks at stable doses).	Methadone 65 mg Methadone 20 mg Buprenorphine 12 mg Buprenorphine 4 mg. Participants were randomized to high or low dose of methadone or buprenorphine. Additional interventions: 1 hour weekly group counselling.	5/3
Schottenfeld et al., 2005 (55) *	N = 162 Heroin dependent patients with a comorbid cocaine	Four groups RCCT. Follow up length: 24 weeks.	Methadone: up to 85 mg/d (Mean = 80 mg/d) Buprenorphine: up to 16 mg/d (Mean = 15 mg/d) CM: vouchers of escalating value until week 12 and thereafter the value was fix (max: 1033.5 $) Control CM: Performance feedback consisting on a slip of paper with the urine screens results.	5/3

	dependence or abuse.	Statistical analysis: NR.	Participants were randomized to methadone + CM, methadone + control CM, buprenorphine + CM, or buprenorphine + control CM. Additional interventions: counselling. Twice a week during the first 12 weeks of the study and weekly during the last 12 weeks.	
Silverman et al., 1996 (56)	N = 37 Newly admitted methadone maintained patients with concurrent cocaine use.	Two groups RCCT. Follow up length: baseline assessments lasted for 5 weeks, follow up 12 weeks and post intervention follow up 4 weeks.	CM: vouchers of escalating value for continuous cocaine abstinence (max: 1155 $). Control intervention: Yoked vouchers conditioned to subject's assistance to the clinic. Participants were randomized to CM or control intervention. Additional interventions: all participants received methadone (50 mg/d) and Individual counselling.	2
Silverman et al., 1998 (57)	N = 59 Newly admitted methadone maintained patients with concurrent cocaine use.	Three groups RCCT. Follow up length: baseline assessments 5 weeks, intervention 12 weeks, post intervention assessment 8 weeks.	CM: Cocaine abstinence based vouchers of escalating value. CM + starting up bonus: Cocaine negative UA based vouchers of escalating value. Besides, patients were intensively reinforced for initiating cocaine abstinence. The maximum amount that could be earned was the same as the CM intervention. Control intervention: Yoked CM. Participants were randomized to CM, CM + starting up bonus or control intervention. Additional interventions: methadone (62 mg/d) and drug counselling.	1
Silverman et al., 2004 (58) *	N = 78 Newly admitted methadone maintained patients with concurrent cocaine use.	Three groups RCCT. Follow up length: baseline assessments: 10 weeks, intervention: 52 weeks, post intervention assessment: 9 weeks (during which voucher intervention was discontinued) and post study assessment: 9 weeks (TH was discontinued).	TH-CM: Heroin and cocaine abstinence based TH privileges. Vouchers-CM: vouchers of escalating value for continuous cocaine abstinence. Control intervention: standard treatment. Participants were randomized to TH-CM, TH-CM + Vouchers-CM or standard treatment. Additional interventions: methadone (60 – 100 mg/d) and drug counselling.	2
Strain et al., 1994 (59) *	N = 51 Heroin dependent cocaine users.	Two groups RCCT. Follow up length: 16 weeks	Methadone: 50-90 mg/d Buprenorphine: 8-16 mg/d Dosage was fixed (Methadone 50 mg/d and Buprenorphine 8 mg/d) for the first 2 weeks and flexible thereafter. Mean opiate dose: methadone: 66.6 mg/d, buprenorphine: 11.2 mg/d Participants were randomized to methadone or buprenorphine. Additional interventions: individual counselling and weekly group therapy.	3

TABLE 2 online: Description of participants, methods and interventions of each study that determined the efficacy of opioid maintenance treatment or adjunctive interventions for dual opioid and cocaine dependent patients. Studies are displayed in alphabetical order.

Abbreviations: BE = Benzoylecgonine; b.i.d. = twice a day; CM = Contingency Management; IDU = Intravenous Drug User; ITT = Intention to treat; MDD = Major Depressive Disorder; NR = Not Reported; PP = *Per Protocol*; OH = alcohol, RCCT = Randomized Controlled Clinical Trial; SD = Standard Deviation; t.i.d. = three times a day; TH = Take-Home, UA = urinalysis.

[a] The Jadad scale assess clinical trial reporting quality. If one study investigated the efficacy of one pharmacological and one psychosocial intervention, two Jadad scores are reported. The first Jadad score indicates the reporting quality of the pharmacological intervention and the second score that of the psychosocial one.

* indicates that the corresponding author provided non-published data.

Ŧ indicates that these two studies were published together as one article.[32]

Comparison	Type of cocaine use disorder		OMT at study inclusion		Study quality
Outcome	Cocaine dependence	Cocaine abuse and dependence	Not on OMT	On OMT	
High vs. low OMT					
Sustained heroin abstinence	2.16 [1.30, 3.60]	2.33 [1.35, 4.00]	NA	NA	2.24 [1.54, 3.24]
Sustained cocaine abstinence	1.04 [0.58, 1.88]	1.36 [0.84, 2.20]	NA	NA	1.22 [0.85, 1.75]
Methadone vs. buprenorphine					
Sustained heroin abstinence	NA	NA	NA	NA	1.39 [1.00, 1.93]
Sustained cocaine abstinence	NA	NA	NA	NA	1.63 [1.20, 2.22]
Indirect DA agonists vs. Placebo					
Sustained cocaine abstinence	1.40 [0.77, 2.52]	1.57 [0.96, 2.56]	1.82 [1.21, 2.74]	1.05 [0.66, 1.67] †	1.82 [1.21, 2.74]
Cocaine free UA across the study	0.27 [-0.03, 0.56]	0.29 [-0.08, 0.65]	0.25 [-0.06, 0.57]	0.30 [-0.04, 0.64]	0.25 [-0.01, 0.50]
CM (only cocaine abstinence is reinforced) vs. Control					
Sustained cocaine abstinence	2.69 [1.52, 4.76]	3.74 [1.42, 9.79]	5.63 [2.34, 13.51]	2.47 [1.34, 4.54] ‡	3.68 [2.07, 6.53]
Cocaine free UA across the study	0.58 [0.12, 1.04]	0.96 [0.65, 1.27]	0.93 [0.59, 1.27]	0.72 [0.33, 1.11]	0.72 [0.42, 1.03]
CM (Simultaneous abstinence of both heroin and cocaine abstinence is reinforced) vs. Control					
Sustained cocaine abstinence	1.22 [0.48, 3.07]	1.16 [0.90, 1.50]	1.17 [0.68, 2.02]	1.16 [0.90, 1.52]	1.17 [0.92, 1.49]
Cocaine free UA across the study	0.19 [-0.14, 0.53]	0.29 [0.08, 0.50]	0.22 [0.04, 0.40]	0.71 [0.15, 1.27]	0.26 [0.09, 0.44]

TABLE 3 online: Analysis of the influence of moderator variables and clinical trial quality on the major study findings. The moderator variables were the type of cocaine use disorder (studies including cocaine dependent patients were analyzed separately from those including both cocaine

abusers and dependent patients) and OMT at study inclusion (studies where patients were induced to OMT during the course of the study were analyzed separately from those that have included patients already on OMT). For the analysis of the influence of study quality on the meta-analysis results, only studies scoring ≥ 3 or ≥ 2 on the Jadad scale for studies assessing the efficacy of pharmacological interventions or psychological interventions, respectively, were included in this subanalysis. Figures represent RR [CI] for sustained heroin abstinence and sustained cocaine abstinence, and SMD [CI] for cocaine free UA across the study. Test for subgroup differences are shown for those comparisons with a p-value < 0.10.

†: Test for “not on OMT” vs. “On OMT” differences: $Chi^2 = 3.04$, df = 1, p = 0.08.

‡: Test for “not on OMT” vs. “On OMT” differences: $Chi^2 = 3.15$, df = 1, p = 0.08.

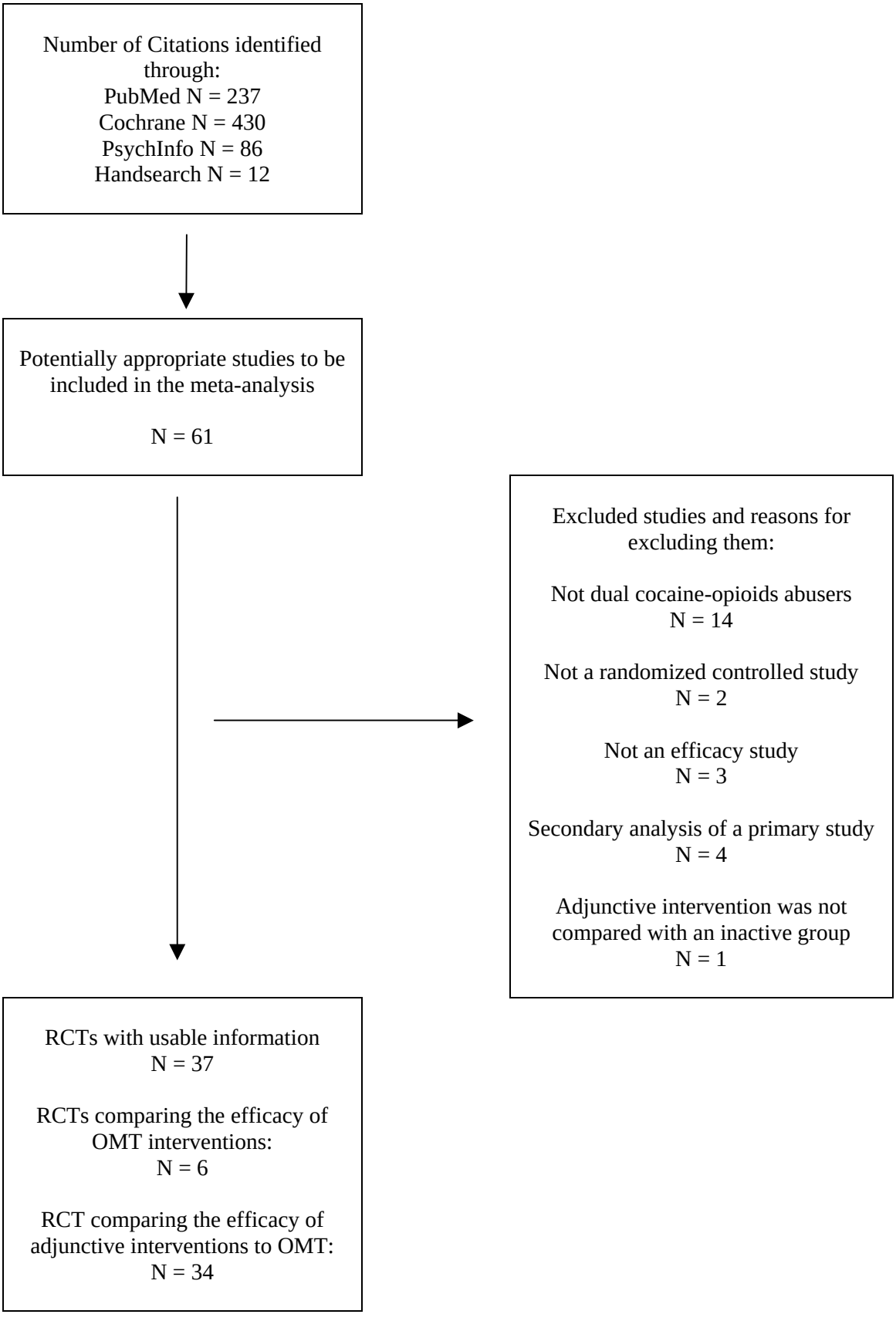

Number of Citations identified through:
PubMed N = 237
Cochrane N = 430
PsychInfo N = 86
Handsearch N = 12
Potentially appropriate studies to be included in the meta-analysis
N = 61
Excluded studies and reasons for excluding them:
Not dual cocaine-opioids abusers
N = 14
Not a randomized controlled study
N = 2
Not an efficacy study
N = 3
Secondary analysis of a primary study
N = 4
Adjunctive intervention was not compared with an inactive group
N = 1
RCTs with usable information
N = 37
RCTs comparing the efficacy of OMT interventions:
N = 6
RCT comparing the efficacy of adjunctive interventions to OMT:
N = 34

FIGURE 1 online: Progress of the articles selection through the stages of this meta-analysis.

Abbreviations: OMT = Opioid Maintenance Treatment, RCT = Randomized Controlled Clinical Trial

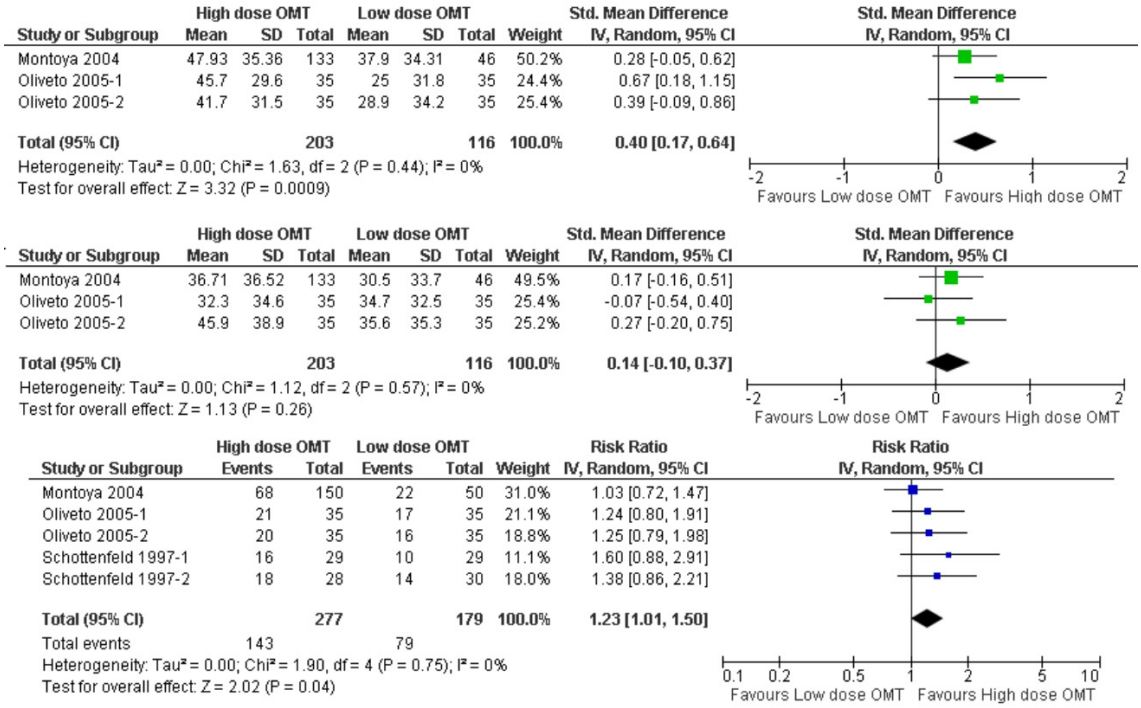


FIGURE 2 online: High vs. Low dose OMT on heroin-free UA (top), cocaine-free UA (middle) and study retention (bottom)

Abbreviations: IV = Inverse Variance, OMT = Opioid Maintenance Treatment, UA = urinalysis

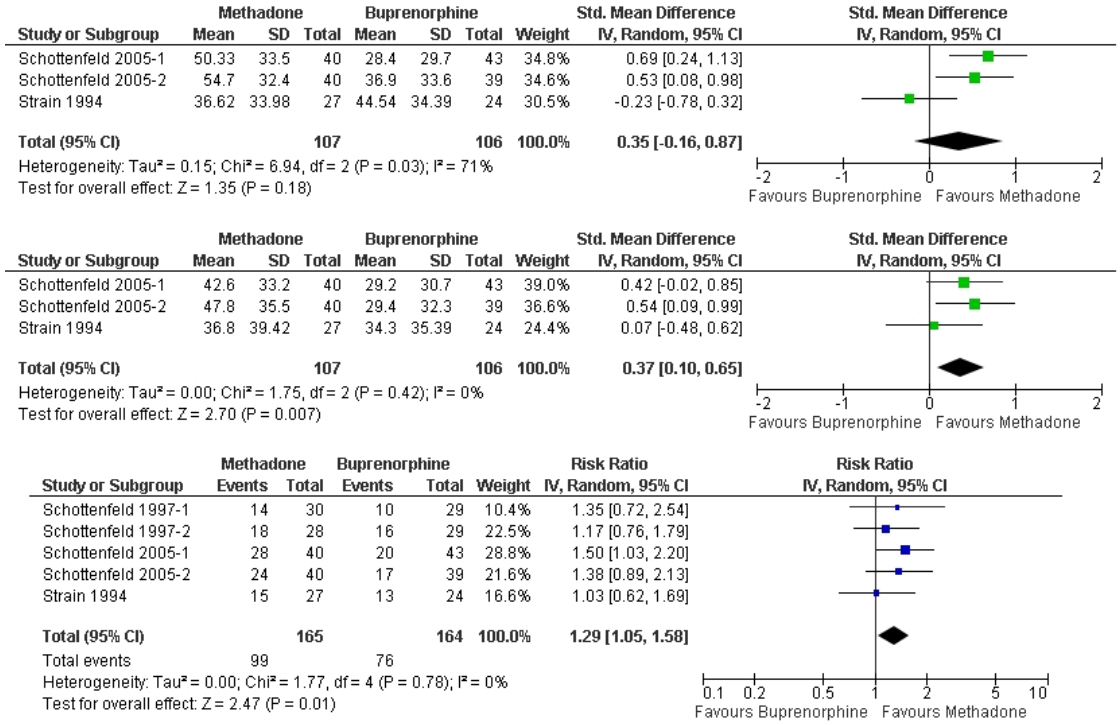


FIGURE 3 online: Methadone vs. Buprenorphine on heroin-free UA (top), cocaine-free UA (middle) and study retention (bottom)

Abbreviations: IV = Inverse Variance, UA = urinalysis

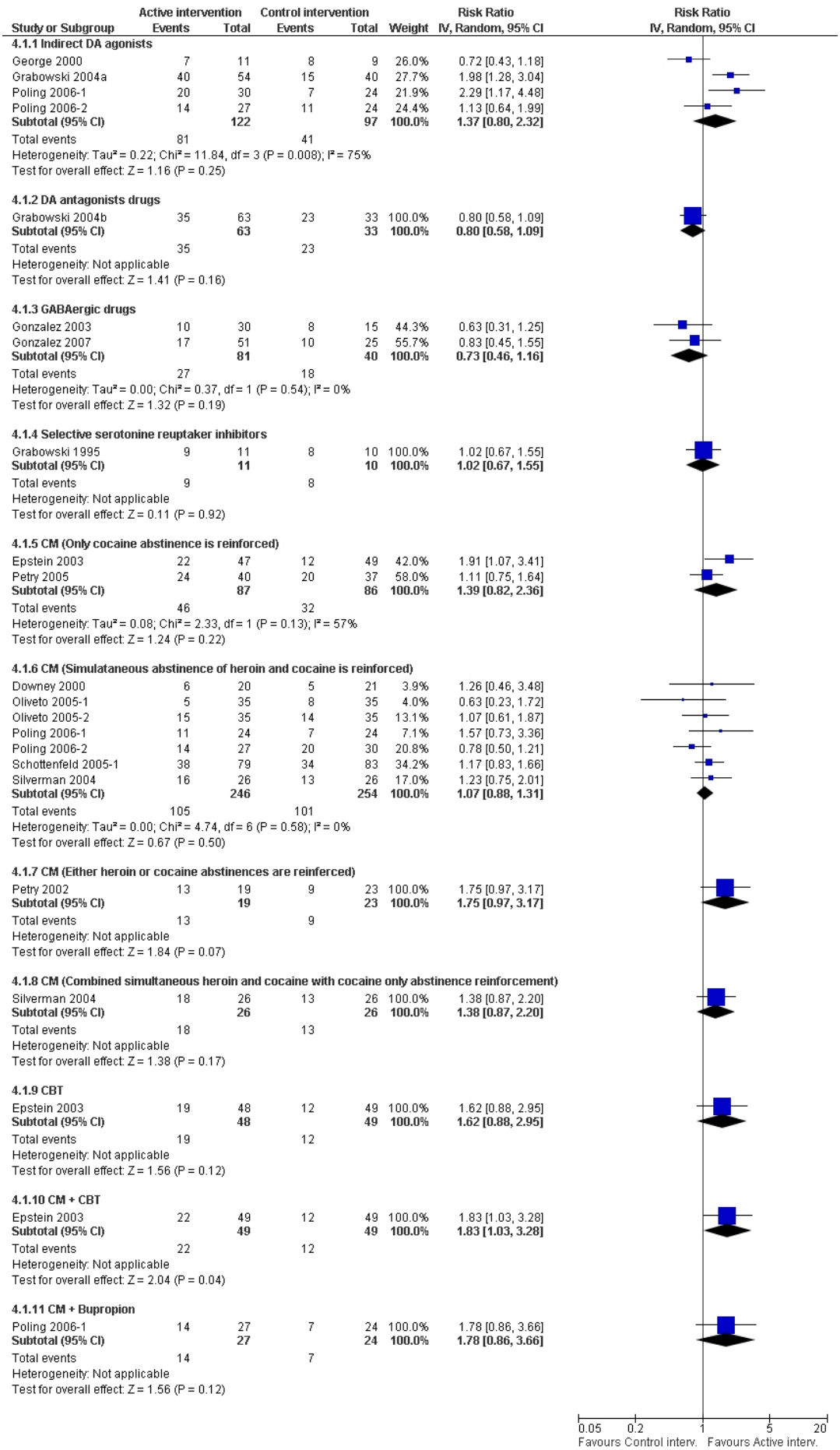

Active intervention
Control intervention
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI
IV, Random, 95% CI
4.1.1 Indirect DA agonists
George 2000 7 11 8 9 26.0% 0.72 [0.43, 1.18]
Grabowski 2004a 40 54 15 40 27.7% 1.98 [1.28, 3.04]
Poling 2006-1 20 30 7 24 21.9% 2.29 [1.17, 4.48]
Poling 2006-2 14 27 11 24 24.4% 1.13 [0.64, 1.99]
Subtotal (95% CI) 122 97 100.0% 1.37 [0.80, 2.32]
Total events 81 41
Heterogeneity: Tau² = 0.22; Chi² = 11.84, df = 3 (P = 0.008); I² = 75%
Test for overall effect: Z = 1.16 (P = 0.25)
4.1.2 DA antagonists drugs
Grabowski 2004b 35 63 23 33 100.0% 0.80 [0.58, 1.09]
Subtotal (95% CI) 63 33 100.0% 0.80 [0.58, 1.09]
Total events 35 23
Heterogeneity: Not applicable
Test for overall effect: Z = 1.41 (P = 0.16)
4.1.3 GABAergic drugs
Gonzalez 2003 10 30 8 15 44.3% 0.63 [0.31, 1.25]
Gonzalez 2007 17 51 10 25 55.7% 0.83 [0.45, 1.55]
Subtotal (95% CI) 81 40 100.0% 0.73 [0.46, 1.16]
Total events 27 18
Heterogeneity: Tau² = 0.00; Chi² = 0.37, df = 1 (P = 0.54); I² = 0%
Test for overall effect: Z = 1.32 (P = 0.19)
4.1.4 Selective serotonine reuptaker inhibitors
Grabowski 1995 9 11 8 10 100.0% 1.02 [0.67, 1.55]
Subtotal (95% CI) 11 10 100.0% 1.02 [0.67, 1.55]
Total events 9 8
Heterogeneity: Not applicable
Test for overall effect: Z = 0.11 (P = 0.92)
4.1.5 CM (Only cocaine abstinence is reinforced)
Epstein 2003 22 47 12 49 42.0% 1.91 [1.07, 3.41]
Petry 2005 24 40 20 37 58.0% 1.11 [0.75, 1.64]
Subtotal (95% CI) 87 86 100.0% 1.39 [0.82, 2.36]
Total events 46 32
Heterogeneity: Tau² = 0.08; Chi² = 2.33, df = 1 (P = 0.13); I² = 57%
Test for overall effect: Z = 1.24 (P = 0.22)
4.1.6 CM (Simulataneous abstinence of heroin and cocaine is reinforced)
Downey 2000 6 20 5 21 3.9% 1.26 [0.46, 3.48]
Oliveto 2005-1 5 35 8 35 4.0% 0.63 [0.23, 1.72]
Oliveto 2005-2 15 35 14 35 13.1% 1.07 [0.61, 1.87]
Poling 2006-1 11 24 7 24 7.1% 1.57 [0.73, 3.36]
Poling 2006-2 14 27 20 30 20.8% 0.78 [0.50, 1.21]
Schottenfeld 2005-1 38 79 34 83 34.2% 1.17 [0.83, 1.66]
Silverman 2004 16 26 13 26 17.0% 1.23 [0.75, 2.01]
Subtotal (95% CI) 246 254 100.0% 1.07 [0.88, 1.31]
Total events 105 101
Heterogeneity: Tau² = 0.00; Chi² = 4.74, df = 6 (P = 0.58); I² = 0%
Test for overall effect: Z = 0.67 (P = 0.50)
4.1.7 CM (Either heroin or cocaine abstinences are reinferced)
Petry 2002 13 19 9 23 100.0% 1.75 [0.97, 3.17]
Subtotal (95% CI) 19 23 100.0% 1.75 [0.97, 3.17]
Total events 13 9
Heterogeneity: Not applicable
Test for overall effect: Z = 1.84 (P = 0.07)
4.1.8 CM (Combined simultaneous heroin and cocaine with cocaine only abstinence reinforcement)
Silverman 2004 18 26 13 26 100.0% 1.38 [0.87, 2.20]
Subtotal (95% CI) 26 26 100.0% 1.38 [0.87, 2.20]
Total events 18 13
Heterogeneity: Not applicable
Test for overall effect: Z = 1.38 (P = 0.17)
4.1.9 CBT
Epstein 2003 19 48 12 49 100.0% 1.62 [0.88, 2.95]
Subtotal (95% CI) 48 49 100.0% 1.62 [0.88, 2.95]
Total events 19 12
Heterogeneity: Not applicable
Test for overall effect: Z = 1.56 (P = 0.12)
4.1.10 CM + CBT
Epstein 2003 22 49 12 49 100.0% 1.83 [1.03, 3.28]
Subtotal (95% CI) 49 49 100.0% 1.83 [1.03, 3.28]
Total events 22 12
Heterogeneity: Not applicable
Test for overall effect: Z = 2.04 (P = 0.04)
4.1.11 CM + Bupropion
Poling 2006-1 14 27 7 24 100.0% 1.78 [0.86, 3.66]
Subtotal (95% CI) 27 24 100.0% 1.78 [0.86, 3.66]
Total events 14 7
Heterogeneity: Not applicable
Test for overall effect: Z = 1.56 (P = 0.12)
0.05 0.2 1 5 20
Favours Control interv. Favours Active interv.

FIGURE 4 online: Efficacy of adjunctive interventions on sustained heroin abstinence

Abbreviations: CBT = Cognitive Behavioral Treatment, CM = Contingency Management, DA = Dopamine, NA = Noradrenaline

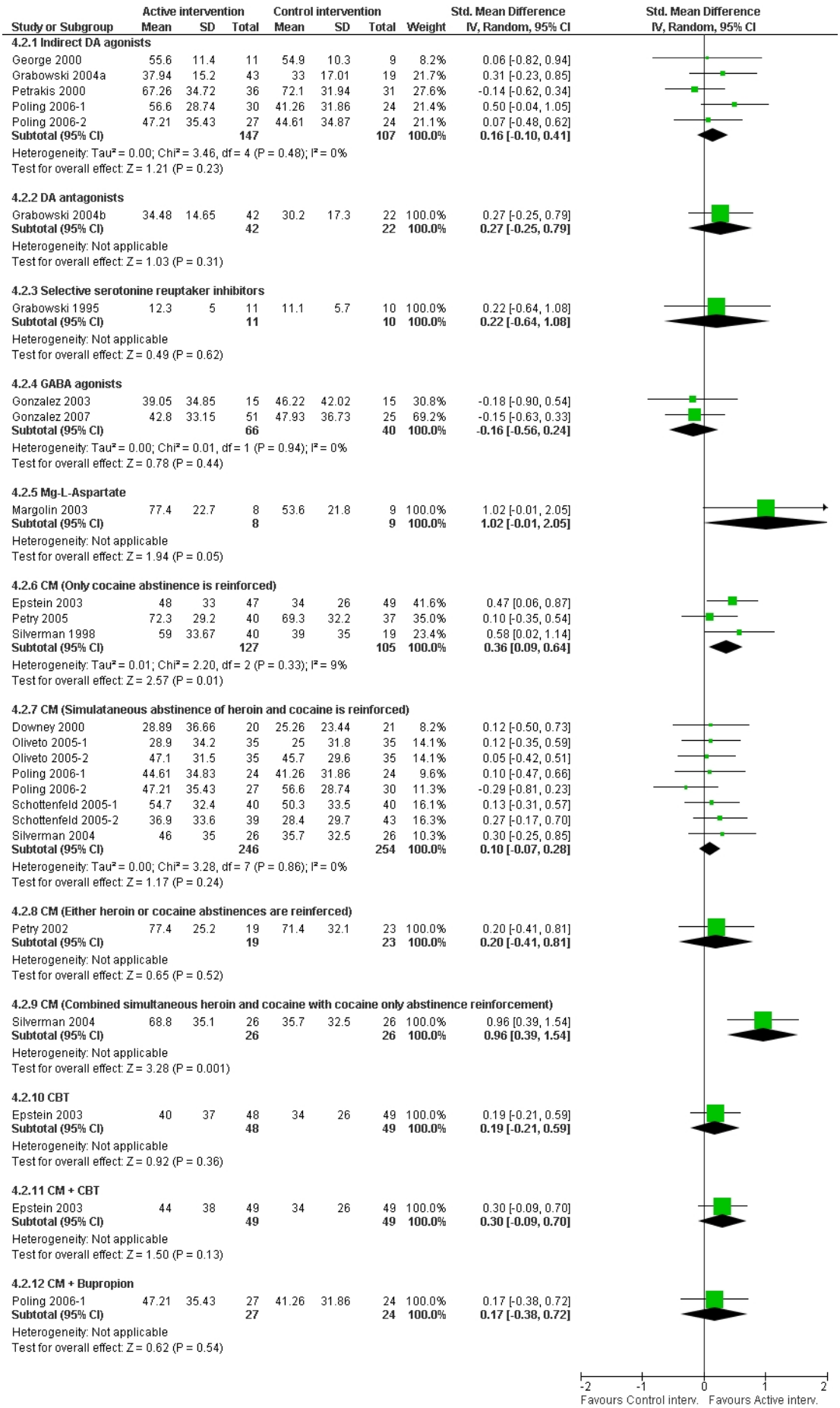

Active intervention
Control intervention
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
4.2.1 Indirect DA agonists
George 2000 55.6 11.4 11 54.9 10.3 9 8.2% 0.06 [-0.82, 0.94]
Grabowski 2004a 37.94 15.2 43 33 17.01 19 21.7% 0.31 [-0.23, 0.85]
Petrakis 2000 67.26 34.72 36 72.1 31.94 31 27.6% -0.14 [-0.62, 0.34]
Poling 2006-1 56.6 28.74 30 41.26 31.86 24 21.4% 0.50 [-0.04, 1.05]
Poling 2006-2 47.21 35.43 27 44.61 34.87 24 21.1% 0.07 [-0.48, 0.62]
Subtotal (95% CI) 147 107 100.0% 0.16 [-0.10, 0.41]
Heterogeneity: Tau² = 0.00; Chi² = 3.46, df = 4 (P = 0.48); I² = 0%
Test for overall effect: Z = 1.21 (P = 0.23)
4.2.2 DA antagonists
Grabowski 2004b 34.48 14.65 42 30.2 17.3 22 100.0% 0.27 [-0.25, 0.79]
Subtotal (95% CI) 42 22 100.0% 0.27 [-0.25, 0.79]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.03 (P = 0.31)
4.2.3 Selective serotonine reuptaker inhibitors
Grabowski 1995 12.3 5 11 11.1 5.7 10 100.0% 0.22 [-0.64, 1.08]
Subtotal (95% CI) 11 10 100.0% 0.22 [-0.64, 1.08]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.49 (P = 0.62)
4.2.4 GABA agonists
Gonzalez 2003 39.05 34.85 15 46.22 42.02 15 30.8% -0.18 [-0.90, 0.54]
Gonzalez 2007 42.8 33.15 51 47.93 36.73 25 69.2% -0.15 [-0.63, 0.33]
Subtotal (95% CI) 66 40 100.0% -0.16 [-0.56, 0.24]
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.78 (P = 0.44)
4.2.5 Mg-L-Aspartate
Margolin 2003 77.4 22.7 8 53.6 21.8 9 100.0% 1.02 [-0.01, 2.05]
Subtotal (95% CI) 8 9 100.0% 1.02 [-0.01, 2.05]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.94 (P = 0.05)
4.2.6 CM (Only cocaine abstinence is reinforced)
Epstein 2003 48 33 47 34 26 49 41.6% 0.47 [0.06, 0.87]
Petry 2005 72.3 29.2 40 69.3 32.2 37 35.0% 0.10 [-0.35, 0.54]
Silverman 1998 59 33.67 40 39 35 19 23.4% 0.58 [0.02, 1.14]
Subtotal (95% CI) 127 105 100.0% 0.36 [0.09, 0.64]
Heterogeneity: Tau² = 0.01; Chi² = 2.20, df = 2 (P = 0.33); I² = 9%
Test for overall effect: Z = 2.57 (P = 0.01)
4.2.7 CM (Simulataneous abstinence of heroin and cocaine is reinforced)
Downey 2000 28.89 36.66 20 25.26 23.44 21 8.2% 0.12 [-0.50, 0.73]
Oliveto 2005-1 28.9 34.2 35 25 31.8 35 14.1% 0.12 [-0.35, 0.59]
Oliveto 2005-2 47.1 31.5 35 45.7 29.6 35 14.1% 0.05 [-0.42, 0.51]
Poling 2006-1 44.61 34.83 24 41.26 31.86 24 9.6% 0.10 [-0.47, 0.66]
Poling 2006-2 47.21 35.43 27 56.6 28.74 30 11.3% -0.29 [-0.81, 0.23]
Schottenfeld 2005-1 54.7 32.4 40 50.3 33.5 40 16.1% 0.13 [-0.31, 0.57]
Schottenfeld 2005-2 36.9 33.6 39 28.4 29.7 43 16.3% 0.27 [-0.17, 0.70]
Silverman 2004 46 35 26 35.7 32.5 26 10.3% 0.30 [-0.25, 0.85]
Subtotal (95% CI) 246 254 100.0% 0.10 [-0.07, 0.28]
Heterogeneity: Tau² = 0.00; Chi² = 3.28, df = 7 (P = 0.86); I² = 0%
Test for overall effect: Z = 1.17 (P = 0.24)
4.2.8 CM (Either heroin or cocaine abstinences are reinforced)
Petry 2002 77.4 25.2 19 71.4 32.1 23 100.0% 0.20 [-0.41, 0.81]
Subtotal (95% CI) 19 23 100.0% 0.20 [-0.41, 0.81]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.65 (P = 0.52)
4.2.9 CM (Combined simultaneous heroin and cocaine with cocaine only abstinence reinforcement)
Silverman 2004 68.8 35.1 26 35.7 32.5 26 100.0% 0.96 [0.39, 1.54]
Subtotal (95% CI) 26 26 100.0% 0.96 [0.39, 1.54]
Heterogeneity: Not applicable
Test for overall effect: Z = 3.28 (P = 0.001)
4.2.10 CBT
Epstein 2003 40 37 48 34 26 49 100.0% 0.19 [-0.21, 0.59]
Subtotal (95% CI) 48 49 100.0% 0.19 [-0.21, 0.59]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.92 (P = 0.36)
4.2.11 CM + CBT
Epstein 2003 44 38 49 34 26 49 100.0% 0.30 [-0.09, 0.70]
Subtotal (95% CI) 49 49 100.0% 0.30 [-0.09, 0.70]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.50 (P = 0.13)
4.2.12 CM + Bupropion
Poling 2006-1 47.21 35.43 27 41.26 31.86 24 100.0% 0.17 [-0.38, 0.72]
Subtotal (95% CI) 27 24 100.0% 0.17 [-0.38, 0.72]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.62 (P = 0.54)
-2 -1 0 1 2
Favours Control interv. Favours Active interv.

FIGURE 5 online: Efficacy of adjunctive interventions on heroin-free UA

Abbreviations: CBT = Cognitive Behavioral Treatment, CM = Contingency Management, DA = Dopamine, IV = Inverse Variance, NA = Noradrenaline, UA = urinalysis

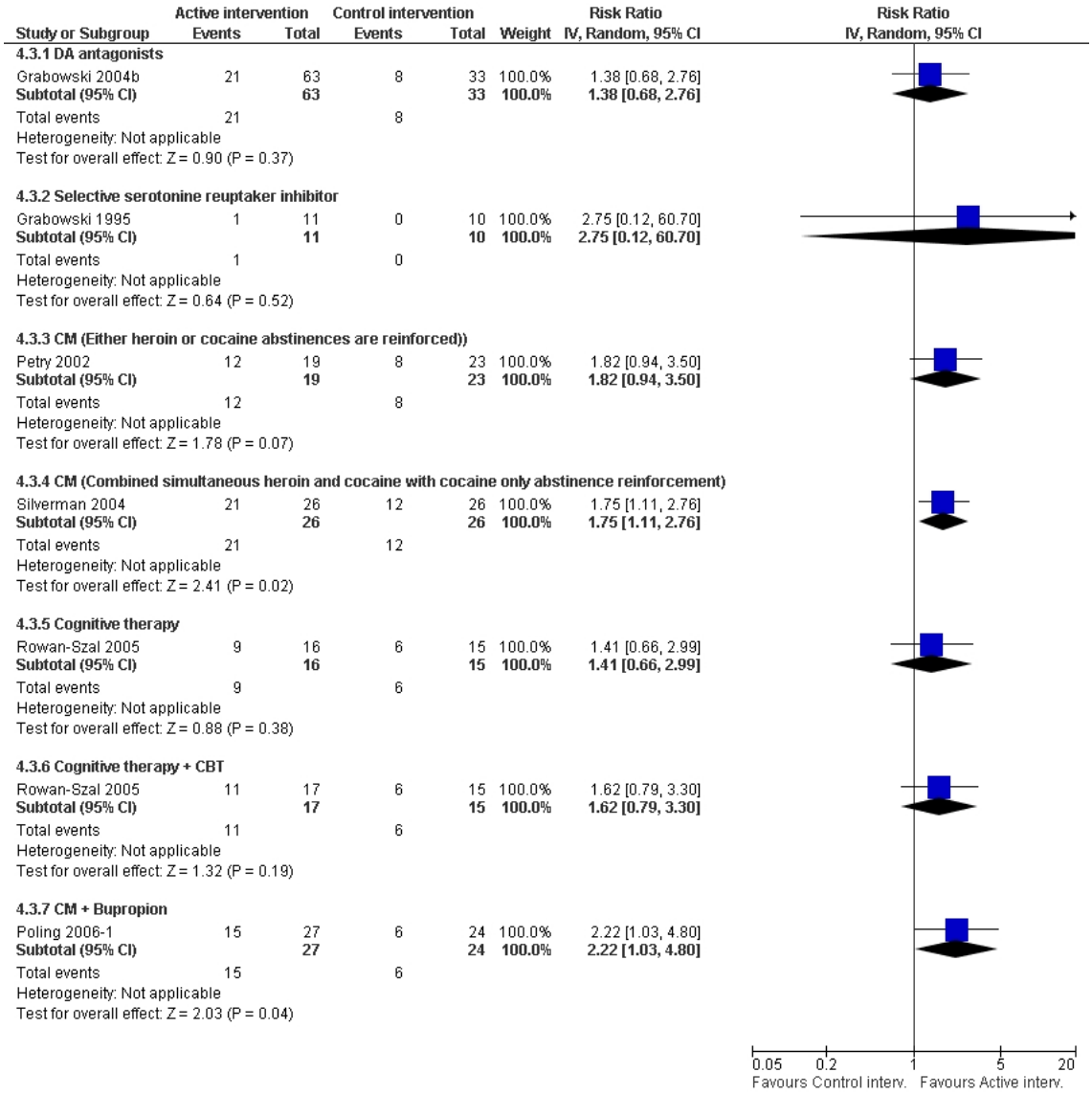


FIGURE 6 online: Efficacy of adjunctive interventions on sustained cocaine abstinence

Abbreviations: CBT = Cognitive Behavioral Treatment, CM = Contingency Management, DA = Dopamine, IV = Inverse Variance

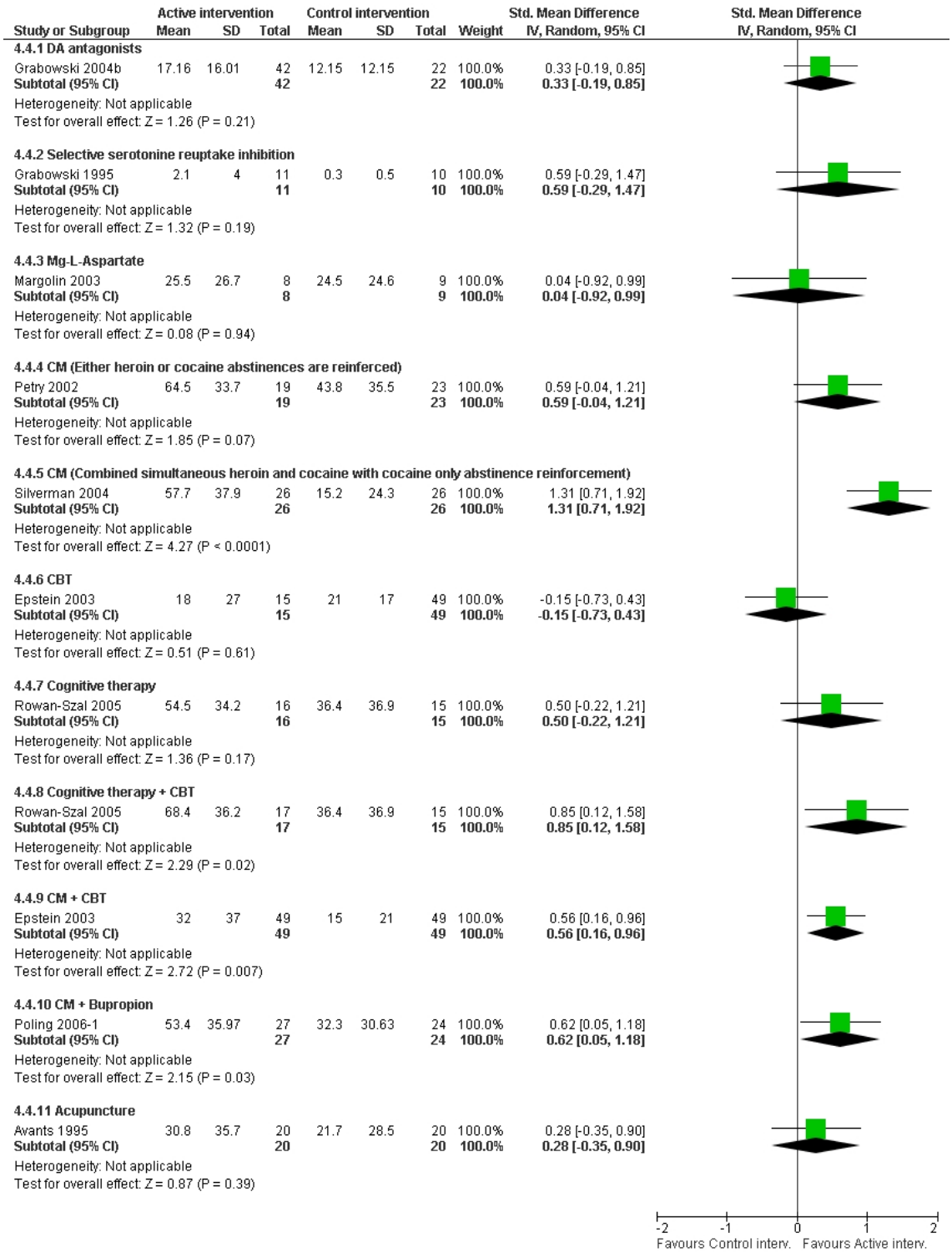


FIGURE 7 online: Efficacy of adjunctive interventions on cocaine-free UA

Abbreviations: CBT = Cognitive Behavioral Treatment, CM = Contingency Management, DA = Dopamine, IV = Inverse Variance, UA = urinalysis

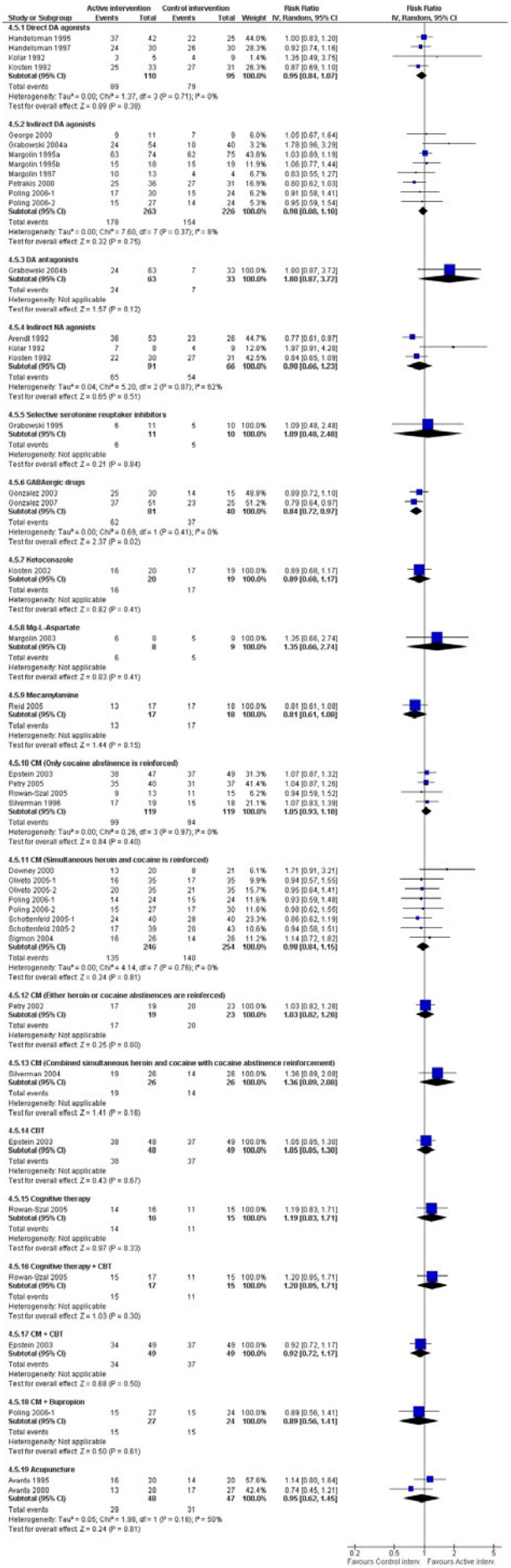

Active intervention
Control intervention
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI
IV, Random, 95% CI
4.5.1 Direct DA agonists
Handelsman 1995 37 42 22 25 44.0% 1.00 [0.83, 1.20]
Handelsman 1997 24 30 26 30 28.3% 0.92 [0.74, 1.16]
Kolar 1992 3 5 4 9 1.4% 1.35 [0.49, 3.75]
Kosten 1992 25 33 27 31 26.3% 0.87 [0.69, 1.10]
Subtotal (95% CI) 110 95 100.0% 0.95 [0.84, 1.07]
Total events 89 79
Heterogeneity: Tau² = 0.00; Chi² = 1.37, df = 3 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.99 (P = 0.32)
4.5.2 Indirect DA agonists
George 2000 9 11 7 9 6.0% 1.05 [0.67, 1.64]
Grabowski 2004a 24 54 10 40 3.2% 1.78 [0.96, 3.29]
Margolin 1995a 63 74 62 75 43.8% 1.03 [0.89, 1.19]
Margolin 1995b 15 18 15 19 11.9% 1.06 [0.77, 1.44]
Margolin 1997 10 13 4 4 6.7% 0.83 [0.55, 1.27]
Petrakis 2000 25 36 27 31 16.9% 0.80 [0.62, 1.03]
Poling 2006-1 17 30 15 24 6.2% 0.91 [0.58, 1.41]
Poling 2006-2 15 27 14 24 5.3% 0.95 [0.59, 1.54]
Subtotal (95% CI) 263 226 100.0% 0.98 [0.88, 1.10]
Total events 178 154
Heterogeneity: Tau² = 0.00; Chi² = 7.60, df = 7 (P = 0.37); I² = 8%
Test for overall effect: Z = 0.32 (P = 0.75)
4.5.3 DA antagonists
Grabowski 2004b 24 63 7 33 100.0% 1.80 [0.97, 3.72]
Subtotal (95% CI) 63 33 100.0% 1.80 [0.97, 3.72]
Total events 24 7
Heterogeneity: Not applicable
Test for overall effect: Z = 1.57 (P = 0.12)
4.5.4 Indirect NA agonists
Arendt 1992 36 53 23 26 44.7% 0.77 [0.61, 0.97]
Kolar 1992 7 8 4 9 12.8% 1.97 [0.91, 4.28]
Kosten 1992 22 30 27 31 42.5% 0.84 [0.65, 1.09]
Subtotal (95% CI) 91 66 100.0% 0.90 [0.66, 1.23]
Total events 65 54
Heterogeneity: Tau² = 0.04; Chi² = 5.20, df = 2 (P = 0.07); I² = 62%
Test for overall effect: Z = 0.65 (P = 0.51)
4.5.5 Selective serotonine reuptaker inhibitors
Grabowski 1995 6 11 5 10 100.0% 1.09 [0.48, 2.48]
Subtotal (95% CI) 11 10 100.0% 1.09 [0.48, 2.48]
Total events 6 5
Heterogeneity: Not applicable
Test for overall effect: Z = 0.21 (P = 0.84)
4.5.6 GABAergic drugs
Gonzalez 2003 25 30 14 15 48.8% 0.89 [0.72, 1.10]
Gonzalez 2007 37 51 23 25 51.2% 0.79 [0.64, 0.97]
Subtotal (95% CI) 81 40 100.0% 0.84 [0.72, 0.97]
Total events 62 37
Heterogeneity: Tau² = 0.00; Chi² = 0.69, df = 1 (P = 0.41); I² = 0%
Test for overall effect: Z = 2.37 (P = 0.02)
4.5.7 Ketoconazole
Kosten 2002 16 20 17 19 100.0% 0.89 [0.68, 1.17]
Subtotal (95% CI) 20 19 100.0% 0.89 [0.68, 1.17]
Total events 16 17
Heterogeneity: Not applicable
Test for overall effect: Z = 0.82 (P = 0.41)
4.5.8 Mg-L-Aspartate
Margolin 2003 6 8 5 9 100.0% 1.35 [0.66, 2.74]
Subtotal (95% CI) 8 9 100.0% 1.35 [0.66, 2.74]
Total events 6 5
Heterogeneity: Not applicable
Test for overall effect: Z = 0.83 (P = 0.41)
4.5.9 Mecamylamine
Reid 2005 13 17 17 18 100.0% 0.81 [0.61, 1.08]
Subtotal (95% CI) 17 18 100.0% 0.81 [0.61, 1.08]
Total events 13 17
Heterogeneity: Not applicable
Test for overall effect: Z = 1.44 (P = 0.15)
4.5.10 CM (Only cocaine abstinence is reinforced)
Epstein 2003 38 47 37 49 31.3% 1.07 [0.87, 1.32]
Petry 2005 35 40 31 37 41.4% 1.04 [0.87, 1.26]
Rowan-Szal 2005 9 13 11 15 6.2% 0.94 [0.59, 1.52]
Silverman 1996 17 19 15 18 21.1% 1.07 [0.83, 1.39]
Subtotal (95% CI) 119 119 100.0% 1.05 [0.93, 1.18]
Total events 99 94
Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 3 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.84 (P = 0.40)
4.5.11 CM (Simultaneous heroin and cocaine is reinforced)
Downey 2000 13 20 8 21 6.1% 1.71 [0.91, 3.21]
Oliveto 2005-1 16 35 17 35 9.9% 0.94 [0.57, 1.55]
Oliveto 2005-2 20 35 21 35 15.7% 0.95 [0.64, 1.41]
Poling 2006-1 14 24 15 24 11.6% 0.93 [0.59, 1.48]
Poling 2006-2 15 27 17 30 11.6% 0.98 [0.62, 1.55]
Schottenfeld 2005-1 24 40 28 40 23.3% 0.86 [0.62, 1.19]
Schottenfeld 2005-2 17 39 20 43 10.6% 0.94 [0.58, 1.51]
Sigmon 2004 16 26 14 26 11.2% 1.14 [0.72, 1.82]
Subtotal (95% CI) 246 254 100.0% 0.99 [0.84, 1.15]
Total events 135 140
Heterogeneity: Tau² = 0.00; Chi² = 4.14, df = 7 (P = 0.76); I² = 0%
Test for overall effect: Z = 0.24 (P = 0.81)
4.5.12 CM (Either heroin or cocaine abstinences are reinforced)
Petry 2002 17 19 20 23 100.0% 1.03 [0.82, 1.28]
Subtotal (95% CI) 19 23 100.0% 1.03 [0.82, 1.28]
Total events 17 20
Heterogeneity: Not applicable
Test for overall effect: Z = 0.25 (P = 0.80)
4.5.13 CM (Combined simultaneous heroin and cocaine with cocaine abstinence reinforcement)
Silverman 2004 19 26 14 26 100.0% 1.36 [0.89, 2.08]
Subtotal (95% CI) 26 26 100.0% 1.36 [0.89, 2.08]
Total events 19 14
Heterogeneity: Not applicable
Test for overall effect: Z = 1.41 (P = 0.16)
4.5.14 CBT
Epstein 2003 38 49 37 49 100.0% 1.05 [0.85, 1.30]
Subtotal (95% CI) 49 49 100.0% 1.05 [0.85, 1.30]
Total events 38 37
Heterogeneity: Not applicable
Test for overall effect: Z = 0.43 (P = 0.67)
4.5.15 Cognitive therapy
Rowan-Szal 2005 14 16 11 15 100.0% 1.19 [0.83, 1.71]
Subtotal (95% CI) 16 15 100.0% 1.19 [0.83, 1.71]
Total events 14 11
Heterogeneity: Not applicable
Test for overall effect: Z = 0.97 (P = 0.33)
4.5.16 Cognitive therapy + CBT
Rowan-Szal 2005 15 17 11 15 100.0% 1.20 [0.85, 1.71]
Subtotal (95% CI) 17 15 100.0% 1.20 [0.85, 1.71]
Total events 15 11
Heterogeneity: Not applicable
Test for overall effect: Z = 1.03 (P = 0.30)
4.5.17 CM + CBT
Epstein 2003 34 49 37 49 100.0% 0.92 [0.72, 1.17]
Subtotal (95% CI) 49 49 100.0% 0.92 [0.72, 1.17]
Total events 34 37
Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
4.5.18 CM + Bupropion
Poling 2006-1 15 27 15 24 100.0% 0.89 [0.56, 1.41]
Subtotal (95% CI) 27 24 100.0% 0.89 [0.56, 1.41]
Total events 15 15
Heterogeneity: Not applicable
Test for overall effect: Z = 0.50 (P = 0.61)
4.5.19 Acupuncture
Avants 1995 18 20 14 20 57.6% 1.14 [0.80, 1.64]
Avants 2000 13 28 17 27 42.4% 0.74 [0.45, 1.21]
Subtotal (95% CI) 48 47 100.0% 0.95 [0.62, 1.45]
Total events 29 31
Heterogeneity: Tau² = 0.05; Chi² = 1.98, df = 1 (P = 0.16); I² = 50%
Test for overall effect: Z = 0.24 (P = 0.81)
0.2 0.5 1 2 5
Favours Control interv. Favours Active interv.

FIGURE 8 online: Efficacy of adjunctive interventions on study retention

Abbreviations: CBT = Cognitive Behavioral Treatment, CM = Contingency Management, DA = Dopamine, NA = Noradrenaline

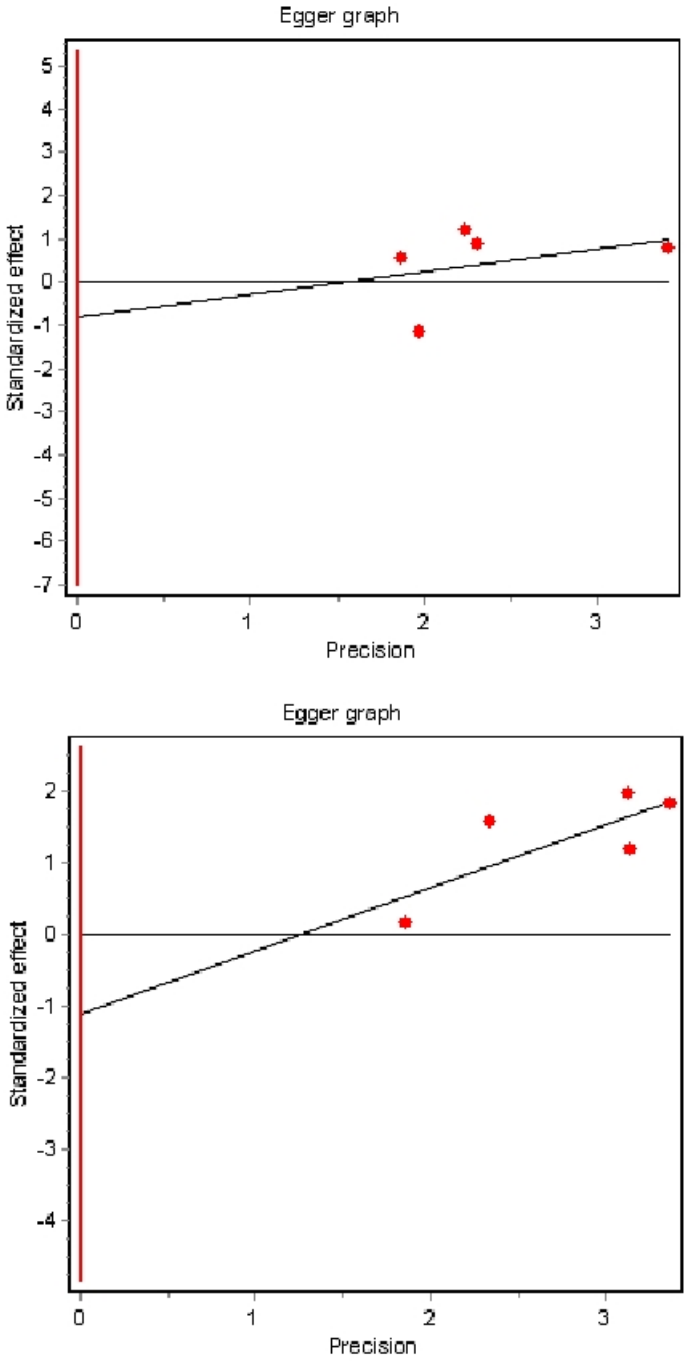
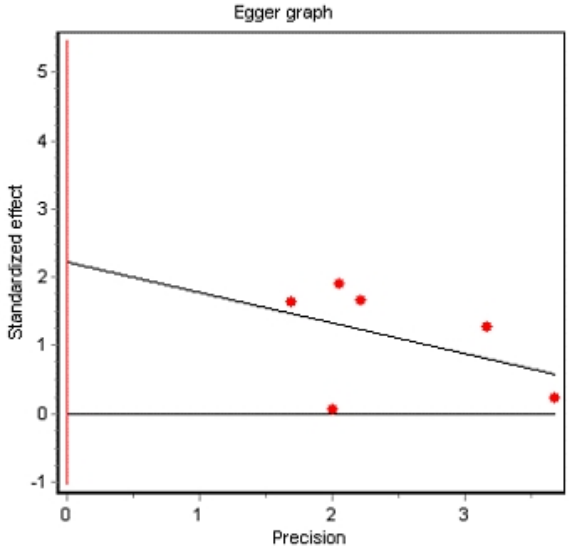
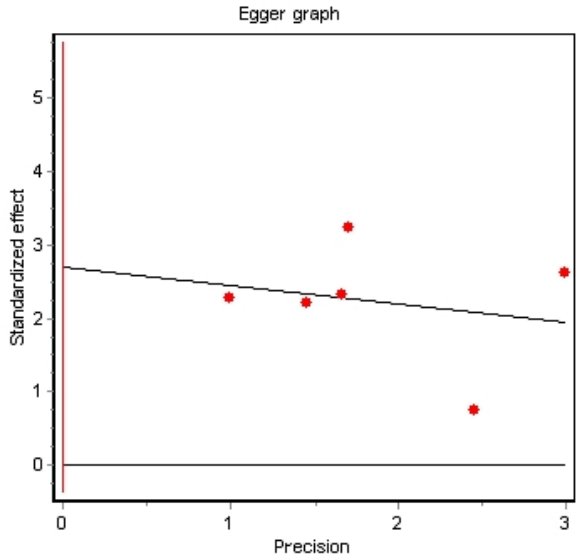


FIGURE 9 online: Egger graph of the comparisons high vs. low OMT (top) and methadone vs. buprenorphine (bottom) on sustained cocaine abstinence.


Egger graph
Standardized effect
Precision
5
4
3
2
1
0
-1
0
1
2
3


Egger graph
Standardized effect
Precision
5
4
3
2
1
0
0
1
2
3

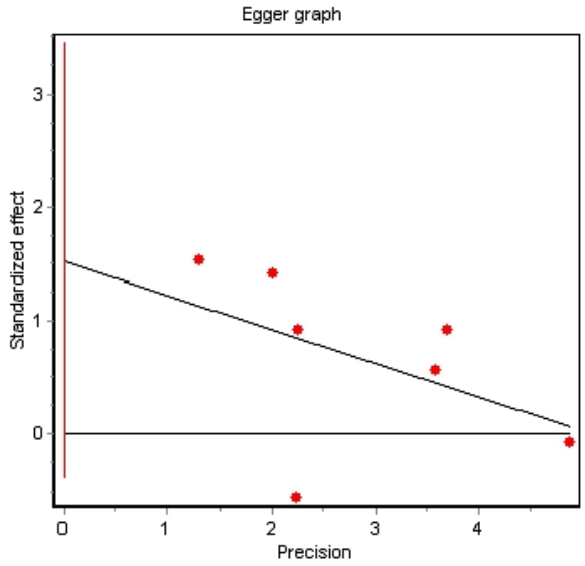

Egger graph
Standardized effect
Precision
3
2
1
0
0
1
2
3
4

FIGURE 10 online: Egger graph of the comparisons indirect DA agonists vs. placebo (top), CM targeting cocaine abstinence vs. control intervention (middle) and CM targeting heroin and cocaine abstinence vs. control intervention (bottom) on sustained cocaine abstinence.

ANNEX II

Castells X, Casas M, Vidal X, Bosch R, Roncero C, Ramos-Quiroga JA, Capellà D. Efficacy of central nervous system stimulant treatment for cocaine dependence: a systematic review and meta-analysis of randomized controlled clinical trials. *Addiction.* 2007;102:1871-87.

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Efficacy of central nervous system stimulant treatment for cocaine dependence: a systematic review and meta-analysis of randomized controlled clinical trials

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ABSTRACT

Aims To evaluate the efficacy of central nervous system (CNS) stimulants compared with placebo for the treatment of cocaine dependence. **Methods** A systematic review and meta-analysis was carried out. Bibliographic databases were searched, reference lists of retrieved studies were hand-searched and the first authors of each study were contacted. All randomized controlled clinical trials (RCCT) comparing the efficacy of any CNS stimulant with placebo in cocaine-dependent patients were included. Quantitative data synthesis was performed for each single CNS stimulant and for all CNS stimulants. **Results** Nine RCCT met the inclusion criteria. These RCCT included 640 patients and compared five CNS stimulants: mazindol, dextroamphetamine, methylphenidate, modafinil and bupropion with placebo. No CNS stimulant improved study retention [RR = 0.94 (0.81–1.09)] or cocaine use [RR = 0.90 (0.79–1.02)]. An exploratory analysis using indirect estimations of cocaine use showed that the proportion of cocaine-positive urine screens was lower with dexamphetamine than with placebo [RR = 0.73 (0.60–0.90)] and that all CNS stimulants pooled together also suggested a significant decrease of cocaine use [RR = 0.87 (0.77–0.99)]. Data on craving could not be meta-analysed due to heterogeneity, but no RCCT found differences in cocaine craving between active drug and placebo except one, whose outcome favoured dexamphetamine. No serious adverse event (AE) was reported. Average of AE-induced dropouts was low and was greater for CNS stimulants than placebo: 4.4% versus 1.3% ($P = 0.03$). **Conclusion** The main outcomes of this study do not support the use of CNS stimulants for cocaine dependence. Nevertheless, secondary analyses provide some hopeful results that encourage further research with these drugs, mainly with dexamphetamine and modafinil.

Keywords CNS stimulants, cocaine dependence, meta-analysis, placebo, randomized controlled trial.

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INTRODUCTION

The prevalence of cocaine dependence has been increasing in recent years and has become a world health problem. During 2000–01, 0.3% of the population world-wide, aged 15 years or more, had used cocaine [1]. In the European Union countries life-time cocaine use prevalence reached 3% of the adult population, with the United Kingdom (6.1%), Spain (5.9%) and Italy (4.6%) at the upper end of this range [2]. In the United States in 2004, life-time and past-year cocaine use among people aged 12 or older was 14.7% and 2.4%, respectively. Among past-year cocaine users, 27.8% were classified as having a cocaine dependence or abuse disorder [3].

A large list of drugs, comprising antidepressants, antipsychotics, dopamine agonists or mood stabilizers, has been studied for cocaine dependence, although none has proved clearly to be effective [4]. As a consequence, no drug has a Food and Drugs Administration (FDA) or European Agency for the Evaluation of Medicinal

Products (EMEA) indication for cocaine dependence treatment. During recent years, replacement therapy with central nervous system (CNS) stimulants has been gaining support [5,6]. Replacement therapy involves substitution of the abused drug, which is often illegal, used parenterally several times a day, by a legal, orally administered one. A substitutive drug has a similar mechanism of action and behavioural effects to the abused drug but with a lower addictive potential, being able to block drug craving and withdrawal, leading to drug abstinence and helping patients to follow medical and psychological assistance [6]. This strategy has proved to be efficacious for heroin [7,8] and nicotine [9] dependence. Substitutive therapy has also been assessed for amphetamine dependence, with encouraging results [10].

CNS stimulants for cocaine dependence were reported first by Khantzian and colleagues [11,12] in attention deficit hyperactivity disorder (ADHD) patients with comorbid cocaine dependence. Initially, the administration of psychostimulants was based on the self-medication hypothesis. This hypothesis posits that cocaine addicts begin substance use in an attempt to relieve ADHD symptoms. In these studies, methylphenidate improved both ADHD and cocaine dependence. Nevertheless, further research did not reproduce these results completely; stimulants improved ADHD symptoms but their efficacy in reducing cocaine use was heterogeneous [13,14].

Subsequently, several studies with CNS stimulants have been carried out on cocaine-dependent patients with and without comorbid ADHD [5,6,15]. A wide range of CNS stimulants have been or are being studied [16], including methylphenidate, amphetamine derivates, modafinil or caffeine. Although these drugs have shown promising results, their efficacy is still inconclusive.

The aim of this study was to review all randomized controlled clinical trials (RCCT) that assessed the efficacy of CNS stimulants for the treatment of cocaine dependence. As well as this, two subanalyses were planned. Because ADHD is a risk factor for substance dependence [17,18], and CNS stimulants improve ADHD symptoms [19,20] and prevent alcohol and drug abuse in children and adolescents with ADHD [21], a subanalysis with those studies that had assessed and included patients with comorbid ADHD was performed. In addition, a subanalysis for RCCT quality was carried out, because quality affects RCCT efficacy results [22].

METHODS

Inclusion and exclusion criteria

Double-blind, randomized, placebo-controlled clinical trials with parallel groups assessing the efficacy of CNS stimulants for cocaine dependence were included. RCCTs that included cocaine abusers were excluded. Only those RCCTs reporting outcomes on study retention, cocaine use assessed with urine analysis (UA) for cocaine metabolites or cocaine craving were considered suitable. There were no publication restrictions.

Search strategy

A PubMed (from 1966 to November 2006), Cochrane Library (from 1966 to November 2006) and Iowa Drug Information System (IDIS) (from 1966 to November 2006) database search was performed twice (last search: 1 December 2006). Bibliographic reference lists of retrieved studies and reviews [4–6,15] were handsearched in order to find additional RCCTs. Furthermore, the first author of selected articles was contacted in order to request additional articles.

Because 'psychostimulant' or 'CNS stimulant' are not terms describing a pharmacological group but a pharmacological effect, there is no single list of drugs with this effect. For this reason CNS stimulants are classified into several groups, according to their main indication, in drug classification systems such as the Anatomical Therapeutic Chemical (ATC) classification [23] and the American Hospital Formulary Service (AHFS) Pharmacologic-Therapeutic Classification System [24]. Consequently, a drug search was performed to obtain a complete list of drugs with psychostimulant effects. For this purpose, all drugs belonging to groups or subgroups suspected of containing potential psychomotor stimulant drugs were extracted. These pharmacological groups were the N06BA (centrally acting sympathomimetics), A08AA (centrally acting anti-obesity products), N06 BC (xanthine derivates), N06BX (other psychostimulants and nootropics), N07BA (drugs used in nicotine dependence) and R03DA (xanthines) from the ATC classification; and 12:92 (miscellaneous autonomic drugs), 28:16.04.92 (antidepressants, miscellaneous), 28:20.04 (amphetamines), 28:20.92 (anorexigenic agents and respiratory and cerebral stimulants, miscellaneous) and 86:16 (respiratory smooth muscle relaxants) from the AHFS classification. Furthermore, drugs metabolized to a known psychostimulant, such as selegiline [25], were included. The World Anti-Doping Agency (WADA) list [26] and other sources of information in pharmacology and psychopharmacology [27–30] were also reviewed. From this list of potential CNS stimulants, only those drugs having at least one published study showing a CNS stimulant effect were included in the definitive list of psychostimulants. CNS stimulant effect was defined as an increased CNS activity resulting in fatigue relief, improved performance in simple tasks, increased locomotor activity and anorexia in healthy subjects [31–33]. The

final CNS stimulants list included (an asterisk indicates that this drug was not available alone or in combination in the US pharmaceutical market in 2006): amphetamine, acefylline piperazine*, adrafinil*, amfebutamone, amfepramone*, aminorex*, aminophylline, bamifylline*, benzphetamine, bufylline*, bupropion, caffeine, cathine*, cathinone*, choline theophyllinate, clobenzorex*, dexamphetamine, dexmethylphenidate, diethylpropion, diprophylline*, doxofylline*, dyphylline, ephedrine, etamiphylline*, ethylamphetamine*, fencamfamine*, fenetylline*, fenozolone*, mazindol*, mefenorex*, mesocarb*, methamphetamine, methylenedioxymethamphetamine*, methylphenidate, modafinil, nicotine, norpseudoephedrine*, pemoline, phentermine, pipradrol*, prolintane*, propentofylline*, proxyphylline*, selegiline, sydnocarb*, theobromine* and theophylline.

Figure 1 shows PubMed search syntax. Search terms for the Cochrane Library were 'cocaine' and for IDIS database 'depend/abuse, cocaine 304.2' and 'study randomized adult 135'.

Data extraction

One author (X. C.) selected the included studies and extracted all relevant data with a standardized report form. Another author (R. B.) checked extraction results. Discrepancies were solved by consensus. Authors were not blinded either by authorship or publication journal. For each study, the following data were extracted: authorship, funding, participants' characteristics, intervention description, study design, sample size, efficacy outcomes definition, assessment methods, retention, efficacy and safety outcomes, dropouts and type of statistical analysis: intention-to-treat (ITT) or per protocol (PP). ITT results were preferred to PP results.

Each RCCT quality was assessed by means of the Jadad scale [35]. This scale assesses the reporting quality of randomized RCCT. It is based upon the description of withdrawals and upon the description and appropriateness of randomization and double-blinding. Its score ranges from 0 to 5, and a score below 3 is imputed as poor quality.

Data synthesis and statistical analysis

Data were entered into the Cochrane Collaboration Review Manager version 4.2.9 package [36] and were summarized in meta-analyses. Study retention and cocaine use were coded as dichotomous variables. Study retention was defined as the rate of patients who completed the RCCT and cocaine use as the proportion of positive UA for benzoylecgonine (BE) along the RCCT for each study group. When this information was not available, it was requested from the authors. If the information was not finally available, these studies were not included in the main efficacy analysis on cocaine use. Nevertheless, if these studies provided data of cocaine use at baseline and at the conclusion of the study, they were included in an exploratory analysis where the proportion of positive UA for BE along the RCCT was estimated from the mean between initial and final proportion of BE positive screens. For trials with more than two groups, each pairwise comparison was included separately and the control group results divided among the comparisons [37].

Statistical analysis was planned a priori for each single drug and for all CNS stimulants. Nevertheless, because it is not clear whether bupropion has CNS stimulant properties in humans, as will be discussed further later, a *post hoc* analysis of the efficacy of all CNS stimulants without bupropion on cocaine dependence outcomes was carried out. In order to explain differences between studies in efficacy outcomes, a group of subanalyses regarding RCCT quality according to the Jadad scale score and for patients with comorbid adult ADHD were performed.

Weighted averages were reported as relative risks (RR), with 95% confidence intervals (CI) and the random-effects model in the calculation of CI were preferred to the odds ratio and fixed-effects model, respectively, because the chosen ones led to a more conservative estimate of treatment effect. To determine whether the results were influenced unduly by a single comparison, meta-analyses were repeated after withdrawing each CNS stimulant versus placebo comparison once and, later, comparing if the sense, direction and confidence intervals were altered significantly with respect to the main analysis. Statistical heterogeneity between studies was assessed by means of the χ^2 test for heterogeneity.

RESULTS

Article search

A total of 582 potential articles were found (Fig. 2) from the initial bibliographic database searches and handsearch. Nine [38–46] RCCT fulfilled the inclusion/exclusion criteria, involving 640 patients (344 treated with a CNS stimulant and 296 with placebo). Four [41,42,44,45] of nine articles were completed with additional author information, leading to a substantial increase in analysed data. Additional information on baseline sample features regarding socio-demographic and clinical data such as comorbidities or type and route of cocaine use was requested. Although all articles reported data on dropouts and cocaine use, authors were also contacted if this information was reported as a figure and not numerically, or if it was not provided as the proportion of positive UA for benzoylecgonine along the study. A more precise description about the additional

Cocaine dependence:	((cocaine OR crack) AND (abstinen* OR dependen* OR addict* OR withdraw* OR *use OR abus*))
	AND
CNS stimulants:	(amphetamine OR acefylline piperazine OR adrafinil OR amfebutamone OR amfepramone OR aminorex OR aminophylline OR bamifylline OR benzphetamine OR bufylline OR bupropion OR caffeine OR cathine OR cathinone OR choline theophyllinate OR clobenzorex OR dexamphetamine OR dexmethylphenidate OR diethylpropion OR diprophylline OR doxofylline OR dyphylline OR ephedrine OR etamiphylline OR ethylamphetamine OR fencamfamine OR fenetylline OR fenozolone OR mazindol OR mefenorex OR mesocarb OR methamphetamine OR methylenedioxymethamphetamine OR methylphenidate OR modafinil OR nicotine OR norpseudoephedrine OR pemoline OR phentermine OR pipradrol OR prolintane OR propentofylline OR proxyphylline OR selegiline OR sydnocarb OR theobromine OR theophylline)
	AND
Controlled clinical trials*:	((randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] clinical trials [mh] OR (clinical trial [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR (latin square [tw]) OR placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR cross-over studies [mh] OR control* [tw] OR prospective* [tw] OR volunteer [tw]) NOT (animal [mh] NOT human [mh]))

Figure 1 PubMed search strategy for retrieving controlled clinical trials with central nervous system stimulants for cocaine dependence. *This search strategy was designed by Robinson & Dickersin [34]

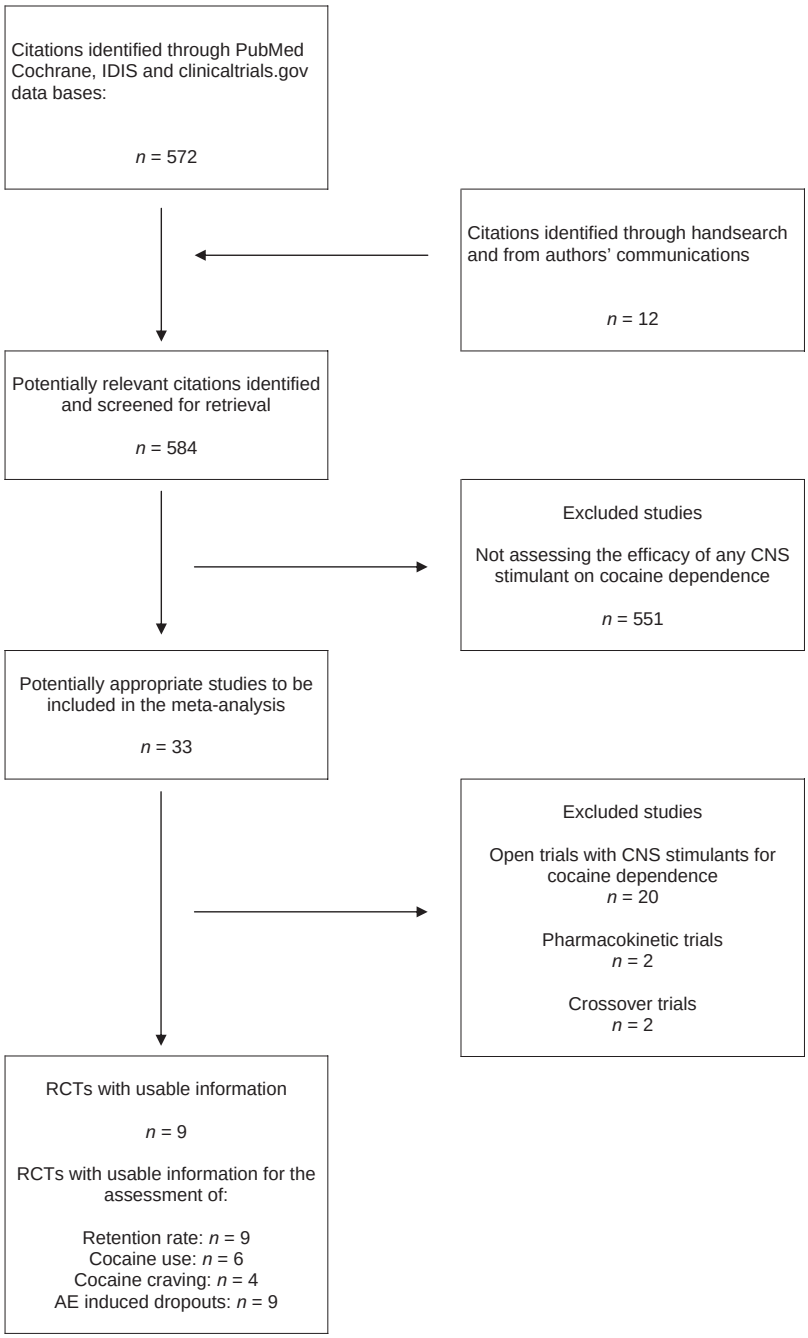

Figure 2 Flow diagram of identified citations and inclusion and exclusion process. AE = adverse events; CNS = central nervous system; RCT = randomized controlled trial; IDIS = Iowa Drug Information System

information provided by the correspondence can be found in Table 1.

Five CNS stimulants have been studied by means of a RCCT methodology: mazindol [39,40], dexamphetamine [42,44,45], methylphenidate [41,43], modafinil [46] and bupropion [38].

Clinical trial and subject features

RCCT characteristics, outcomes and quality score according to the Jadad scale are shown in Table 1. Sample sizes ranged from 30 to 149 days and planned follow-up from 42 to 182 days. Seven RCCT were two-armed [37–41,43,44] and two [42,45] had three intervention arms, resulting in 11 CNS stimulants versus placebo comparisons. One study [45] consisted of two RCCT. The first study assessed the efficacy of dexamphetamine, whereas the second assessed the efficacy of risperidone. Because risperidone has no CNS stimulant properties, only the dexamphetamine RCCT has been included in this review. All studies were conducted by public institutions or university researchers and are almost entirely publicly funded, principally by the National Institute on Drug Abuse (NIDA), which funded eight of nine trials.

Table 1 Description of the characteristics of the clinical trials included in this systematic review and their quality score according to the Jadad scale [33].

Reference, author affiliation and study funding	*Participants*	*Methods*	*Interventions*	*Measures of interest: assessment method*	*Outcomes*	*Jadad score*
Margolin *et al.* 1995 [39] Authors' affiliation: university Study funding: co-funding public and private (Wyeth)	$n = 37$ Cocaine-dependent methadone-maintained patients abstinent from cocaine use for at least 2 weeks Patients dependent on other substances were not excluded Adult ADHD assessment: NS	Two-group, parallel arms, randomized, placebo-controlled, double-blind clinical trial Randomization: eligible subjects were randomized to placebo or active compound Follow up length: 84 days Statistical analysis: NS	Mazindol 1 mg/day Psychotherapy: psychosocial therapy integrated by: case management, behavioural contingency and group psychotherapy	Cocaine use: BE presence in urine three times a week Cocaine craving: VAS Adverse events: NS	No difference in dropout rate, cocaine use or craving was found	3
Stine *et al.* 1995 [40] Authors' affiliation: university and medical centres Study funding: co-funding public and private (Wyeth)	$n = 43$ Cocaine-dependent patients according to DSM-III-TR criteria, reporting cocaine use of at least 12 g in the 3 months prior to entering the study Patients dependent on substances other than cocaine or nicotine were excluded Adult ADHD assessment: NS	Two-group, parallel-arms, randomized, placebo-controlled, double- blind multi-centre (2 sites) clinical trial Randomization: eligible subjects were randomized to placebo or active compound Follow up length: 42 days Statistical analysis: ITT	Mazindol 2 mg/day q.d. Psychotherapy: 6 sessions of group therapy with counselling sessions	Cocaine use: BE presence in urine once a week Cocaine craving: 5-point analogue scale Adverse events: NS	No difference in dropout rate, cocaine use or craving was found	3
Grabowski *et al.* 2001 [42] Authors' affiliation: university Study funding: entirely public	*n*: ITT sample 128; PP sample = 112 Cocaine-dependent patients according to DSM-IV criteria Patients dependent on substances other than cocaine and nicotine were excluded Adult ADHD#: excluded	Three-group, parallel arms, randomized, placebo-controlled, double-blind clinical trial Randomization: eligible subjects were assigned randomly to placebo or one of two active d-amphetamine doses Follow-up length: 101 days Statistical analysis: only those patients with at least 1 urine analysis+ for BE (PP sample) at baseline were compared	Dexamphetamine-SR 15–30 mg/d b.i.d. versus dexamphetamine-SR 30–60 mg/day b.i.d. versus placebo Psychotherapy: 13 sessions cognitive behavioural psychosocial therapy	Cocaine use#: BE presence in urine twice a week AE#: by means of a 33-item checklist	No difference in dropout rate was found Cocaine use was lower with dexamphetamine regardless of the measure used, a dichotomous indicator or a creatinine-adjusted quantitative one	3

Table 1 *Cont.*

Reference, author affiliation and study funding	*Participants*	*Methods*	*Interventions*	*Measures of interest: assessment method*	*Outcomes*	*Jadad score*
Grabowski *et al.* 2004 [45] Authors' affiliation: university Study funding: entirely public	*n*: ITT sample 94 (PP sample = 62) Cocaine- and methadone-naive heroin-dependent patients according to DSM-IV criteria Adult ADHD#: excluded	Three-group, parallel arms, randomized, placebo-controlled, double-blind clinical trial Randomization: eligible participants were randomized to placebo or one of two active d-amphetamine doses Follow up length: 182 days Statistical analysis: outcomes on cocaine use are assessed in the so-called 'evaluable sample' which consists of those patients who have taken at least one administration of study medication (62/84 = 73.8% of the ITT sample)	Dexamphetamine-SR 15–30 mg/day b.i.d. + methadone 1.1 mg/kg/day versus dexamphetamine- SR 30–60 mg/day b.i.d. + methadone 1.1 mg/kg/day versus placebo + methadone 1.1 mg/kg/day Psychotherapy: 26 sessions of psychosocial therapy	Cocaine use#: BE presence in urine twice a week AE#: 33-item checklist	No difference in dropout rate was found Cocaine use was lower with dexamphetamine regardless of the measure used, a dichotomous indicator or a creatinine-adjusted quantitative one	4
Shearer *et al.* 2003 [44] Authors' affiliation: university and hospital Study funding: public grant and pharmaceutical industry help	*n* = 30# Cocaine-dependent patients according to DSM-IV criteria Cocaine administration route: i.v. Adult ADHD: Not assessed	Two-group, parallel arms, randomized, placebo-controlled, multi-centre, double-blind clinical trial Randomization: performed by independent pharmacy staff using randomization schedules stratified by gender Follow-up length: 98 days Statistical analysis: ITT	Dexamphetamine-IR 20–60 mg/day (medication schedule: q.d.)# Psychotherapy: drug and alcohol counselling	Cocaine use#: urine BE assessment once every 2 weeks Cocaine craving: VAS Adverse events: AE check list	No difference in dropout rate and cocaine use was found Cocaine craving was lower with dexamphetamine	3
Schubiner *et al.* 2002 [43] Authors' affiliation: university Study funding: entirely public	*n* = 48 Cocaine-dependent patients according to DSM-IV Adult ADHD according to DSM-IV	Two-group, parallel arms, randomized, placebo-controlled, double-blind clinical trial Randomization: stratified by gender, men were further stratified by APD and women by BPD Follow-up length: 84 days Statistical analysis: NS	Methylphenidate-IR 30–90 mg/day t.i.d. versus placebo Psychotherapy: 24 sessions of group CBT for cocaine dependence + individual CBT for ADHD with comorbid SUD	Cocaine use: urine BE assessment 3 times a week and cocaine use self-report Craving: Tiffany cocaine craving Adverse events: AE check list	No difference in dropout rate, cocaine use and craving was found Methylphenidate was superior to placebo in improving ADHD symptoms	2

Table 1 *Cont.*

Reference, author affiliation and study funding	*Participants*	*Methods*	*Interventions*	*Measures of interest: assessment method*	*Outcomes*	*Jadad score*
Grabowski *et al.* 1997 [41] Authors' affiliation: university Study funding: entirely public	*n* = 49 Cocaine-dependent patients according to DSM-IV Patients dependent on substances other than cocaine, nicotine were excluded Adult ADHD: excluded	Two-group, parallel arms, randomized, placebo-controlled, double-blind clinical trial Randomization: subjects were randomized to placebo or active medication Follow-up length: 91 days Statistical analysis: NS	Methylphenidate IR + SR 45 mg/day b.i.d, versus placebo, with 2 weeks of medication stabilization, 11 weeks of trial and 2 weeks of post-trial discharge Psychotherapy: 11 sessions of psychosocial therapy	Cocaine use#: urine BE assessment twice a week Cocaine craving: NA Adverse events#: AE check list	No difference in dropout rate or in cocaine use was found	3
Dackis *et al.* 2005 [46] Authors' affiliation: university and medical centre Study funding: co-funding public and private (Cephalon)	*n* = 62 Cocaine-dependent patients according to DSM-IV criteria who had used at least US$200 worth of cocaine in the past 30 days Adult ADHD: not assessed	Two-group, parallel arms, randomized, placebo-controlled, double-blind clinical trial Randomization: after eligibility, patients were allocated randomly to placebo or active medication Follow-up length: 56 days Statistical analysis: ITT	Modafinil 200–400 mg/day q.d. Psychotherapy: 16 sessions of CBT	Cocaine use: BE presence in urine three times a week Cocaine craving: BSCS Adverse events: NS	No difference in dropout rate or craving was found Cocaine use was lower with modafinil	3
Margolin *et al.* 1995 [38] Authors' affiliation: university, medical centres and NIDA Study funding: co-funding public and from a private foundation	*n* = 149 Cocaine- and opioid-dependent patients according to DSM-III-TR criteria in methadone maintenance treatment ADHD assessment: NS	Two-group, parallel arms, randomized, placebo-controlled, double-blind, clinical, multi-centre (3 sites) trial Randomization: treatment assignment was performed sequentially and was stratified by the presence of comorbid APD Follow-up length: 84 days Statistical analysis: NS	Bupropion 200–300 mg/day t.i.d. Psychotherapy: group or individual psychotherapy for patients on MMT	Cocaine use: BE presence in urine three times a week Cocaine craving: VAS Adverse events: NS	No difference in dropout rate, cocaine use or craving was found	2

ADHD = attention deficit hyperactivity disorder; AE = adverse events; APD = antisocial personality disorder; BE = benzoylecgonine; b.i.d. = twice a day; BPD = borderline personality disorder; BSCS = Brief Substance Craving Scale; CBT = cognitive behavioral therapy; ITT = intention-to-treat; IR = immediate release; i.v. = intravenous; MMT = methadone maintenance treatment; NA = not assessed; NS = not specified; PP = per protocol; q.d. = once a day; SR = sustained release; SUD = substance use disorder; t.i.d. = threetimes a day; VAS = visual analogue scale. Hash (#) indicates that additional information was requested and obtained from the first author.

Table 2 Baseline characteristics of the patients included in RCCT that have assessed the efficacy of central nervous system stimulants in cocaine-dependent patients. Only those baseline characteristics that have been described in at least 40% of patients included in this meta-analysis are presented.

Sample size	640
Gender	
% female	11.9
Age:	
Mean age	34.9
Race	
% white	48.3
% black	40.9
% other races	10.8
Employment status	
% currently employed	28.6
Length of cocaine use:	
Range of mean lifetime cocaine use (years)	7.7–14.0
Type of cocaine	
% crack	65.3
Cocaine route of use	
% i.n.	12.8
% i.p.	51.4
% i.v.	35.8
Comorbidities	
% opioid dependents	46.9
ADHD	7.6

RCCT = randomized controlled clinical trials; ADHD = attention deficit hyperactivity disorder; i.n. = intranasal; i.p. = intrapulmonary; i.v. = intravenous.

In Table 2, baseline patient characteristics are presented for those trials reporting this information. Gender, age and the proportion of opioid-dependent patients were available from all RCCT, whereas race from six, length of cocaine use and type of cocaine from five and employment status, the cocaine route of use and the proportion of ADHD from four RCCT. RCCT featured mainly male (89.1%), middle-aged (mean: 34.9 years), unemployed patients (71.4%). With regard to the characteristics of cocaine use, the patients were mainly crack users (65.8%) and intrapulmonary (i.p.) route users (51.4%), and only a minority (12.8%) were intranasal (i.n.) cocaine users. It is noteworthy that almost half the included subjects were also opioid-dependent. Most (88.1%) of these dual cocaine and opioid-dependent patients were included in three studies [38,39,45] for which this condition was an inclusion criterion. Three studies [40,42,43] provided no data on cocaine use along the study and were excluded from the main efficacy analysis on this outcome. Nevertheless, estimates of cocaine use along the study could be assessed from the baseline and the final data on cocaine use and were included in an exploratory analysis.

Efficacy and safety

Two studies with dexamphetamine [42,45] and one study with modafinil [46] showed that these drugs decrease cocaine use (Table 1). Nevertheless, no study showed a decrease in the dropout rate compared with placebo. When all the studies were pooled together, no differences in retention (Fig. 3) or cocaine use (Fig. 4a) were found between any single CNS stimulant or all CNS stimulants and placebo. No significant changes in efficacy outcomes were found after withdrawing each CNS stimulant versus placebo comparison once.

An exploratory analysis (Fig. 4b) including also those RCCT reporting baseline and final cocaine use showed a significant superiority of dexamphetamine over placebo on cocaine use [RR (CI) = 0.73 (0.60–0.90)] and of all CNS stimulants pooled together [RR (CI) = 0.87 (0.77–0.99)] with bupropion and without it [RR (CI) = 0.82 (0.71–0.94)].

In Table 3, a summary of cocaine craving outcomes of those trials reporting this information is shown. Only one trial with dexamphetamine [44] showed a decrease of cocaine craving; the rest found no differences with placebo. Unfortunately, craving outcomes could not be meta-analysed due to great heterogeneity: five RCCT reported data on craving, which was assessed by means of four different instruments.

Secondary analysis showed that those trials with superior reporting quality (Jadad scale score ≥ 3) had no different results than those with lower reporting quality (Jadad scale score < 3). Subanalysis of the impact of comorbid adult ADHD on the efficacy of CNS stimulants on cocaine dependence could not be carried out because only one study [43] reported data on that issue.

Although it was not planned initially, a subanalysis was carried out of those studies for which dual cocaine and opioid dependence was an inclusion criterion [38,39,45]. The results did not differ substantially from the main analysis and showed a RR of 0.85 (0.56–1.30) for the dropout rate and 0.86 (0.68–1.09) for cocaine use.

Regarding safety, the most commonly reported adverse events (AE) were sleeping problems, anxiety or jitteriness. The administration of a CNS stimulant, compared to placebo, was associated with a higher AE-induced dropout rate: 15/344 (4.4%) versus 4/296 (1.3%) ($P = 0.03$). The specific AE responsible for patients' dropout were not generally described. No study reported abuse of study medication.

DISCUSSION

The results of this meta-analysis do not support that CNS stimulants are more efficacious than placebo for cocaine

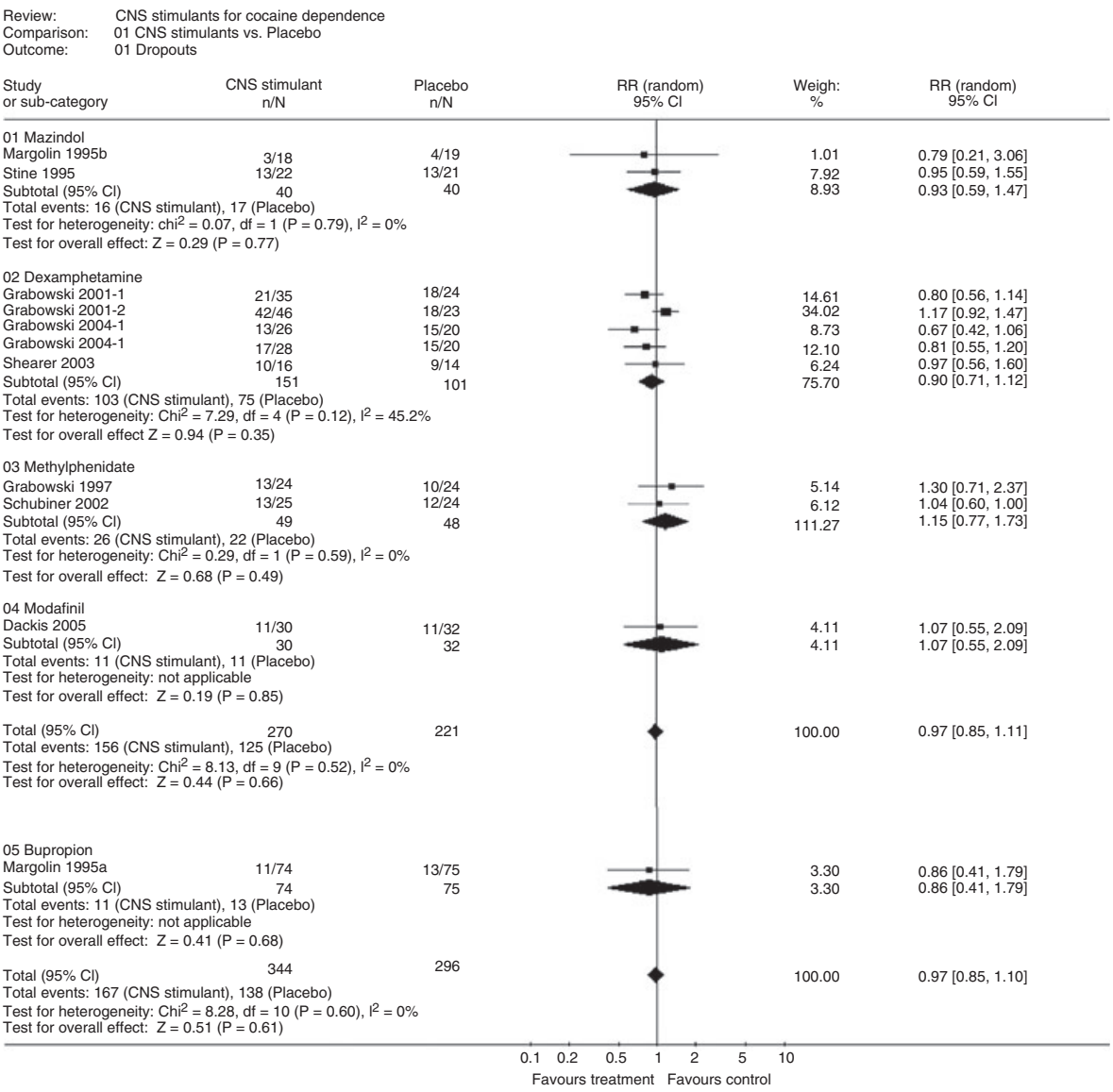

Figure 3 Efficacy of central nervous system stimulants versus placebo on dropout rate

dependence. CNS stimulants did not improve study retention or cocaine use in cocaine-dependent patients. Data on craving could not be meta-analysed due to heterogeneity. One trial with dexamphetamine [44] reported favourable outcomes on craving, whereas the rest found no difference with placebo. Nevertheless, promising results exist, mainly with dexamphetamine and modafinil. It is striking that the efficacy of CNS stimulants has been studied mainly in middle-aged men, long-term and i.p. cocaine users, half of them with comorbid opioid dependence.

Information on adverse drug reactions is too limited to draw conclusions about CNS stimulants toxicity. Dose-dependent, reversible, noradrenalin agonism-related AE were the most commonly reported. No study reported abuse of study medication. A higher AE-related dropout rate has been found with CNS stimulants, but of only 4.4%.

Substitution therapy has proved to be efficacious for heroin [7,8] and nicotine dependence [9]. Although the main outcomes of this meta-analysis do not support that this strategy is efficacious for cocaine dependence, there are data suggesting that these drugs could have some therapeutic role in the treatment of cocaine use that deserve further research. On one hand, dexamphetamine and modafinil show a trend toward a higher efficacy over placebo on cocaine use. Also, the original modafinil study [46] showed a statistically significant beneficial effect on cocaine use. None the less, due to meta-analytical constraints, data were transformed in order to homogenize

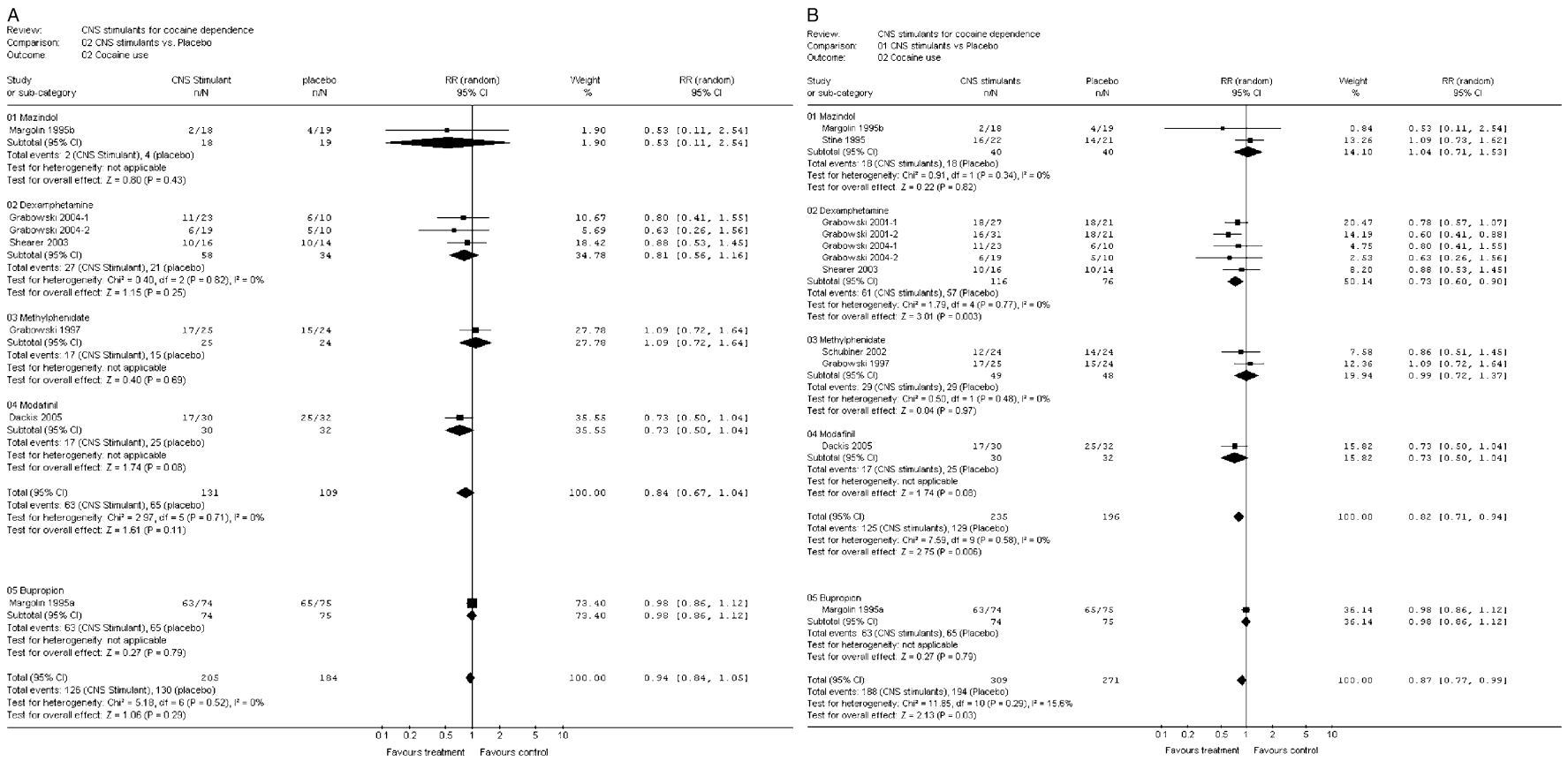

Figure 4 Efficacy of central nervous system stimulants versus placebo on cocaine use assessed by means of urine analysis (UA). (A) Only studies that provided cocaine use as the proportion of positive UA along the study are included. (B) Studies for which indirect estimates of the proportion of positive UA along the study could be calculated are also included

Table 3 Comparison of cocaine craving between central nervous system stimulants and placebo.

				CNS stimulant		*Placebo*		
Reference	*Drug*	*Craving scale*	*Craving outcome*	*Baseline*	*Final*	*Baseline*	*Final*	*P-value*
Margolin *et al.* 1995 [39]	Mazindol	Likert 0–10	Mean craving score along clinical trial		2.12 (2.22)		2.22 (1.91)	
Stine *et al.* 1995 [40]	Mazindol	VAS (5 points)	Basal craving versus final craving	13.0 (1.2)	4.2 (1.6)	13.0 (1.3)	4.3 (2.1)	
Shearer *et al.* 2003 [44]	Dexamphetamine	VAS	Basal craving versus final craving	77	51	77	67	< 0.01
Schubiner *et al.* 2002 [44]	Methylphenidate IR	Tiffany cocaine craving	Basal craving versus final craving	NR	NR	NR	NR	
Dackis *et al.* 2005 [46]	Modafinil	CSSA, BCSC, CCQ		NR	NR	NR	NR	
Margolin *et al.* 1995 [38]	Bupropion	VAS	Basal craving versus final craving	53.7 (27.3)	26.0 (24.6)	56.9 (24.7)	22.8 (24.1)	

BCSC = Brief Substance Craving Scale; CCQ = cocaine craving questionnaire; CSSA = cocaine selective severity assessment; IR = immediate release; VAS = visual analogue scale; NR = not reported.

with the rest of the pooled studies. As a result of this conversion, the data turned into a statistical trend. Moreover, an exploratory analysis, including the three studies for which cocaine use was estimated from the baseline and final cocaine use, shows a 27% reduction of the proportion of BE-positive UA in the group of patients treated with dexamphetamine in comparison with those treated with placebo, and of 13% or 18% with all CNS stimulants, without or with bupropion, respectively.

On the other hand, methodological flaws of the included studies regarding sample size, concomitant interventions and baseline patient features may have made it difficult to prove that CNS stimulants are efficacious. At first, most RCCTs were pilot studies with a small sample size. If the data obtained from the exploratory analysis were used to assess the sample size for a RCCT with CNS stimulants with a power of 80%, a two-tailed *P*-value of 0.05 and a dropout rate of 50% [4], a sample size ranging from 144 to 584 subjects per arm would be necessary. This is higher than the sample size of any included study, thus a lack of power could explain that no efficacy was found. Additionally, some studies included concomitant behavioural therapies which have proved to be efficacious for cocaine dependence [47]. This could have diluted the efficacy of CNS stimulants. This meta-analysis could not assess the impact of these interventions on CNS stimulants efficacy because these interventions were very heterogeneous. Thirdly, baseline patient characteristics (Table 2) show that the sample was biased towards the inclusion of patients with bad prognoses, such as i.v. or i.p. users [48,49], unemployed [50] and patients with comorbid opioid dependence [51]. Also, most studies did not assess the presence of comorbid ADHD, which has been associated with drug use and poor prognosis [52]. Although it was planned initially, the impact of ADHD comorbid disorder could not be studied because ADHD was assessed in only one trial [43]. However, in Grabowski's studies with dexamphetamine, ADHD was an exclusion criterion and they showed a decrease of cocaine use. This highlights the need for assessing the presence of this disorder in future studies.

Regarding study retention, although no CNS stimulant showed to be superior to placebo, it is also true that studies featuring dual heroin- and cocaine-dependent patients [38,39,45] showed a higher retention than the studies including subjects dependent only on cocaine. The explanation is that all dual participants were treated with methadone, which has been shown clearly to increase study retention [53], and the study intervention focused specifically on the treatment of comorbid cocaine dependence. It should be noted that one [45] of these three RCCT with dual heroin and cocaine dependence, in comparison with studies including heroin-dependent patients, showed a lower than expected retention rate,

highlighting that dual heroin–cocaine dependence is a more complex disorder than heroin dependence. Indeed, cocaine use has been associated with poor outcomes of heroin dependence treatment [54,55].

Three studies assessed the efficacy of dexamphetamine for cocaine dependence, two of them showing a decrease in cocaine use [42,45] and one [44] showing no differences with placebo. The use of different dexamphetamine formulations and administration schedule could explain, in part, the difference in their findings. While one study [44] used an immediate release (IR) formulation that was administered once a day in the morning, the other two [42,45] used a twice-a-day sustained-release (SR) formulation, which has a slower onset of action and longer half-life than the IR formulation [56]. As substitution therapy involves the administration of a drug with the same effects but a slower onset of action and longer half-life than the abused drug, it is not strange that those studies using a SR formulation show improved outcomes on cocaine use. An additional explanation for these differences is that Grabowski *et al*.'s studies [42,45] show positive outcomes on cocaine use after withdrawing those participants who dropped out from the study [42] or those who never provided a positive BE urine screen [45], suggesting that dexamphetamine could be efficacious mainly for cocaine-dependent subjects who are using cocaine actively. Finally, differences in baseline sample features could also explain the results of the dexamphetamine RCCT. The study by Shearer *et al*. [44], using IR dexamphetamine, was conducted in a community clinic and featured a extremely marginalized sample, with 45% of sex workers, 55% of participants with a history of criminal activities and 42% facing penal charges, all in all hampering the possibility of proving the efficacy of this drug in cocaine use.

The fact that we have pooled together drugs with notable differences in their mechanisms of action, behavioural effects and classified into different pharmacological groups deserves an explanation. All these drugs, although dissimilar, share common ground and have some behavioural effects in common. At first, all of them, among other mechanisms of action, block dopamine reuptake (mazindol [57], dexamphetamine [58], methylphenidate [59], modafinil [60] and bupropion [61,62]), which has been shown to be responsible for cocaine's reinforcing properties [63,64]. It should be noted that modafinil's affinity for dopamine transporter (DAT), considered essential for its stimulating properties [65,66], seems to be lower than that of other CNS stimulants. Moreover, other mechanisms seem to be involved in its stimulating properties, such as actions on glutamate, gamma-aminobutyric acid, histamine and hypocretin systems [67]. These differences set modafinil into a different group of CNS stimulants from those amphetamine-related ones. Secondly, these drugs have substitutive properties for cocaine and for other prototypical CNS stimulants in discriminative stimulus studies [68–77]. Thirdly, these drugs also share some behavioural effects. Human behavioural studies show that dexamphetamine, methylphenidate and modafinil have CNS-stimulating properties [78–82]. It should be stressed that, whereas dexamphetamine and methylphenidate also have euphorigenic effects, thus having abuse potential [83,84], modafinil does not show this [80–82] and therefore its abuse potential is low [85]. Conversely, there are no behavioural studies in healthy volunteers assessing CNS stimulant properties of mazindol. Nevertheless, in clinical sample studies, mazindol shows an increase in alertness and a decrease in appetite [86,87]. In contrast, bupropion has several behavioural studies showing contradictory results indicating that it has no, or at most few, CNS stimulant properties in humans [88–93] and has shown stimulant properties only in non-human animal studies [94,95]. For this reason, bupropion is not a clear CNS stimulant in humans and, consequently, the polled efficacy analysis is presented with and without bupropion in this meta-analysis.

Finally, in accordance with these pharmacological similarities, most of these drugs have been shown to be effective for the treatment of disorders such as ADHD (methylphenidate [96,97], dexamphetamine [96,97], bupropion [98] and modafinil [99]), fatigue relief, sleepiness, somnolence or narcolepsy (mazindol [86], methylphenidate, dexamphetamine, modafinil [100] and bupropion [101]) and are or have been used for weight loss (mazindol [102], dexamphetamine [103], bupropion [102] and modafinil [104]). Therefore, from a pharmacological viewpoint all these drugs could substitute cocaine in dependent patients leading to a decrease in cocaine use.

The results of this meta-analysis should be interpreted in light of several limitations, some of which are related to the meta-analytical approach. Information bias, leading to an excess of effect because negative studies are not reported, has been controlled by using multiple database sources, hand-searching the bibliographical references of all retrieved RCCT and contacting authors. Heterogeneity among studies is another limitation of meta-analysis. Heterogeneity arises from different sample features and different RCCT designs. The presence or absence of comorbid ADHD and opioid dependence accounts largely for this probable heterogeneity. Although a heterogeneity test found no statistically significant heterogeneity, this test is very specific but not too sensitive. To limit meta-analytical flaws, recommendations from the 'quality of reporting of meta-analyses' (QUOROM) statement [105] have been used to carry out this study.

Data about cocaine use of two RCCT [42,45] are PP. Nevertheless, it should be noted that the reported cause for withdrawing patients and carrying out a PP analysis in these studies does not appear to be related to drug effect, thus bias is unlikely.

Limitations regarding patients' baseline characteristics must be stressed. As stated previously, the sample is over-represented by patients with bad prognoses. The sample consisted of a high rate of i.v. and i.p. users and dual opiod and cocaine addicts. This may have hindered proving the efficacy of CNS stimulants and has limited the external validity of these studies and of this meta-analysis.

Finally, the study variable for cocaine use in this meta-analysis is the proportion of BE-positive UA in each group along the clinical trial. It would have been more powerful to use the mean and standard deviation of the proportion of positive UA for each patient in each group. Nevertheless, cocaine use was reported in this manner in only one study [40]. This highlights the need that future studies should report cocaine use as a continuous variable. If a categorical variable was used, it would be preferable to use a variable such as the proportion of abstinent patients, in order to facilitate understanding and enable comparison across studies [106].

In the context of these limitations, this meta-analysis does not support that CNS stimulants are more efficacious than placebo for the treatment of cocaine dependence. Nevertheless, some promising data, especially with dexamphetamine and modafinil, exist. Hence, it is not surprising that CNS stimulants are currently the group of drugs with most ongoing trials for cocaine dependence [16]. A follow-up meta-analysis with the inclusion of ongoing RCCT is warranted.

CONCLUSION

Many CNS stimulants exist; only five of them have been studied for the treatment of cocaine dependence. This systematic review and meta-analysis does not show that CNS stimulants decrease dropout rate, cocaine use or craving compared to placebo. However, promising results exist for dexamphetamine and modafinil, suggesting the need for further research with this group of drugs.

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ANNEX III

Castells X, Casas M, Pérez-Mañá C, Roncero C, Vidal X, Capellà D. Efficacy of psychostimulant drugs for cocaine dependence. *Cochrane Database Syst Rev* 2010:CD007380.

Efficacy of Psychostimulant Drugs for Cocaine Dependence (Review)

Castells X, Casas M, Pérez-Mañá C, Roncero C, Vidal X, Capellà D

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[Intervention Review]

Efficacy of Psychostimulant Drugs for Cocaine Dependence

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ABSTRACT

Background

Cocaine dependence is an increasingly prevalent disorder for which no medication is approved yet. Likewise opioid for heroin dependence, replacement therapy with psychostimulant could be efficacious for cocaine dependence.

Objectives

To ascertain the efficacy of psychostimulants for cocaine dependence on cocaine use, sustained cocaine abstinence and retention in treatment. The influence of type of drug, comorbid disorders and clinical trial reporting quality over psychostimulants efficacy has also been studied.

Search strategy

MEDLINE, EMBASE, PsycINFO, CENTRAL, references of obtained articles and experts in the field.

Selection criteria

Randomized parallel group controlled clinical trials comparing the efficacy of a psychostimulant against placebo have been included.

Data collection and analysis

Two authors evaluated and extracted data. The Relative Risk (RR) was used to assess dichotomous outcomes except for adverse event (AE) induced dropouts for which the risk difference (RD) was preferred. The Standardized Mean Difference (SMD) was used to assess continuous outcomes. To determine the influence of moderating variables, a stratified analysis was conducted. Funnel plots were drawn to investigate the possibility of publication bias.

Main results

Sixteen studies have been included, which have enrolled 1,345 patients. Seven drugs with psychostimulant effect or metabolized to a psychostimulant have been investigated: bupropion, dexamphetamine, methylphenidate, modafinil, mazindol, methamphetamine and selegiline. Psychostimulants did not reduce cocaine use (SMD 0.11, 95%CI: -0.07 to 0.29), showed a statistical trend over improving sustained cocaine abstinence (RR 1.41, 95%CI: 0.98 to 2.02, p=0.07) and did not improve retention in treatment (RR 0.97, 95%CI:

0.89 to 1.05). The proportion of AE induced dropouts was similar for psychostimulants and placebo (RD 0.01, 95%CI: -0.02 to 0.03). When the type of drug was included as a moderating variable, it was shown that the proportion of patients achieving sustained cocaine abstinence was higher with bupropion and dextroamphetamine, and also with modafinil, at a statistical trend of significance, than with placebo. Nevertheless, no studied drug was efficacious on any of the remaining outcomes. Besides, psychostimulants appeared to increase the proportion of patients achieving sustained cocaine and heroin abstinence amongst methadone maintained dual heroin-cocaine addicts. The main findings did not seem to be influenced by clinical trial reporting quality. No evidence of publication bias was found.

Authors' conclusions

This review found mixed results, therefore evidence of the efficacy of psychostimulants for cocaine dependence is inconclusive. Nevertheless promising results exist for methadone maintained dual heroin-cocaine addicts and for some specific drugs such as dexamphetamine and bupropion.

PLAIN LANGUAGE SUMMARY

Efficacy of Psychostimulant Drugs for Cocaine Dependence

Cocaine dependence is a frequent disorder for which no medication has clearly proved to be efficacious. Substitution therapy involves the replacement of abused drug, which is often illegal, used several times a day, by a legal, orally administered one. A substitutive drug has similar effects to the abused one, but with a lower addictive potential therefore leading to drug abstinence and involving patients to follow medical and psychological assistance. This strategy has proved to be efficacious for heroin and nicotine dependence. In this review we investigated if psychostimulant substitution was efficacious for cocaine dependence. We found that sixteen studies that had enrolled 1,345 patients investigated the efficacy of psychostimulants against placebo for cocaine dependence. Seven drugs with psychostimulant effect or metabolized to a psychostimulant have been investigated: bupropion, dexamphetamine, methylphenidate, modafinil, mazindol, methamphetamine and selegiline. Psychotherapy was provided in all clinical trials. Study length ranged from 6 to 24 weeks. Psychostimulants did not improve cocaine use, had an unclear beneficial effect over sustained cocaine abstinence and were not associated with higher retention in treatment. Psychostimulants did not increase risk of serious adverse events. It was found that psychostimulants could be efficacious for some groups of patients, such as methadone maintained dual heroin-cocaine addicts. Therefore, psychostimulants, though have not proved yet their efficacy for cocaine dependence, deserve further investigation.

BACKGROUND

Cocaine use disorders, including cocaine abuse and cocaine dependence (DSM IV), prevalence is growing and cocaine use related disorders have become a worldwide public health problem. It is estimated that, approximately 1.9 million Americans were currently using cocaine in 2007, with approximately one quarter of that group smoking crack cocaine (SAMSHA 2008). In addition, 1.1 million people used cocaine for the first time during that year, representing an slight increase over the previous 3 years. In the European Union (EU) cocaine use has been uninterruptedly increasing since mid 1990. 3.6% of the EU adult population has used cocaine in their life, being more than 5 % in Spain, Italy, Ireland and the United Kingdom. Use over the past year prevalence is 1.3 % on average, but above 2% in Spain, Italy and the United Kingdom (EMCDDA 2008).

The prevalence of cocaine use and cocaine related disorders is specially high in vulnerable populations such as patients with Attention Deficit/Hyperactivity Disorder (ADHD) or opioid dependence. Thirty five percent of patients with ADHD have a comorbid cocaine abuse (Levin 1998). Besides, cocaine is found as a secondary drug in 25 % of opioid dependents seeking treatment in the EU (EMCDDA 2008) and up to 50% in the United States (Kosten 1987;Kidorf 1993).

Description of the condition

Cocaine use disorders comprise two clinical entities, cocaine abuse and cocaine dependence, which are characterized by continuous cocaine use despite recurring significant physical, psychical and social problems associated with such use (DSM IV). While cocaine abuse is featured by a hazardous cocaine use, cocaine dependence is a compulsive drug use that can result in tolerance or withdrawal (DSM IV).

From biologic point of view, cocaine addiction appears to be featured by a dopaminergic and glutamate dysregulation. Cocaine is a dopamine (DA) and norepinephrine (NE) reuptake inhibitor and thus, it increases DA in the nucleus accumbens. DA release in the nucleus accumbens has been associated with drug reinforcing properties (Koob 1988; Volkow 1997a). With repeated cocaine use a down-regulation of both DA release and DA_2 receptors in striatum (Volkow 1990; Volkow 1996; Volkow 1997b; Volkow 2004) has been observed. The DAergic dysfunction could explain two core features of cocaine dependence: tolerance and withdrawal. Together with a DA dysfunction, a glutamate hyperactivity, mainly at the prefrontal cortex and amygdala, has been shown (Kalivas 2005). It has been proposed that this glutamatergic dysfunction could be involved in the two remaining cocaine dependence characteristics: a compulsive pattern of cocaine use and relapse to cocaine use after a cocaine-free period (Kalivas 2005).

Description of the intervention

Replacement therapy involves the substitution of abused drug, which is often illegal, used parenterally several times a day, by a legal, orally administered one with long half life. A substitutive drug has a similar mechanism of action and behavioral effects to the abused one, but with a lower addictive potential, being able to block drug craving and withdrawal, and leading to drug abstinence and involving patients to follow medical and psychological assistance (Gorelick 2004, Grabowski 2004). This strategy has proved to be efficacious for heroin (Dole 1969; Mattick 2003) and nicotine (Silagy 2004) dependence.

How the intervention might work

CNS stimulants indirectly increase DA and, if administered orally, with long lasting compounds, could normalize the DA dysfunction that features cocaine addiction. During the last decade, replacement therapy with CNS stimulants has been gaining support (Gorelick 2004). Several CNS stimulants have been studied for the treatment of patients with cocaine abuse, some of them showing a comorbid disorder such as Attention Deficit/Hyperactivity Disorder (ADHD) or opioid dependence (Castells 2007).

Why it is important to do this review

Around 50 drugs have been assessed for the treatment of cocaine dependence, but none of them has clearly shown to be efficacious (Kleber 2007), consequently no drug has yet been approved by the FDA or the EMEA for the treatment of cocaine dependence. However, since promising results have been shown with CNS stimulants (Castells 2007), several clinical trials are currently being carried out with these drugs (clinicaltrial.gov).

OBJECTIVES

To assess the efficacy and safety of CNS stimulants for cocaine abuse with and without coexisting comorbidities by means of a meta-analysis in the context of a systematic review.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised parallel group placebo controlled clinical trials were included.

Types of participants

Participants were adults meeting criteria for cocaine abuse or cocaine dependence using DSM criteria, irrespective of the DSM edition. In both disorders, cocaine is chronically misused leading to impairment in functioning. While cocaine abuse is featured by a hazardous cocaine use, cocaine dependence is a compulsive drug use despite related problems. This repeated cocaine use can result in tolerance or withdrawal. Studies enrolling patients with comorbid conditions were also included.

Types of interventions

Experimental intervention: CNS stimulants for cocaine abuse. Because "psychostimulant" or "CNS stimulant" are not terms describing a pharmacological group but a pharmacological effect, there is not a single list of drugs with this effect. For this reason CNS stimulants are classified into several groups, according to their main indication, in drug classification systems such as the Anatomical Therapeutic Chemical (ATC) Classification (ATC 2009) and the American Hospital Formulary Service Pharmacologic-Therapeutic Classification System (AHFS 2009). Consequently, a drug search was performed to obtain a complete list

of drugs with psychostimulant effect. For this purpose, all drugs belonging to groups or subgroups suspected of containing potential psychomotor stimulant drugs were extracted. These pharmacological groups were the N06BA (Centrally acting sympathomimetics), A08AA (Centrally acting anti obesity products), N06BC (Xanthine derived), N06BX (Other psychostimulants and nootropics), N07BA (Drugs used in nicotine dependence) and R03DA (Xanthines) from the ATC Classification; and 12:92 (Miscellaneous autonomic drugs), 28:16.04.92 (Antidepressants, miscellaneous), 28:20.04 (Amphetamines), 28:20.92 (Anorexigenic agents and respiratory and cerebral stimulants, miscellaneous) and 86:16 (Respiratory smooth muscle relaxants) from the AHFS Classification. Furthermore, drugs metabolised to a known psychostimulant such as selegiline were included. The World Anti-Doping Agency (WADA) list and other sources of information in pharmacology and psychopharmacology were reviewed too. From this list of potential CNS stimulants, only those drugs having at least one published study showing a CNS stimulant effect were included in the definitive list of psychostimulants. CNS stimulant effect was defined as an increased CNS activity resulting in fatigue relief, improved performance in simple tasks, increased locomotor activity and anorexia in healthy subjects.

Control intervention: placebo.

Types of outcome measures

Primary outcomes

1. Efficacy on cocaine use assessed by mean (SD) proportion of negative UA across the study per patient.
2. Sustained cocaine abstinence (number of patients who achieved sustained cocaine abstinence).
3. Retention in treatment (number of patients who finished the study).

Secondary outcomes

1. Safety outcomes:

- Number of patients who dropped out the study due to any adverse events (AE).
- Number of patients who abused study medication.
- Number of patients who dropped out the study due to any cardiovascular AE.

2. Secondary efficacy outcomes:

- Self-reported cocaine use.
- Cocaine craving (assessed by a quantitative scale).
- Survival.
- Clinical severity assessed by the Clinical Global Impression.
- Global Activity Functioning
- Anxiety symptoms assessed by a standardised instrument
- Depressive symptoms assessed by a standardised instrument

Only for studies including dual opioid-cocaine abusers:

- Heroin use assessed by mean (SD) proportion of negative UA across the study per patient.
- Sustained heroin abstinence (number of subjects who achieved sustained heroin abstinence).
- Self-reported heroin use.

Only for studies including dual ADHD-cocaine abusers:

- ADHD symptoms severity assessed by a standardised instrument

Search methods for identification of studies

Electronic searches

Relevant randomised trials were identified by searching the following electronic databases:

1. Cochrane Central Register of Controlled Trials (The Cochrane Library 2008, issue 4)
2. MEDLINE (January 1966 to January 2009)
3. EMBASE (January 1988 to January 2009)
4. PsycINFO (1985 to January 2009)

See Appendix 1, Appendix 2, Appendix 3 and Appendix 4 for the search strategies developed for each electronic database.

We searched and identified for ongoing clinical trials and unpublished studies via Internet searches on the following sites:

1. http://www.controlled-trials.com;
2. http://clinicalstudyresults.org;
3. http://centerwatch.com

Searching other resources

Personal Contact

The contact author of all included studies, and experts in the field and pharmaceutical companies were contacted and asked to identify other published, unpublished or ongoing trials.

Citations

1. The reference lists of retrieved studies and relevant review articles were inspected to identify any further studies.
2. For each included study, a citation search were performed in ISI Web of Knowledge to identify any later studies that may have cited it.

All searches included non-English language literature and studies with English abstracts were assessed for inclusion. When considered likely to meet inclusion criteria, studies were translated.

Data collection and analysis

Selection of studies

Abstracts of potentially relevant studies were inspected by two reviewers (XC, CP) and the full article of those studies deemed to be relevant were requested. Where unpublished trials are identified, the coordinators were contacted to request data.

Data extraction and management

Full papers were inspected by two reviewers (XC, CP) using a piloted data extraction sheet. Any disagreement was resolved by consensus or appeal to a third author (DC). In case of missing information, authors were emailed and missing data were requested. A second approach was made if no answer is obtained after one month from the first email.
The following data were extracted:
Study description and funding:

- Author
- Year of publication
- Country
- Authors ascription affiliation: Pharmaceutical industry (Yes/No)
- Study funding: Pharmaceutical industry (Yes/No)

Methods:

- Sequence generation
- Allocation concealment
- Blinding of patients/clinicians/therapists/assessors
- Design: single site/multiple site
- Study length (from randomisation to treatment completion)
- Number of participants
- Handling of drop-outs (ITT vs. PP)
- Instruments administered to assess study outcomes.

Participants:

- Inclusion/Exclusion criteria
- Gender
- Age (Mean, SD)
- Race (% Caucasian, % Afro-American, % other)
- Employment status (% unemployed)
- Comorbid disorders (% with comorbid psychiatric disorders)

Intervention:

- Type of CNS stimulant
- Dose
- Pharmaceutical presentation
- Assessment of compliance (method used to assess treatment compliance)
- Adjunctive psychological interventions (description of the adjunctive psychological interventions)

Outcomes:

- Cocaine use by means of urine screen (mean (SD) of the proportion of cocaine-free UA across the study per patient)
- Sustained cocaine abstinence. The number of patients achieving sustained cocaine abstinence assessed with UA was extracted irrespective of the abstinence length definition used.
- Self-reported cocaine use (mean (SD) days of cocaine use across the study)
- Heroin use by means of urine screen (mean (SD) of the proportion of heroin-free UA across the study per patient)
- Sustained heroin abstinence. The number of patients achieving sustained heroin abstinence assessed with UA was extracted irrespective of the abstinence length definition used.
- Self-reported heroin use (mean (SD) days of heroin use across the study)
- Cocaine craving (mean (SD) cocaine craving score at study conclusion)
- ADHD severity (mean ADHD (SD) cocaine craving score at study conclusion and % of patients achieving a 30% decrease in the ADHD severity score)
- Clinical impression (% patients achieving an ICG score of 1 or 2 at study conclusion)
- Anxiety symptoms severity (mean (SD) cocaine anxiety score at study conclusion)
- Depressive symptoms severity (mean (SD) cocaine depression score at study conclusion)
- Patients who dropped out due to adverse events (% patients who dropped out due to any adverse event, % patients who dropped out due to CV adverse events)
- Number of patients who abused study medication
- Number of patients who finished the study

Assessment of risk of bias in included studies

The risk of bias assessment for RCTs in this review was performed using the 5 criteria recommended by the Cochrane Handbbok (Higgins 2008). The recommended approach for assessing risk of bias in studies included in Cochrane Review is a two-part tool, addressing five specific domains (namely sequence generation, allocation concealment, blinding, incomplete outcome data, and other issues). The first part of the tool involves describing what was reported to have happened in the study. The second part of the tool involves assigning a judgement relating to the risk of bias for that entry. This is achieved by answering a pre-specified question about the adequacy of the study in relation to the entry, such that a judgement of "Yes" indicates low risk of bias, "No" indicates high risk of bias, and "Unclear" indicates unclear or unknown risk of bias. To make these judgments we used the criteria indicated by the handbook adapted to the addiction field. See Table 1 for details.

Table 1. Criteria for Risk of bias in RCTs

	Item	Judgment	Description
	Was the method of randomisation adequate?	Yes	The investigators describe a random component in the sequence generation process such as: random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization
		No	The investigators describe a non-random component in the sequence generation process such as: odd or even date of birth; date (or day) of admission; hospital or clinic record number; alternation; judgement of the clinician; results of a laboratory test or a series of tests; availability of the intervention
		Unclear	Insufficient information about the sequence generation process to permit judgement of 'Yes' or 'No'.
2	Was the treatment allocation concealed?	Yes	Investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based, and pharmacy-controlled, randomization); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.
		No	Investigators enrolling participants could possibly foresee assignments because one of the following method was used: open random allocation schedule (e.g. a list of random numbers); assignment envelopes without appropriate safeguards (e.g. if envelopes were unsealed or non opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
		Unclear	Insufficient information to permit judgement of 'Yes' or 'No'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement
3	Was knowledge of the allocated interventions adequately prevented during the study? (blinding of patients, provider, outcome assessor) Objective outcomes	Yes	Blinding of participants, providers and outcome assessor and unlikely that the blinding could have been broken; Either participants or providers were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias. No blinding, but the objective outcome measurement are not likely to be influenced by lack of blinding
4	Was knowledge of the allocated interventions adequately prevented during the study? (blinding of patients, provider, outcome assessor)	Yes	Blinding of participants, providers and outcome assessor and unlikely that the blinding could have been broken; Either participants or providers were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce

Table 1. Criteria for Risk of bias in RCTs (*Continued*)

	Subjective outcomes		bias.
		No	No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding; Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken; Either participants or outcome assessor were not blinded, and the non-blinding of others likely to introduce bias
		Unclear	Insufficient information to permit judgement of 'Yes' or 'No';
5	Were incomplete outcome data adequately addressed? For all outcomes except retention in treatment or drop out	Yes	No missing outcome data; Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; Missing data have been imputed using appropriate methods All randomised patients are reported/analysed in the group they were allocated to by randomisation irrespective of non-compliance and co-interventions (intention to treat)
		No	Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation;
		Unclear	Insufficient reporting of attrition/exclusions to permit judgement of 'Yes' or 'No' (e.g. number randomised not stated, no reasons for missing data provided; number of drop out not reported for each group);
	Was the study apparently free of other problems that could put it at risk of bias	Yes	The study appears to be free of other sources of bias.

Table 1. Criteria for Risk of bias in RCTs (*Continued*)

		NO	There is at least one important risk of bias. For example, the study: Had a potential source of bias related to the specific study design used; or Stopped early due to some data-dependent process (including a formal-stopping rule); or Had extreme baseline imbalance; or Has been claimed to have been fraudulent; or Had some other problem.
		Unclear	There may be a risk of bias, but there is either: Insufficient information to assess whether an important risk of bias exists; or Insufficient rationale or evidence that an identified problem will introduce bias.

The domains of sequence generation and allocation concealment (avoidance of selection bias) will be addressed in the tool by a single entry for each study.

Blinding of participants, personnel and outcome assessor (avoidance of performance bias and detection bias) will be considered separately for objective outcomes (e.g. drop out, use of substance of abuse measured by urine-analysis, subjects relapsed at the end of follow up, subjects engaged in further treatments) and subjective outcomes (e.g. duration and severity of signs and symptoms of withdrawal, patient self-reported use of substance, side effects, social functioning as integration at school or at work, family relationship).

Incomplete outcome data (avoidance of attrition bias) will be considered for all outcomes except for the drop out from the treatment, which is very often the primary outcome measure in trials on addiction. It will be assessed separately for results at the end of the study period and for results at follow up

Measures of treatment effect

Treatment effect measures were introduced to RevMan 5.0 to be pooled together. Three different measures of treatment effect were calculated:

1. Count data, such as the efficacy on drug use, were treated as continuous ones. We extracted the mean (SD) of the proportion of drug free-UA over the planned number of UA per patient. We did not compare the proportion of negative urinalysis between active intervention and placebo, but the mean (SD) of the proportion of drug free-UA across the study with active treatment against the mean (SD) of the proportion of drug free-UA across the study with Placebo. The standardized mean difference (SMD) was calculated for each comparison to allow combination.

2. For categorical efficacy outcomes, such as sustained drug abstinence, the relative risk (RR) was calculated for each comparison.

3. For categorical safety outcomes, such as the number of patients who dropped out the study due to any AE, the risk difference (RD) was calculated. RD was preferred to RR because several studies had 0 events for both the active and control interventions, therefore preventing us from calculating the RR for these studies, which would result in an overestimation of the intervention effect on AE-induced dropouts.

95% confidence intervals (95%CI) were calculated for each measure of treatment effect.

Unit of analysis issues

Not applicable because cross-over clinical trials and cluster trial were not included.

Dealing with missing data

The ITT sample size was used as denominator for categorical variables such as the number of patients achieving sustained cocaine abstinence.

For continuous data, the sample size used in the calculations of the mean and SD was entered into RevMan 5.0.

No imputations was used to deal with missing data.

Assessment of heterogeneity

Heterogeneity was investigated by means of the I^2 and chi^2 test for heterogeneity.

Assessment of reporting biases

Funnel plots were drawn to investigate any relationship between effect size and study precision (closely related to sample size). Such a relationship could be due to publication or related biases or due to systematic differences between small and large studies. If a relationship was identified, clinical diversity of the studies was further examined as a possible explanation (Egger 1997).
Besides, if a a statistically significant result is found, the number of negative studies with an average sample size needed to neutralize this effect was calculated.

Data synthesis

Weighted averages and 95% confidence intervals (CI) were calculated by means of the random and the fixed effects model when $I^2 > 0$ and $I^2 = 0$, respectively.

Subgroup analysis and investigation of heterogeneity

Irrespective of statistical heterogeneity is found, the following subgroup analysis were planned.

1. Type of CNS stimulant: amphetamine derivative, bupropion, modafinil,...
2. Clinical definition of cocaine use disorder: are cocaine abusers included? (Yes vs. No)
3. Comorbidities: the presence of a comorbidity (opioid dependence, ADHD) was an inclusion criteria (Yes vs. No)
4. Study quality and risk of bias: High risk of bias vs. Intermediate or Low.
5. Type of administered scales: self vs. hetero-administered.
6. Single site vs. multiple sites.
7. Funding: with vs. without pharmaceutical industry funding.

Subgroup analyses were performed only when results from at least 2 studies were available.
The analysis of the influence of the type of administered scale was not finally performed because there were too few studies reporting outcomes for which this subanalysis was suitable (depressive symptoms and ADHD severity).
The analysis of the impact of the source of funding was neither performed because all studies were publicly funded and pharmaceutical industry funding only involved the supply of study medication in few studies.

Sensitivity analysis

A sensitivity analysis was carried out for safety outcomes. RR was calculated instead of RD, which was used in the primary analysis.

RESULTS

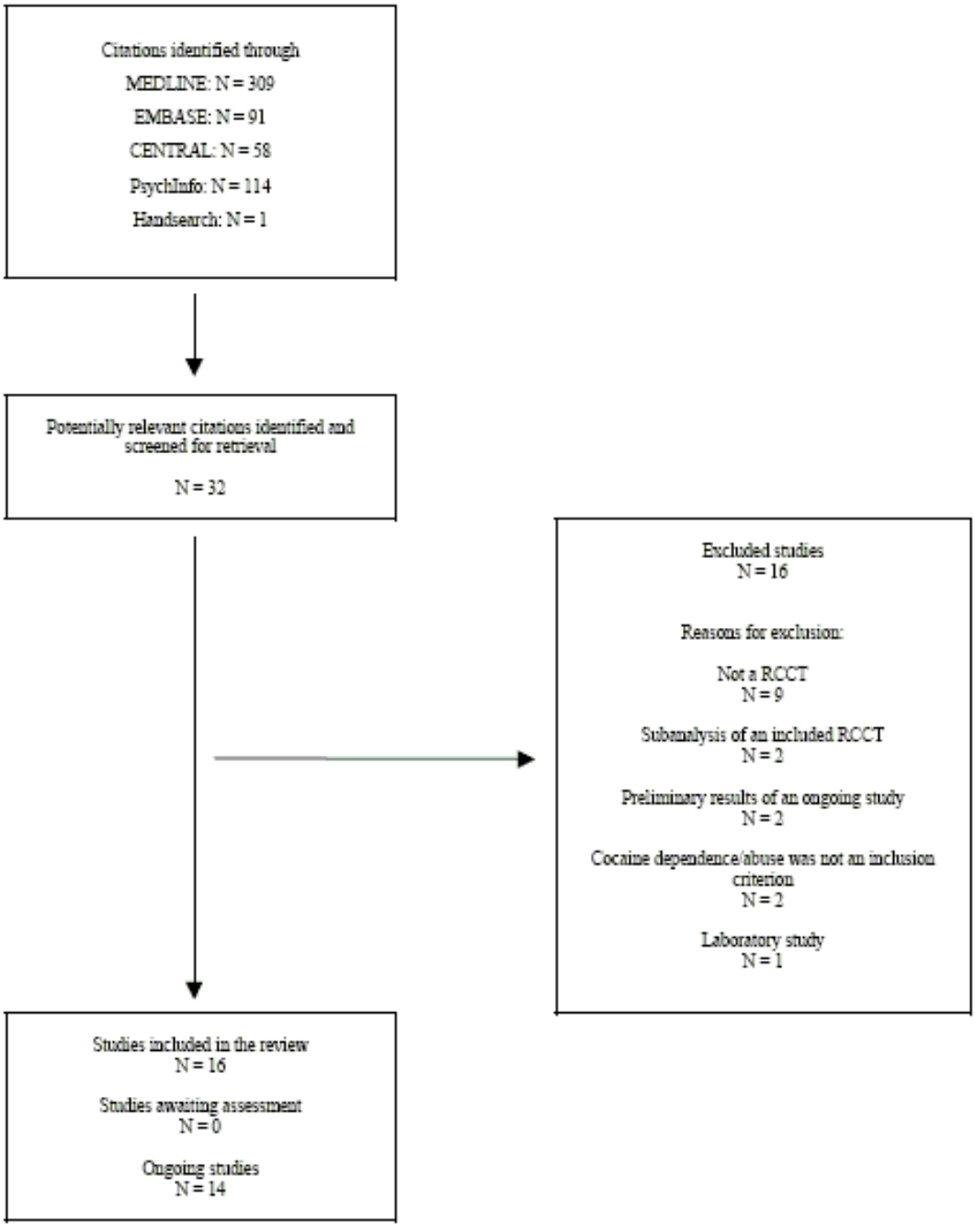
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

Figure 1 shows the flow chart of the studies included in this review. Full text was inspected for 32 studies of which 16 were excluded because did not meet inclusion criteria. Sixteen studies have been included in this review. Fourteen clinical trials were still ongoing.

Figure 1. Flow chart for selection of studies



Included studies

Sixteen studies met the inclusion criteria of this review. A psychostimulant drug was the investigated intervention in all studies but one that had a factorial design and also assessed the efficacy of a behavioral intervention. All studies were conducted by university researchers and pharmaceutical industry helped at funding 7 (43.8%) of them. (A detailed description of study characteristics can be found in Table 2)

Table 2. Baseline characteristics of the patients included in the clinical trials of the meta-analysis

Sample size (n)	1,345
Gender % female	26.2
Age Mean age	37.4
Race % Caucasian % Afro-American % Other	41.5 44.6 13.9
Employment status % currently employed	38.2
Days of cocaine use/month Range	11-30
Lenght of cocaine use Range of mean lifetime cocaine use (years)	7.7-16.5
Route of cocaine use % intranasal % intrapulmonary % intravenous	16.8 66.8 16.4
Comorbidities % opioid dependent % ADHD	49.3 32.2

Baseline patient characteristics are presented for those trials reporting this information. Gender and age were available for all studies, whereas race from 13 studies, opioid dependence from 12, ADHD from 7, lifetime cocaine use from 8, days of cocaine use in a month from 7 and employment and route of cocaine use in 6.

Patients

These studies randomised 1,345 patients, mostly middle age unemployed men. Slightly more than 40% of patients were Caucasian or Afro-American. Mean life-time cocaine use ranged from 7.7 to 16.5 years and the most common route of cocaine use was pulmonary. Most participants had a dual disorder. One half had a comorbid opioid dependence and one third a comorbid ADHD. Patients with dual alcohol and cocaine dependence were excluded in the available studies.

Interventions and settings

Seven drugs with psychostimulant effect or metabolized to a psychostimulant were studied, namely bupropion in 3 studies (Margolin 1995 a, Poling 2006, Shoptaw 2008), dexamphetamine in 3 (Grabowski 2001, Grabowski 2004, Shearer 2003), methylphenidate in 3 (Grabowski 1997, Levin 2007, Schubiner 2002), modafinil in 1 (Dackis 2005), mazindol in 4 (Margolin 1995 b, Margolin 1997, Perry 2004, Stine 1995), methamphetamine in 1 (Mooney 2009) and selegiline in 1 study (Elkashef 2006).

Psychotherapy was provided in addition to the studied intervention in all studies. Cognitive behavioral therapy (CBT) was provided in 6 studies, counselling in 5, CBT + counselling in 1, CBT + contingency management (CM) in 1, modified CBT + motivational intervention in 1 and case management + behavioral contingency + group psychotherapy in 1.

Ten studies were single site and 4 multiple site. All studies were conducted in the US except 1 that was performed in Australia (Shearer 2003).

Study length ranged from 6 to 24 weeks with an average length of 13.2 weeks.

Excluded studies

Sixteen studies were excluded from the review (See table characteristics of the excluded studies and figure 3). Nine (56.3%) of them were not RCT, 2 (12.5%) were subanalyses of already included studies, in 2 cocaine dependence/abuse was not an inclusion criterion and 1 (6.3%) was a laboratory study without outpatient follow-up.

Risk of bias in included studies

A comprehensive description of the risk of bias for each study can be found in the table "characteristics of the included studies". This information is summarized in Figure 2 and Figure 3.

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

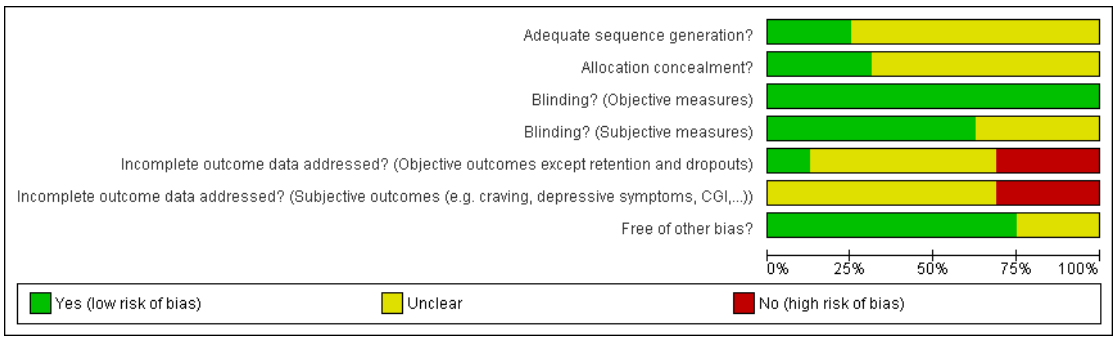
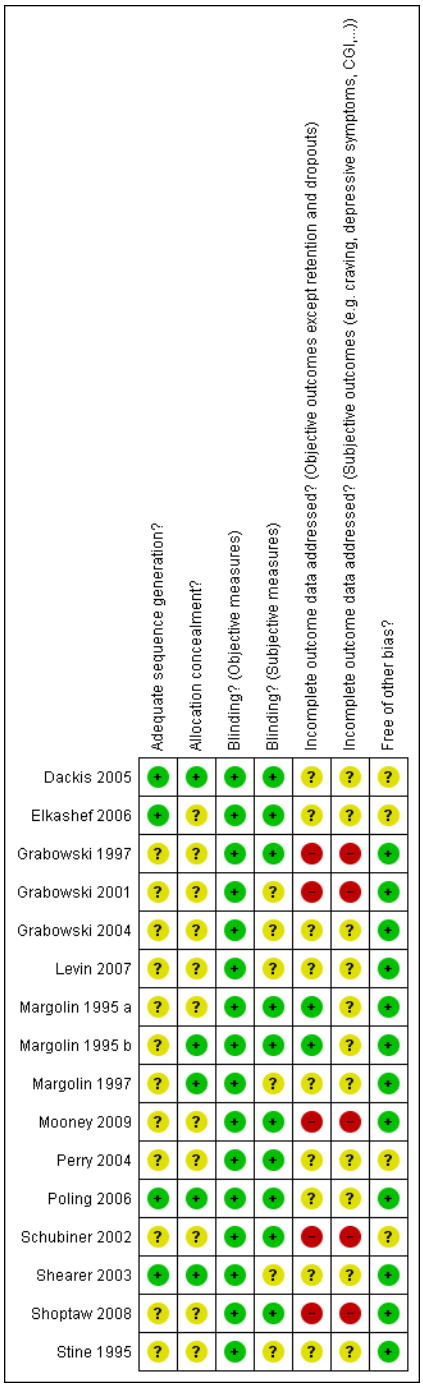


Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Sequence generation

Four studies had an adequate sequence generation (Dackis 2005, Elkashef 2006, Poling 2006, Shearer 2003), and it was unclear for the remaining.

Allocation

Allocation concealment was deemed adequate in 5 studies (Dackis 2005, Margolin 1995 b, Margolin 1997, Shearer 2003), and it was unclear for the remaining.

Blinding

Blinding of objective measures deemed suitable for all studies and for subjective outcomes it was suitable for 10 studies (Dackis 2005; Elkashef 2006; Grabowski 1997; Margolin 1995 a; Margolin 1995 b; Mooney 2009; Perry 2004; Poling 2006; Schubiner 2002; Shoptaw 2008).

Incomplete outcome data

Attrition was high in most studies. In such instance, no statistical method appears to guarantee unbiased results. Only two studies (Margolin 1995 a, Margolin 1995 b) whose attrition was low seemed to be free of bias caused by outcome data incompleteness.

Other potential sources of bias

Eleven studies were free of other bias. One study (Schubiner 2002) excluded patients from the analysis and three (Dackis 2005, Elkashef 2006, Perry 2004) had unbalanced baseline patient characteristics and were considered to have an unclear risk of bias.

Effects of interventions

Primary results are shown in Figures 4 to 6. Secondary results are shown in Figures 7-29.

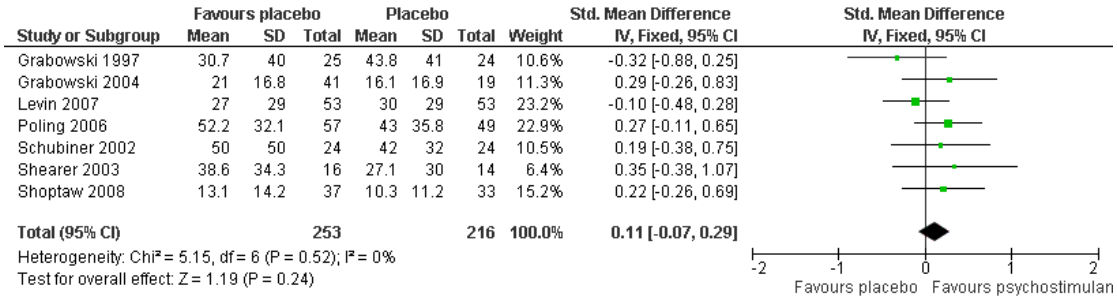
Primary outcomes

Cocaine use assessed by the mean (SD) of the proportion of cocaine-free UA across the study per patient:

(01) Any psychostimulant vs. placebo

Seven studies (Grabowski 1997, Grabowski 2004, Levin 2007, Poling 2006, Schubiner 2002, Shearer 2003, Shoptaw 2008), 469 patients, see comparison 01, outcome 01, Figure 4, SMD 0.11, 95%CI: -0.07 to 0.29, this result was not statistically significant. No heterogeneity was found.

Figure 4. Forest plot of comparison: 1 Psychostimulants vs. Placebo: Primary analysis, outcome: 1.1 Cocaine use by means of urine screen.

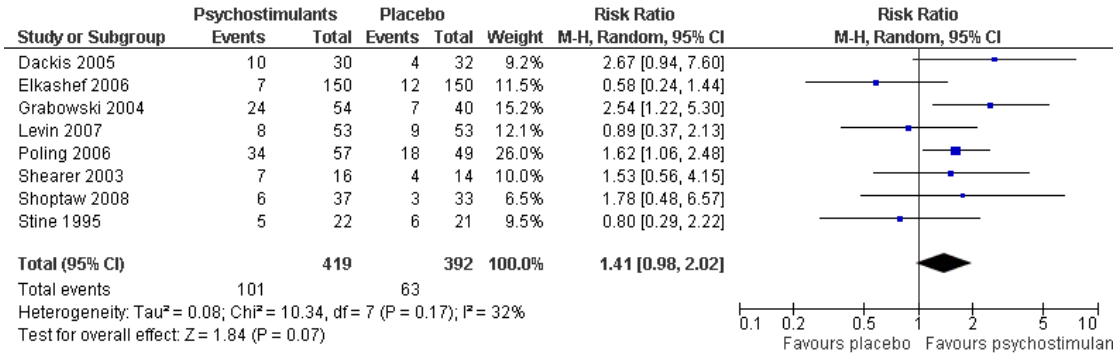


Sustained cocaine abstinence:

(01) Any psychostimulant vs. placebo

Eight studies (Dackis 2005, Elkashef 2006, Grabowski 2004, Levin 2007, Poling 2006, Shearer 2003, Shoptaw 2008, Stine 1995), 811 patients, see comparison 01, outcome 02, Figure 5, RR 1.41, 95%CI: 0.98 to 2.02, this result showed a statistical trend of significance (p=0.07). Moderate heterogeneity was found (I^2 = 32%).

Figure 5. Forest plot of comparison: 1 Psychostimulants vs. Placebo: Primary analysis, outcome: 1.2 Sustained cocaine abstinence.

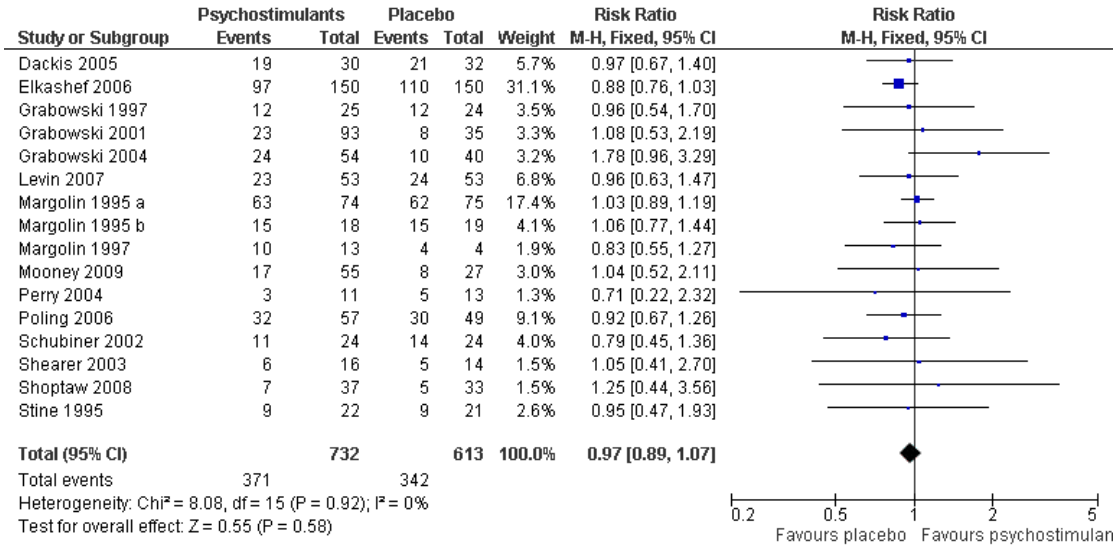


Number of patients who finished the study (Retention in treatment):

(01) Any psychostimulant vs. placebo

This outcome was available from all studies, 1,345 patients, see comparison 01, outcome 03, Figure 6, RR 0.97, 95%CI: 0.89 to 1.05, this result was not statistically significant. No heterogeneity was found.

Figure 6. Forest plot of comparison: 1 Psychostimulants vs. Placebo: Primary analysis, outcome: 1.3 Number of patients who finished the study (retention).



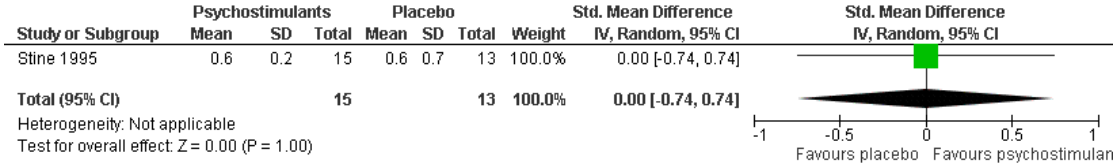
Secondary outcomes

Self reported cocaine use:

(01) Any psychostimulant vs. placebo

One study reported this outcome (Stine 1995), 28 participants, see comparison 01, outcome 04, Figure 7, SMD 0.00, 95%CI: -0.74 to 0.74, this result was not statistically significant.

Figure 7. Forest plot of comparison: 1 Psychostimulants vs. Placebo: Primary analysis, outcome: 1.4 Self-reported cocaine use.

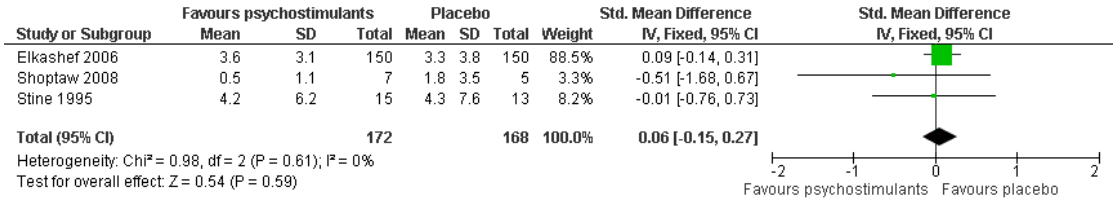


Cocaine craving:

(01) Any psychostimulant vs. placebo

This outcome was available from 3 studies (Elkashef 2006, Shoptaw 2008, Stine 1995), 340 patients, see comparison 01, outcome 05, Figure 8, SMD 0.06, 95%CI: -0.15 to 0.27, this result was not statistically significant. No heterogeneity was found.

Figure 8. Forest plot of comparison: 1 Psychostimulants vs. Placebo: Primary analysis, outcome: 1.5 Cocaine craving.



Survival:

(01) Any psychostimulant vs. placebo

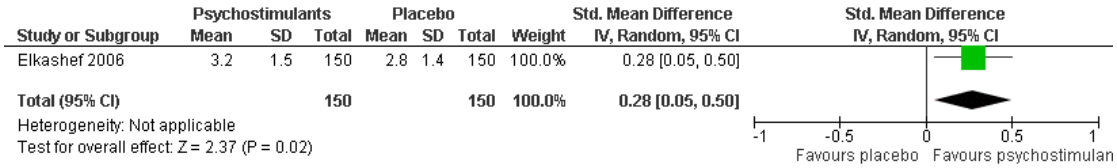
This outcome was not available from any study and could not be analyzed.

Addiction severity (Patient-rated CGI-Severity Scale):

(01) Any psychostimulant vs. placebo

One study (Elkashef 2006), 300 participants, see comparison 01, outcome 06, Figure 9, SMD 0.28, 95%CI: 0.05 to 0.50, this result was statistically significant (p=0.02).

Figure 9. Forest plot of comparison: 1 Psychostimulants vs. Placebo: Primary analysis, outcome: 1.7 CGI patient at the end.

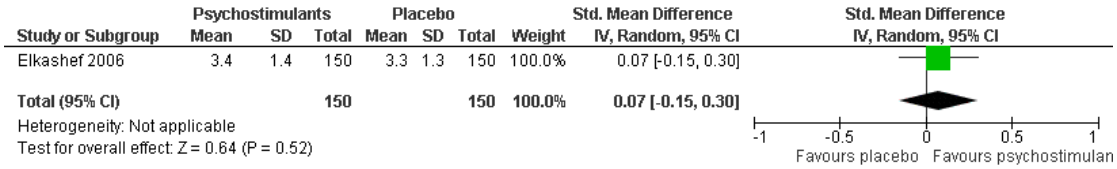


Addiction severity (Investigator-rated CGI-Severity Scale):

(01) Any psychostimulant vs. placebo

One study (Elkashef 2006), 300 participants, see comparison 01, outcome 07, Figure 10, SMD 0.07, 95%CI: -0.15 to 0.30, this result was not statistically significant.

Figure 10. Forest plot of comparison: 1 Psychostimulants vs. Placebo: Primary analysis, outcome: 1.8 CGI investigator at the end.

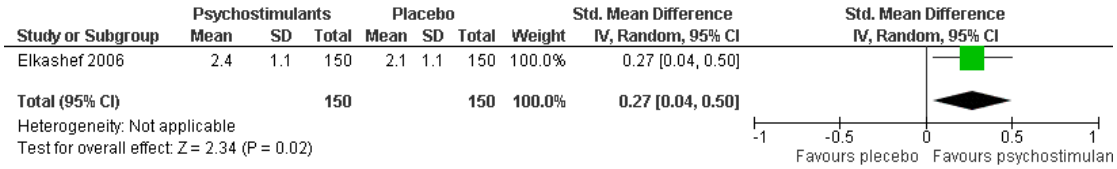


Addiction severity improvement (Patient-rated CGI-Improvement Scale):

(01) Any psychostimulant vs. placebo

One study (Elkashef 2006), 300 participants, see comparison 01, outcome 08, Figure 11, SMD 0.27, 95%CI: 0.04 to 0.50, this result was statistically significant (p=0.02).

Figure 11. Forest plot of comparison: 1 Psychostimulants vs. Placebo: Primary analysis, outcome: 1.9 CGI patient change.

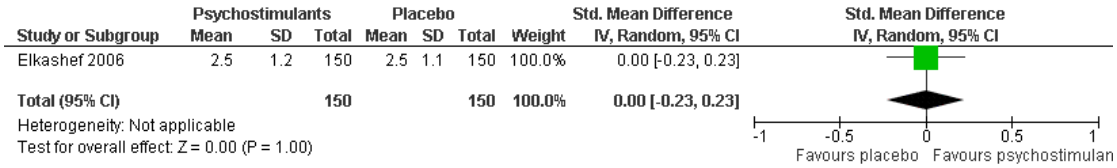


Addiction severity improvement (Investigator-rated CGI-Improvement Scale):

(01) Any psychostimulant vs. placebo

One study (Elkashef 2006), 300 participants, see comparison 01, outcome 09, Figure 12, SMD 0.00, 95%CI: -0.23 to 0.23, this result was not statistically significant.

Figure 12. Forest plot of comparison: 1 Psychostimulants vs. Placebo: Primary analysis, outcome: 1.10 CGI investigator change.

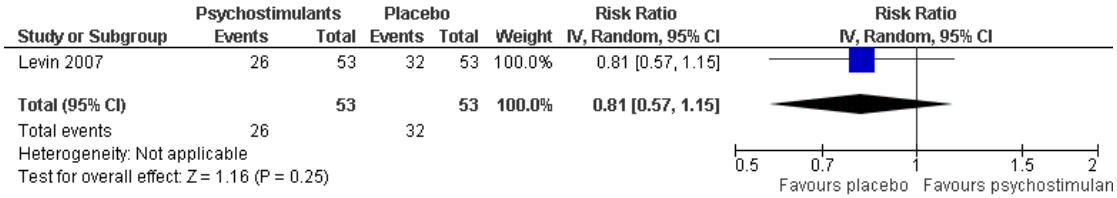


Substantial addiction severity improvement (Investigator-rated CGI-Improvement Scale = 1 or 2):

(01) Any psychostimulant vs. placebo

One study (Levin 2007), 106 participants, see comparison 01, outcome 10, Figure 13, RR 0.81, 95%CI: 0.57 to 1.15, this result was not statistically significant.

Figure 13. Forest plot of comparison: 1 Psychostimulants vs. Placebo: Primary analysis, outcome: 1.11 CGI investigator improvement =1or 2.



Global activity functioning:

(01) Any psychostimulant vs. placebo

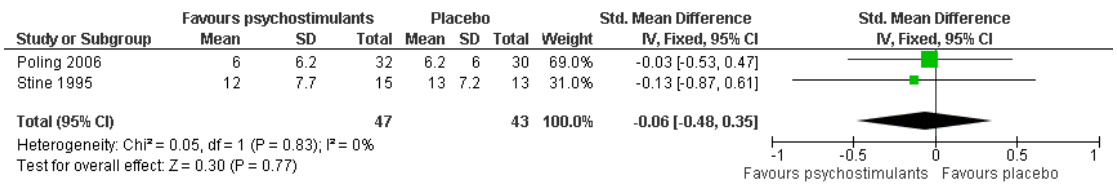
This outcome was not available from any study and could not be analyzed.

Depressive symptoms:

(01) Any psychostimulant vs. placebo

Two studies (Poling 2006, Stine 1995), 90 participants, see comparison 01, outcome 11, Figure 14, SMD -0.06, 95%CI: -0.48 to 0.35, this result was not statistically significant. No heterogeneity was found.

Figure 14. Forest plot of comparison: 1 Psychostimulants vs. Placebo: Primary analysis, outcome: 1.14 Depressive symptoms severity.

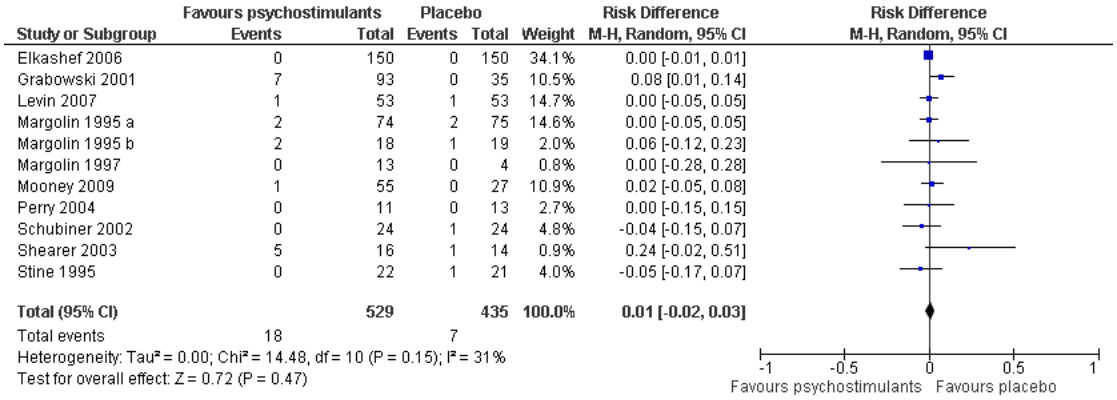


Dropouts due to any adverse event:

(01) Any psychostimulant vs. placebo

Eleven studies (Elkashef 2006, Grabowski 2001, Levin 2007, Margolin 1995 a, Margolin 1995 b, Margolin 1997, Mooney 2009, Perry 2004, Schubiner 2002, Shearer 2003, Stine 1995), 964 participants, see comparison 01, outcome 12, Figure 15, RD 0.01, 95%CI: -0.02 to 0.03, this result was not statistically significant. Moderate heterogeneity was found (I^2 = 31%).

Figure 15. Forest plot of comparison: 1 Psychostimulants vs. Placebo: Primary analysis, outcome: 1.15 Patients dropped out due to any adverse events.

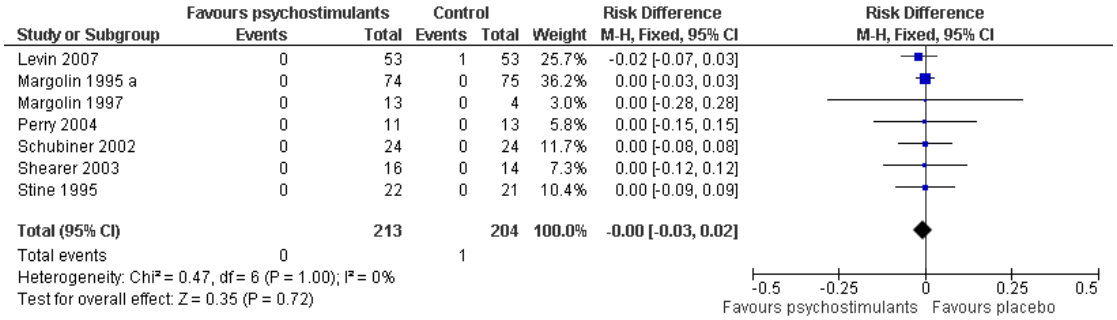


Dropouts due to CV adverse events:

(01) Any psychostimulant vs. placebo

Seven studies (Levin 2007, Margolin 1995 a, Margolin 1997, Perry 2004, Schubiner 2002, Shearer 2003, Stine 1995), 417 participants, see comparison 01, outcome 13, Figure 16, RD -0.00, 95%CI: -0.03 to 0.02, this result was not statistically significant. No heterogeneity was found.

Figure 16. Forest plot of comparison: 1 Psychostimulants vs. Placebo: Primary analysis, outcome: 1.16 Patients dropped out due to cardiovascular adverse events.



Medication abuse:

(01) Any psychostimulant vs. placebo

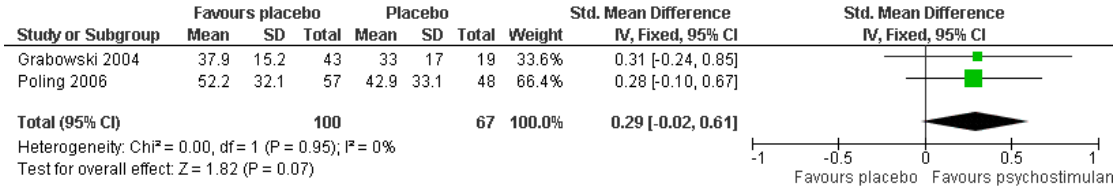
This outcome was not available from any study and could not be analysed.

Heroin use assessed by the mean (SD) of the proportion of heroin-free UA across the study per patient:

(01) Any psychostimulant vs. placebo

Two studies (Grabowski 2004, Poling 2006), 167 participants, see comparison 01, outcome 14, Figure 17, SMD 0.29, 95%CI: -0.02 to 0.61, this result showed a statistical trend of significance (p=0.07). No heterogeneity was found.

Figure 17. Forest plot of comparison: 1 Psychostimulants vs. Placebo: Primary analysis, outcome: 1.18 Heroin use by means of urine screen.

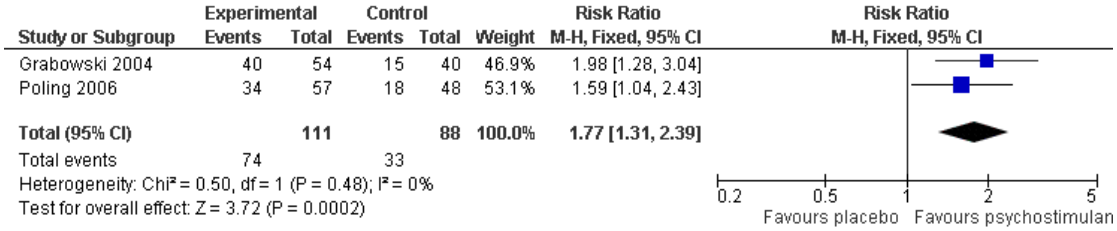


Sustained heroin abstinence:

(01) Any psychostimulant vs. placebo

Two studies (Grabowski 2004, Poling 2006), 199 participants, see comparison 01, outcome 15, Figure 18, RR 1.77, 95%CI: 1.31 to 2.39, this result was statistically significant (p=0.0002). No heterogeneity was found.

Figure 18. Forest plot of comparison: 1 Psychostimulants vs. Placebo: Primary analysis, outcome: 1.19 Sustained heroin abstinence.



Self-reported heroin use:

(01) Any psychostimulant vs. placebo

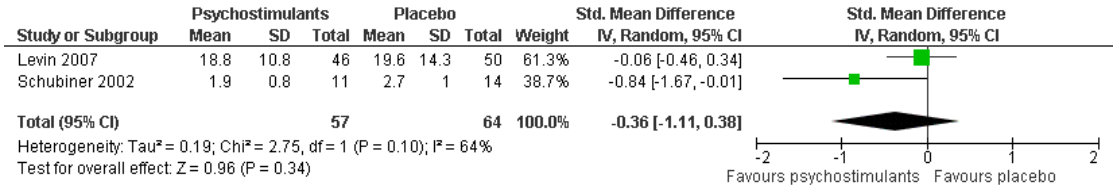
This outcome was not available from any study and could not be analyzed.

ADHD severity:

(01) Any psychostimulant vs. placebo

Two studies (Levin 2007, Schubiner 2002), 121 participants, see comparison 01, outcome 16, Figure 19, SMD -0.36, 95%CI: -1.11 to 0.38, this result was not statistically significant. Substantial heterogeneity was found (I^2 = 64%).

Figure 19. Forest plot of comparison: 1 Psychostimulants vs. Placebo: Primary analysis, outcome: 1.21 ADHD severity.



Subgroup analyses

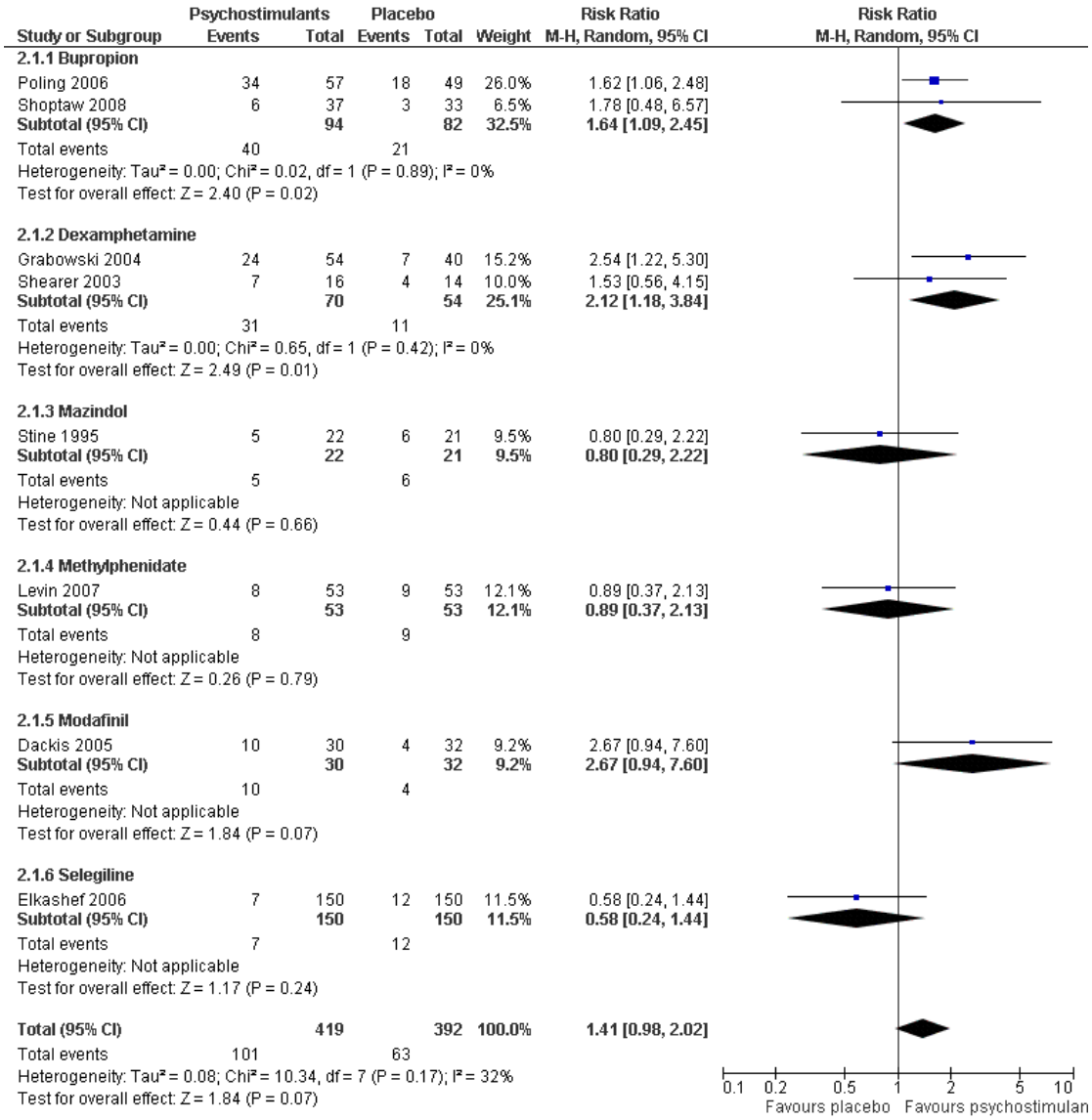
Subgroup analysis are reported for the outcome "Sustained cocaine abstinence" because this was the only primary outcome for which some statistical heterogeneity was found (I^2=32%), therefore meriting further analysis to investigate the influence of moderating variables. The remaining subgroup analysis were conducted and showed no difference between subgroups.

Sustained cocaine abstinence:

(01) Sustained cocaine abstinence:

Subcategory 01: bupropion vs. placebo, two studies (Poling 2006, Shoptaw 2008), 176 patients, see comparison 02, outcome 01, subcategory 01, Figure 20, RR 1.64, 95%CI: 1.09 to 2.45, this result was statistically significant. No heterogeneity was found.

Figure 20. Forest plot of comparison: 2 Subgroup analysis: Sustained cocaine abstinence, outcome: 2.1 Type of drug.



Subcategory 02: dexamphetamine vs. placebo, two studies (Grabowski 2004, Shearer 2003), 124 patients, see comparison 02, outcome 01, subcategory 02, Figure 20, RR 2,12, 95%CI: 1,18 to 3,84, this result was statistically significant.

Subcategory 03: mazindol vs. placebo, one study (Stine 1995), 43 patients, see comparison 02, outcome 01, subcategory 03, Figure 20, RR 0.80, 95%CI: 0.29 to 2.22, this result was not statistically significant.

Subcategory 04: methylphenidate vs. placebo, one study (Levin 2007), 106 patients, see comparison 02, outcome 01, subcategory 04, Figure 20, RR 0,89, 95%CI: 0,37 to 2,13, this result was not statistically significant.

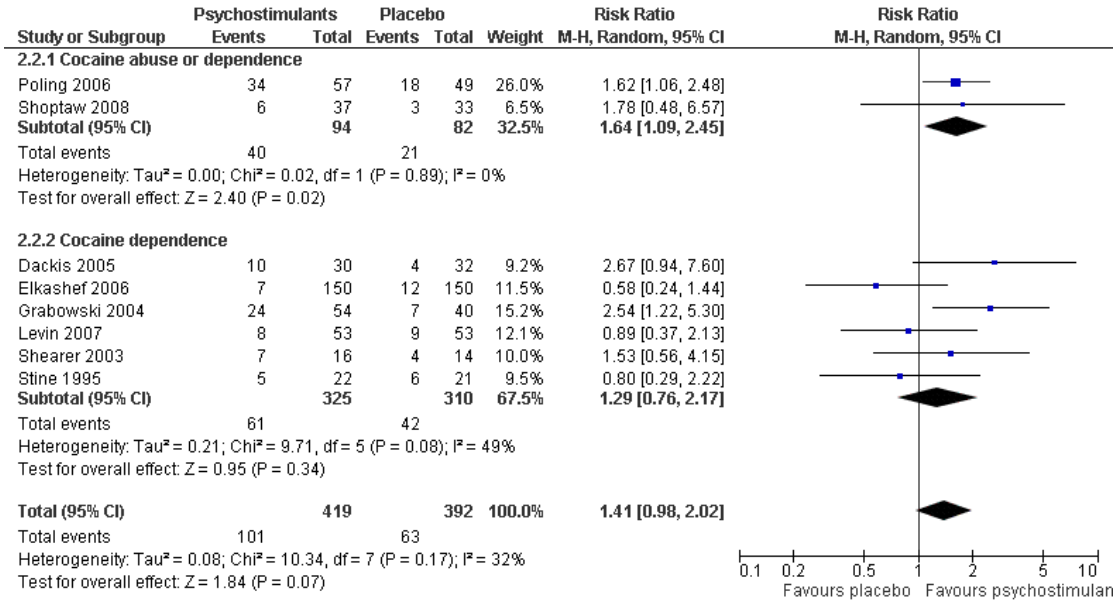
Subcategory 05: modafinil vs. placebo, one study (Dackis 2005), 62 patients, see comparison 02, outcome 01, subcategory 05, Figure 20, RR 2.67, 95%CI: 0.94 to 7.60, this result showed a statistical trend of significance (p=0.07).

Subcategory 06: selegiline vs. placebo, one study (Elkashef 2006), 300 patients, see comparison 02, outcome 01, subcategory 06, Figure 20, RR 0.58, 95%CI: 0.24 to 1.44, this result was not statistically significant.

(02) Definition of cocaine use disorder:

Subcategory 01: Cocaine abuse or dependence: psychostimulants placebo, two studies (Poling 2006, Shoptaw 2008), 176 patients, see comparison 02, outcome 02, subcategory 01, Figure 21, RR 1.64, 95%CI: 1.09 to 2.45, this result was statistically significant (p=0.02). No heterogeneity was found.

Figure 21. Forest plot of comparison: 2 Subgroup analysis: Sustained cocaine abstinence, outcome: 2.2 Definition of cocaine use disorder.

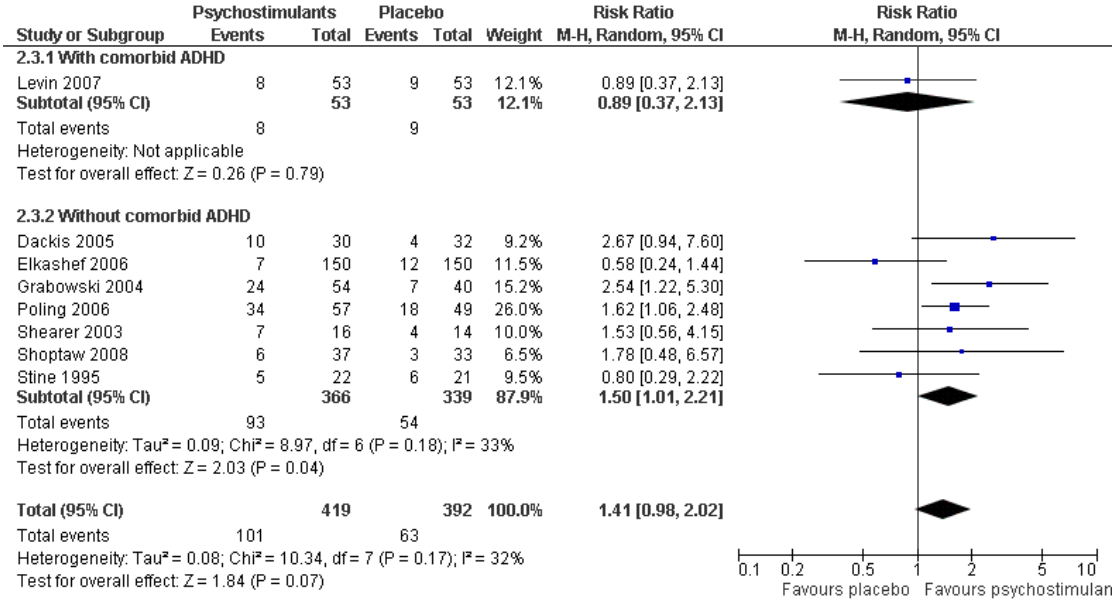


Subcategory 02: Cocaine dependence: psychostimulants placebo, six studies (Dackis 2005, Elkashef 2006, Grabowski 2004, Levin 2007, Shearer 2003, Stine 1995), 635 patients, see comparison 02, outcome 02, subcategory 02, Figure 21, RR 1.29, 95%CI: 0.76 to 2.17, this result was statistically not significant. Moderate heterogeneity was found (I^2=49%).

(03) Comorbid ADHD as inclusion criterion:

Subcategory 01: With a comorbid ADHD: psychostimulants placebo, one study (Levin 2007), 106 patients, see comparison 02, outcome 03, subcategory 01, Figure 22, RR 0.89, 95%CI: 0.37 to 2.13, this result was not statistically significant. No heterogeneity was found.

Figure 22. Forest plot of comparison: 2 Subgroup analysis: Sustained cocaine abstinence, outcome: 2.3 Comorbid ADHD as inclusion criterion.

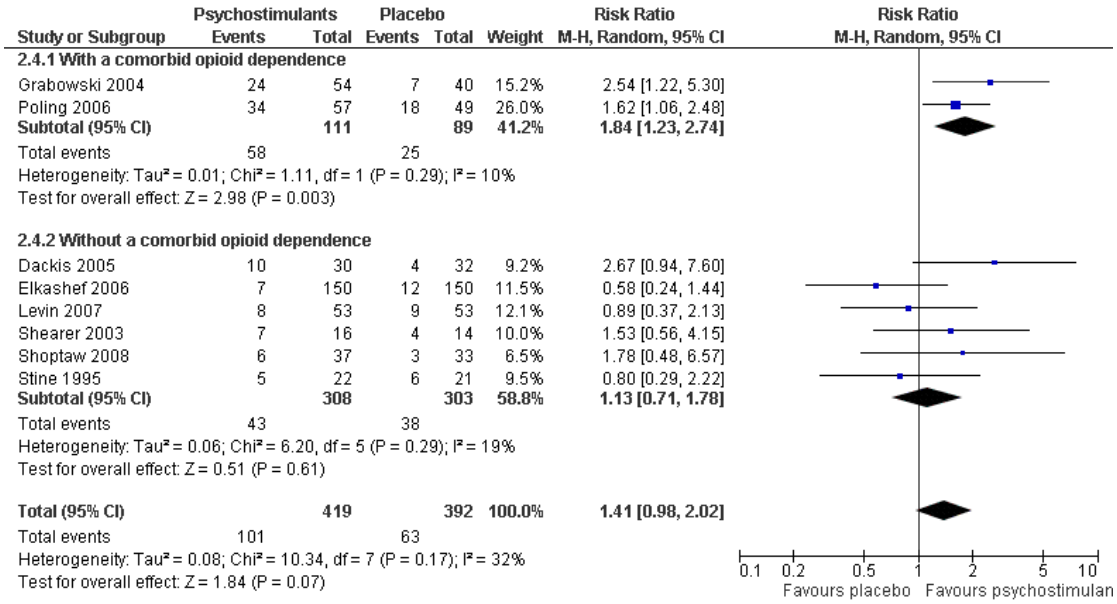


Subcategory 02: Without a comorbid ADHD: psychostimulants placebo, seven studies (Dackis 2005, Elkashef 2006, Grabowski 2004, Poling 2006, Shearer 2003, Shoptaw 2008, Stine 1995), 705 patients, see comparison 02, outcome 03, subcategory 02, Figure 22, RR 1.50, 95%CI: 1.01 to 2.21. This result was statistically significant (p=0.04). Moderate heterogeneity was found (I^2=33%).

(04) Comorbid opoid dependence as inclusion criterion:

Subcategory 01: With a comorbid opioid dependence: psychostimulants placebo, two studies (Grabowski 2004, Poling 2006), 200 patients, see comparison 02, outcome 04, subcategory 01, Figure 23, RR 1.84, 95%CI: 1.23 to 2.74, this result was statistically significant (p=0.003). No heterogeneity was found.

Figure 23. Forest plot of comparison: 2 Subgroup analysis: Sustained cocaine abstinence, outcome: 2.4 Comorbid opioid dependence as inclusion criterion.

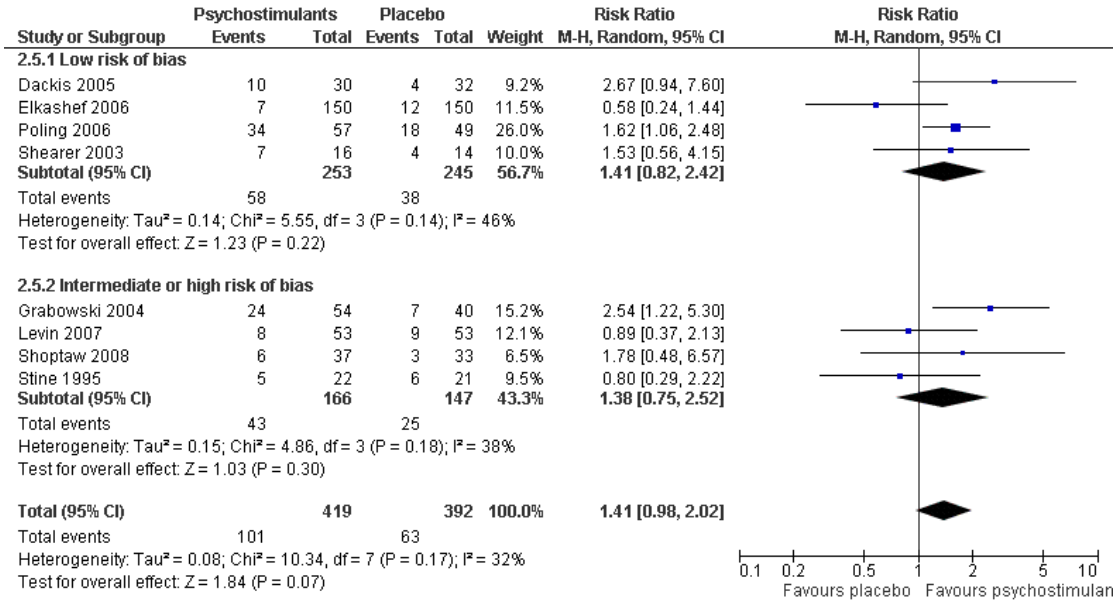


Subcategory 02: Without a comorbid opioid dependence: psychostimulants placebo, six studies (Dackis 2005, Elkashef 2006, Levin 2007, Shearer 2003, Shoptaw 2008, Stine 1995), 611 patients, see comparison 02, outcome 04, subcategory 02, Figure 23, RR 1.13, 95%CI: 0.71 to 1.78. This result was not statistically significant. Small heterogeneity was found (I^2=19%).

(05) Clinical trial reporting quality: Sequence generation:

Subcategory 01: Low risk of bias: psychostimulants placebo, four studies (Dackis 2005, Elkashef 2006, Poling 2006, Shearer 2003), 498 patients, see comparison 02, outcome 05, subcategory 01, Figure 24, RR 1.41, 95%CI: 0.82 to 2.42, this result was not statistically significant. Substantial heterogeneity was found (I^2=46%).

Figure 24. Forest plot of comparison: 2 Subgroup analysis: Sustained cocaine abstinence, outcome: 2.5 Clinical trial reporting quality: Sequence generation.

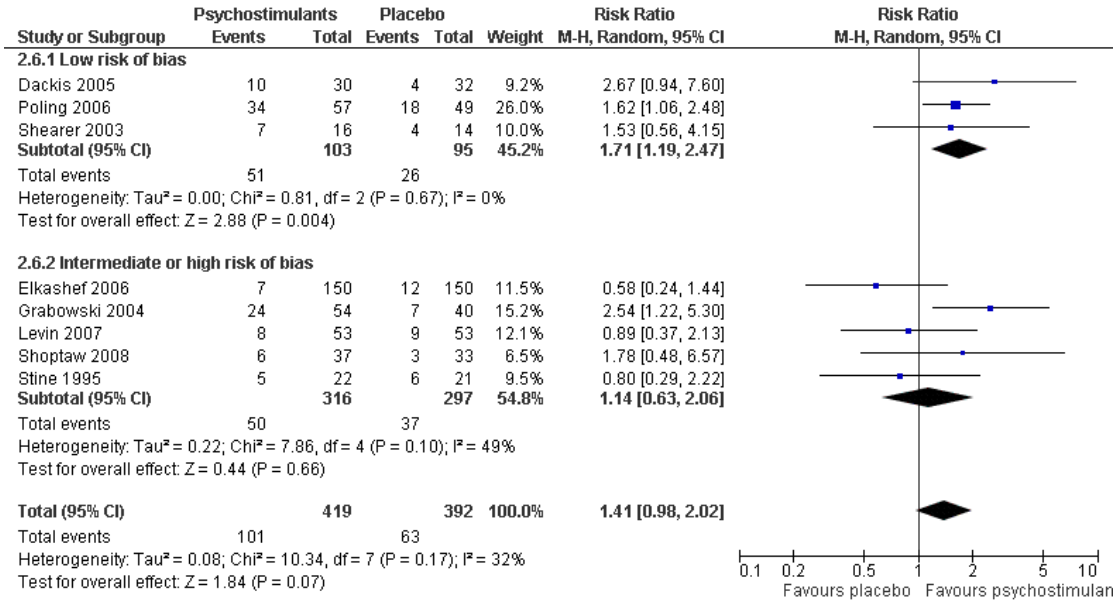


Subcategory 02: Intermediate or high risk of bias: psychostimulants placebo, four studies (Grabowski 2004, Levin 2007, Shoptaw 2008, Stine 1995), 313 patients, see comparison 02, outcome 05, subcategory 02, Figure 24, RR 1.38, 95%CI: 0.75 to 2.52. This result was not statistically significant. Moderate heterogeneity was found (I^2=38%).

(06) Clinical trial reporting quality: Allocation concealment:

Subcategory 01: Low risk of bias: psychostimulants placebo, three studies (Dackis 2005, Poling 2006, Shearer 2003), 198 patients, see comparison 02, outcome 06, subcategory 01, Figure 25, RR 1.71, 95%CI: 1.19 to 2.47, this result was statistically significant (p=0.004). No heterogeneity was found.

Figure 25. Forest plot of comparison: 2 Subgroup analysis: Sustained cocaine abstinence, outcome: 2.6 Clinical trial reporting quality: Allocation concealment.

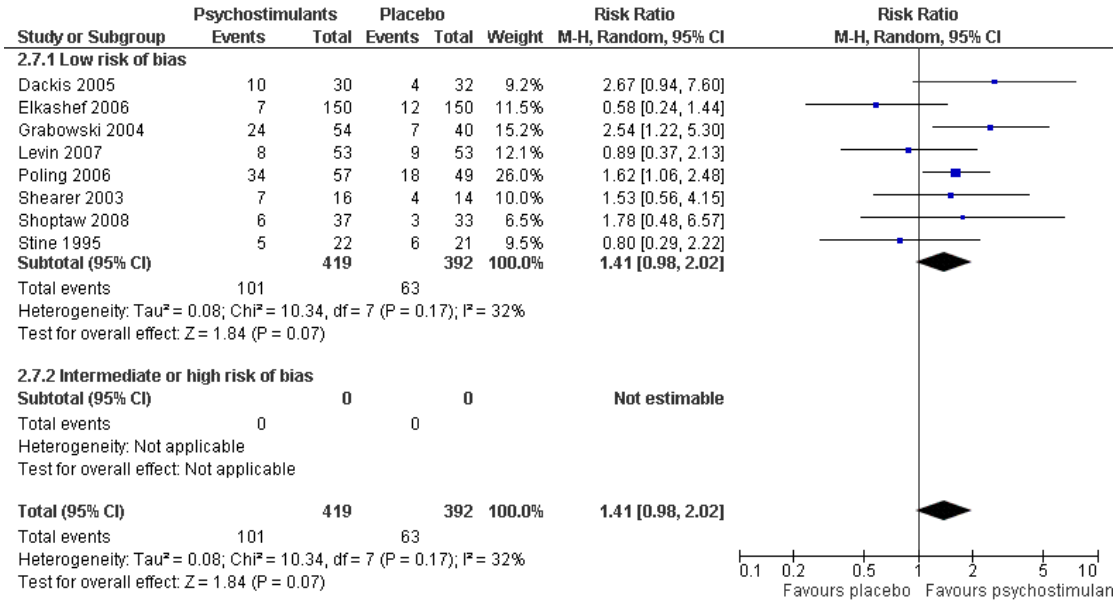


Subcategory 02: Intermediate or high risk of bias: psychostimulants placebo, four studies (Elkashef 2006, Grabowski 2004, Levin 2007, Shoptaw 2008, Stine 1995), 613 patients, see comparison 02, outcome 06, subcategory 02, Figure 25, RR 1.14, 95%CI: 0.63 to 2.06. This result was not statistically significant. Moderate heterogeneity was found (I^2=49%).

(07) Clinical trial reporting quality: Blinding

Subcategory 01: Low risk of bias: psychostimulants placebo, Eight studies (Dackis 2005, Elkashef 2006, Grabowski 2004, Levin 2007, Poling 2006, Shearer 2003, Shoptaw 2008, Stine 1995), 811 patients, see comparison 02, outcome 07, subcategory 01, Figure 26, RR 1.41, 95%CI: 0.98 to 2.02, this result showed a statistical trend of significance (p=0.07). Moderate heterogeneity was found (I^2 = 32%).

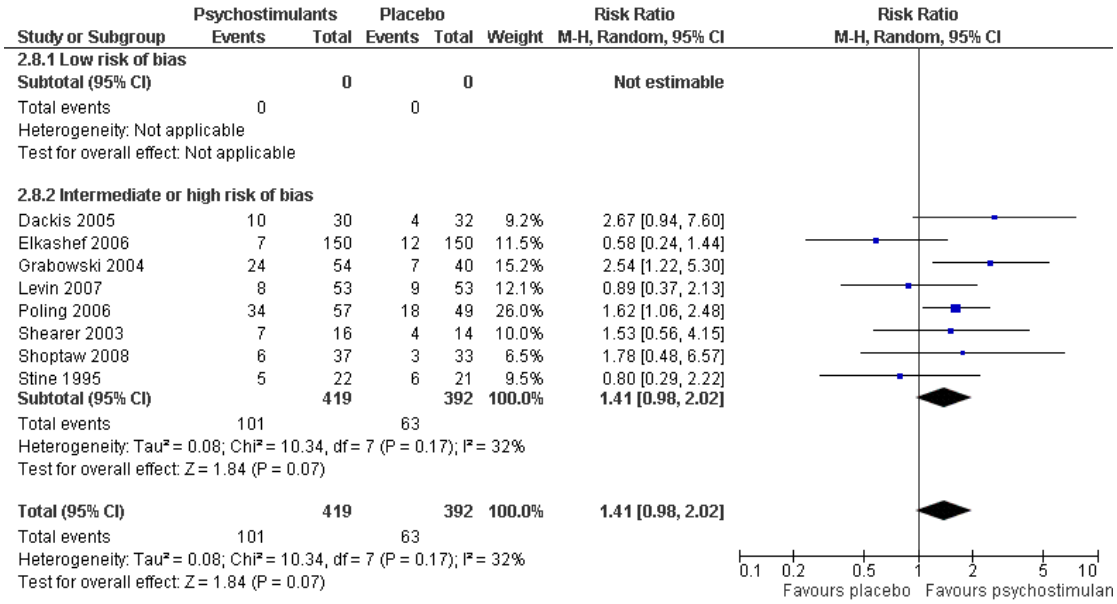
Figure 26. Forest plot of comparison: 2 Subgroup analysis: Sustained cocaine abstinence, outcome: 2.6 Clinical trial reporting quality: Blinding.



(07) Clinical trial reporting quality: Incomplete outcome reporting:

Subcategory 01: Low risk of bias: psychostimulants placebo, eight studies (Dackis 2005, Elkashef 2006, Grabowski 2004, Levin 2007, Poling 2006, Shearer 2003, Shoptaw 2008, Stine 1995), 811 patients, see comparison 02, outcome 08, subcategory 01, Figure 27, RR 1.41, 95%CI: 0.98 to 2.02, this result showed a statistical trend of significance (p=0.07). Moderate heterogeneity was found (I^2 = 32%).

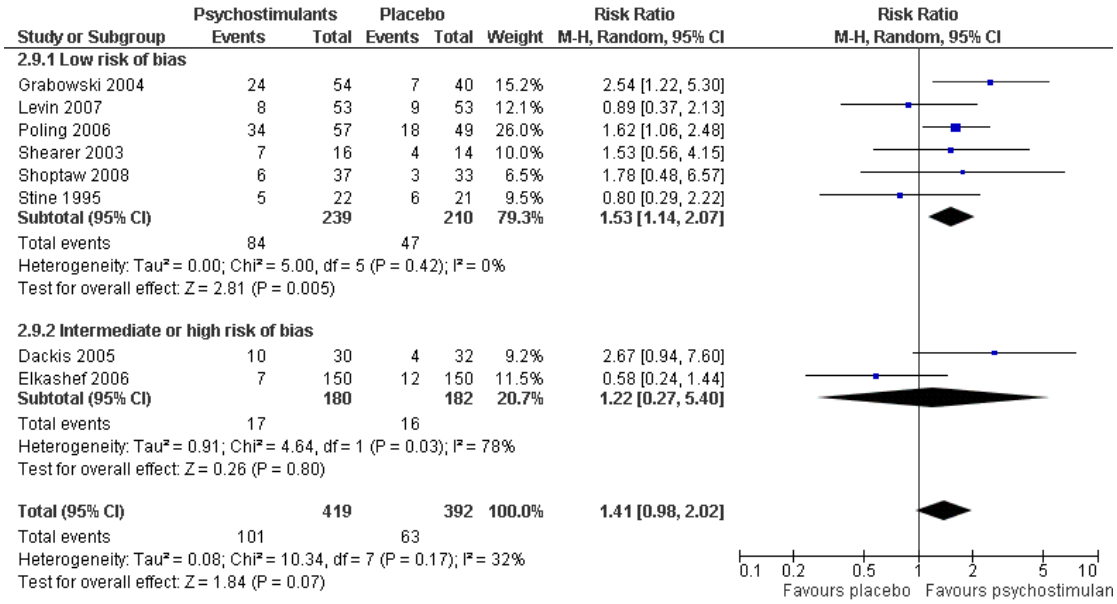
Figure 27. Forest plot of comparison: 2 Subgroup analysis: Sustained cocaine abstinence, outcome: 2.7 Clinical trial reporting quality: Incomplete outcome data.



(08) Clinical trial reporting quality: Other bias:

Subcategory 01: Low risk of bias: psychostimulants placebo, six studies (Grabowski 2004, Levin 2007, Poling 2006, Shearer 2003, Shoptaw 2008, Stine 1995), 449 patients, see comparison 02, outcome 09, subcategory 01, Figure 28, RR 1.53, 95%CI: 1.14 to 2.07, this result was statistically significant (p=0.005). No heterogeneity was found.

Figure 28. Forest plot of comparison: 2 Subgroup analysis: Sustained cocaine abstinence, outcome: 2.8 Clinical trial reporting quality: Other bias.

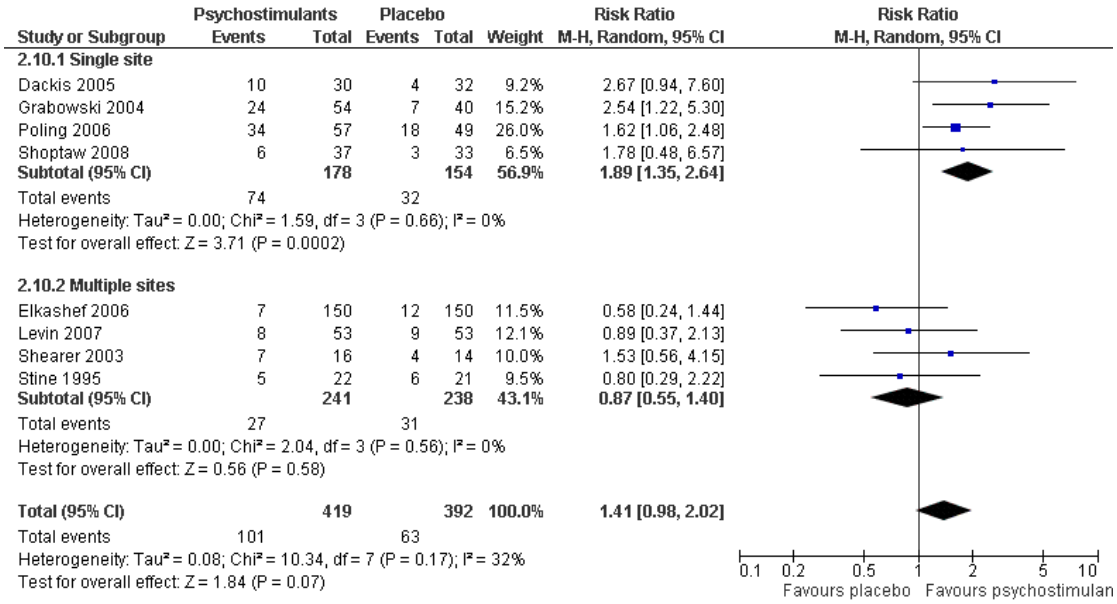


Subcategory 02: Intermediate or high risk of bias: psychostimulants placebo, two studies (Dackis 2005, Elkashef 2006), 362 patients, see comparison 02, outcome 09, subcategory 02, Figure 28, RR 1.22, 95%CI: 0.27 to 5.40. This result was not statistically significant. Large heterogeneity was found (I^2=78%).

(09) Single vs. Multiple sites:

Subcategory 01: Low risk of bias: psychostimulants placebo, three studies (Dackis 2005, Grabowski 2004, Poling 2006, Shoptaw 2008), 198 patients, see comparison 02, outcome 10, subcategory 01, Figure 29, RR 1.71, 95%CI: 1.19 to 2.47, this result was statistically significant (p=0.004). No heterogeneity was found.

Figure 29. Forest plot of comparison: 2 Subgroup analysis: Sustained cocaine abstinence, outcome: 2.9 Single vs. Multiple sites.



Subcategory 02: Intermediate or high risk of bias: psychostimulants placebo, four studies (Elkashef 2006, Levin 2007, Shearer 2003, Stine 1995), 613 patients, see comparison 02, outcome 10, subcategory 02, Figure 29, RR 1.14, 95%CI: 0.63 to 2.06. This result was not statistically significant. Moderate heterogeneity was found (I^2=49%).

Reporting bias analysis

Funnel plots of the three primary variables (Figure 30, Figure 31 and Figure 32) were drawn and none of them was suggestive of reporting bias.

Figure 30. Funnel plot of comparison: 1 Psychostimulants vs. Placebo: Primary analysis, outcome: 1.1 Cocaine use by means of urine screen.

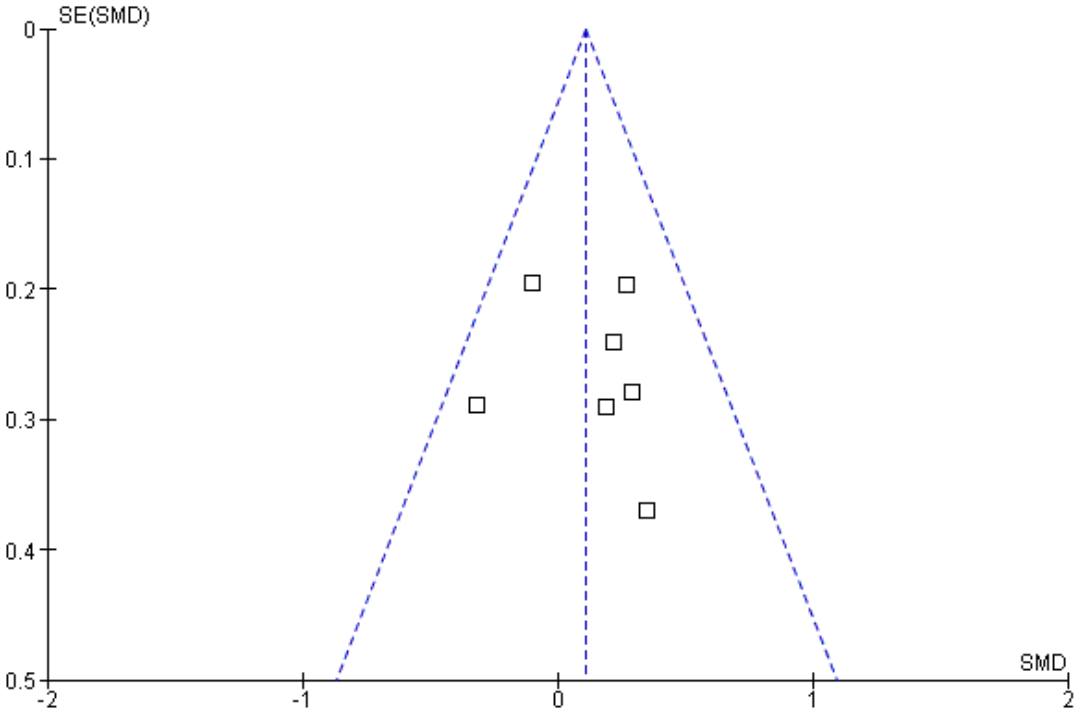


Figure 31. Funnel plot of comparison: 1 Psychostimulants vs. Placebo: Primary analysis, outcome: 1.2 Sustained cocaine abstinence.

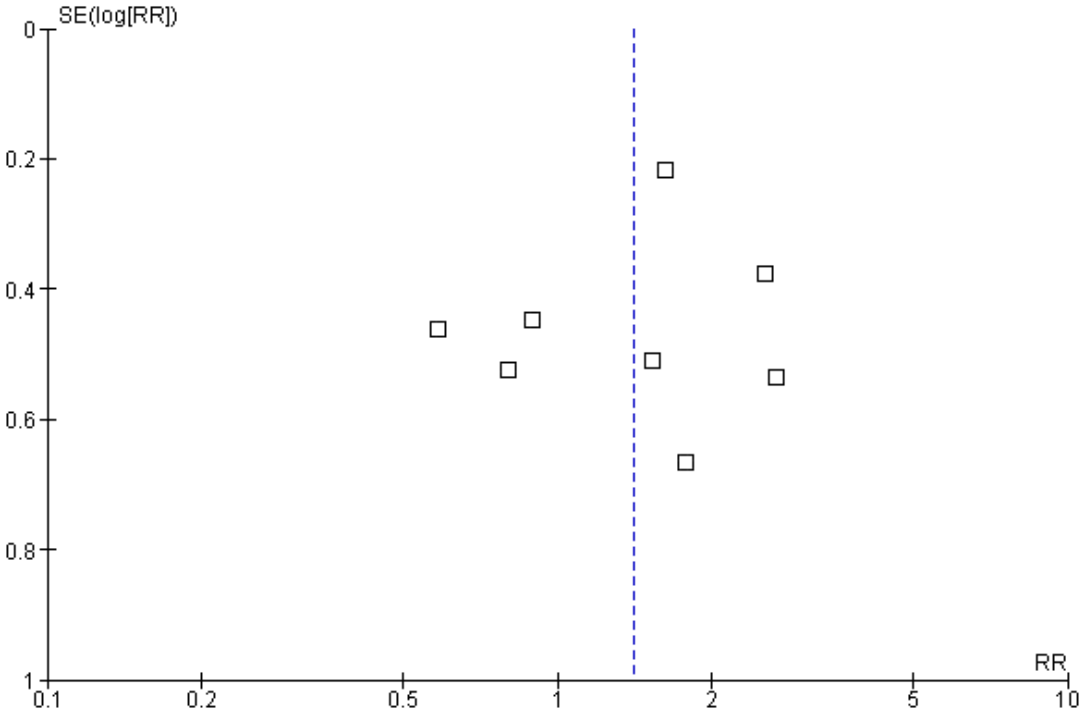
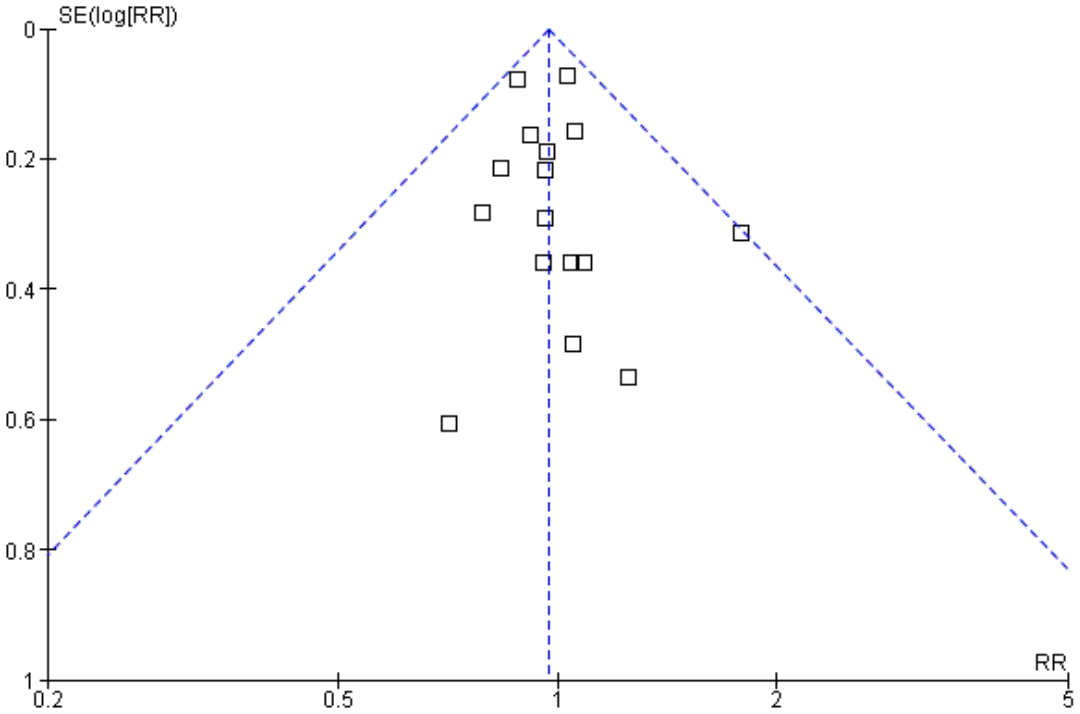


Figure 32. Funnel plot of comparison: 1 Psychostimulants vs. Placebo: Primary analysis, outcome: 1.3 Number of patients who finished the study (retention).

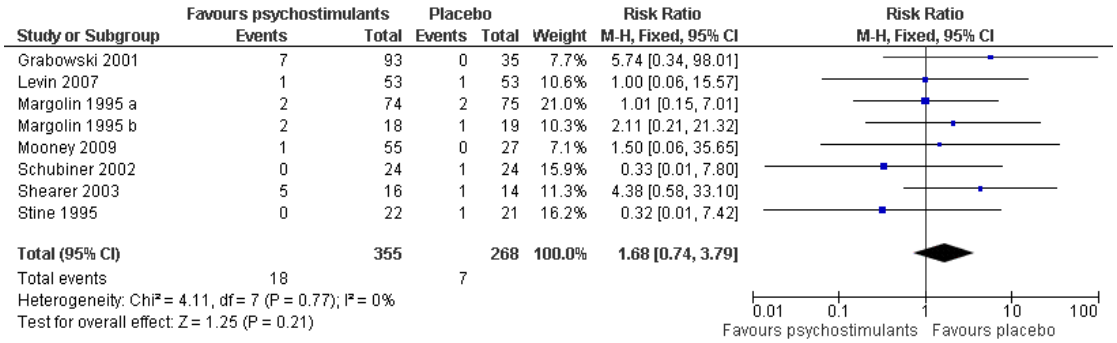


The number of studies needed to neutralize the effect of psychostimulants was not calculated because no statistically significant result was found for any primary analysis.

Sensitivity analysis

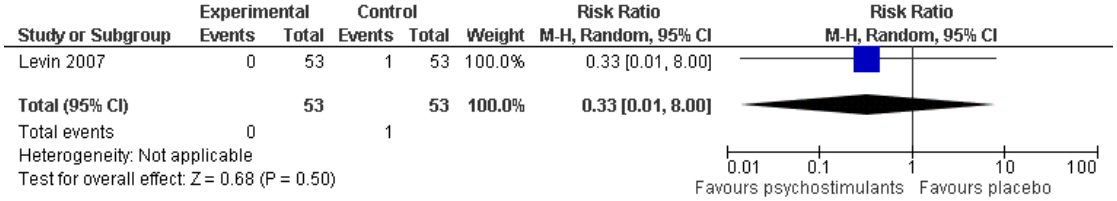
The sensitivity analysis of the outcome "patients dropped out due to any AE" was conducted using data from 8 (Grabowski 2001, Levin 2007, Margolin 1995 a, Margolin 1995 b, Mooney 2009, Schubiner 2002, Shearer 2003, Stine 1995) out of 11 studies that could be used in the primary analysis. This analysis included 964 patients, see comparison 12, outcome 01, Figure 33, RR 1.68, 95%CI: 0.74 to 3.79, this result was not statistically significant. No heterogeneity was found.

Figure 33. Forest plot of comparison: 12 Psychostimulants vs. Placebo: Sensitivity analyses of the safety measures, outcome: 12.1 Patients dropped out due to any adverse events.



For the sensitivity analysis of the outcome "patients dropped out due to any cardiovascular AE" only one study (Levin 2007) was used, which included 106 patients, see comparison 12, outcome 02, Figure 34, RR 0.33, 95%CI: 0.01 to 8.00, this result was not statistically significant.

Figure 34. Forest plot of comparison: 12 Psychostimulants vs. Placebo: Sensitivity analyses of the safety measures, outcome: 12.2 Patients dropped out due to cardiovascular adverse events.



DISCUSSION

Summary of main results

This review of the efficacy of psychostimulants for the treatment of cocaine dependence showed inconclusive evidence. Psychostimulants did not decrease cocaine use or cocaine craving or improve study retention in comparison to placebo. However, a higher rate of patients achieved sustained cocaine abstinence with psychostimulants than with placebo, at a statistical trend. Psychostimulants did not improve depressive symptoms. We could not meta-analyze data on anxiety symptoms or on global activity functioning because these data were not reported in a way to allow aggregation by means of meta-analysis. Psychostimulants appeared safe and showed a good short-term safety and no differences were found with placebo on the rate of AE induced dropouts. Nevertheless, it must be noted that this review focused on AE that had to be serious enough to deserve study withdrawal. Thus, a comprehensive revision of psychostimulants safety including mild and long-term AE should be carried out.

Seven drugs with psychostimulant effect were studied: bupropion, dexamphetamine, mazindol, methamphetamine, methylphenidate, modafinil and selegiline. None of them was superior to placebo on most studied outcomes, with the exception of bupropion and dexamphetamine that were more efficacious than placebo in achieving sustained cocaine abstinence and also modafinil, at a statistical trend of significance. Selegiline appeared to improve CGI, but only when it was investigator-rated. It must be stressed that some of the included drugs, bupropion, modafinil or selegiline, are not usually seen as psychostimulants neither classified within the psychostimulant section in drug classification systems (ATC 2009, AHFS 2009). Selegiline is not a

psychostimulant itself, but it is metabolised to amphetamine and methamphetamine (Shin 1997). However, its psychostimulant and reinforcing effects appear to be stereoselective, being more pronounced with D-selegiline than with the L-isomer that is used in the clinical practice (Yasar 2006a). Besides the therapeutic dose of selegiline is lower than the administered one in laboratory studies that have assessed its psychostimulant and reinforcing effects (Engberg 1991, Mahmood 1997, Yasar 2006b). Unlike selegiline, modafinil and bupropion appear to have psychostimulant properties by themselves, as indicated by some studies showing that, like cocaine and other psychostimulants, modafinil and bupropion block the dopamine transporter (Madras 2006, Zolkowska 2009, Volkow 2009, Learned-Coughlin 2003, Dwoskin 2006) and have locomotor stimulating effects (Zolkowska 2009, Makris 2007, Redolat 2005, Cousins 2001). In addition, both drugs have some substitutive properties for cocaine and for other prototypical CNS stimulants in discriminative stimulus studies (Craft 1996, Dopheide 2007, Katz 2000, Evans 1987). Nevertheless, it must be noted that bupropion or modafinil are infrequently misused (Langguth 2009, Welsh 2002, McCormick 2002, Jasinski 2000)

Most studies limited the participation to patients with cocaine dependence, but some also included patients with cocaine abuse. Nevertheless, amongst those studies that included cocaine abusers, most patients had a cocaine dependence. Therefore, grouping the included RCTs into two categories according to the definition of cocaine use has not resulted in two clearly different groups of patients. As a consequence of that, it is not surprising that no differences were found between these two groups on most studied outcomes, and where differences were found (achievement of sustained cocaine abstinence) it is unlikely that the definition of cocaine use is the explanation for the observed difference (see "Potential biases in the review process" subheading for a more detailed explanation).

Psychostimulants have shown to be efficacious for adults with ADHD in several meta-analyses and clinical trials (Koesters 2008, Peterson 2008). However, their efficacy in ADHD patients with comorbid substance use disorders remains a controversial issue (Mariani 2007). This review included only two relatively small trials with patients with ADHD-cocaine dependence and found that psychostimulants did not improve cocaine use outcomes. Regarding their efficacy for ADHD symptoms, this review showed heterogeneous results. Methylphenidate was more efficacious than placebo in one study (Schubiner 2002) but it was not in another one (Levin 2007). One reason for this discrepancy could be the formulation used to deliver methylphenidate. While in the study by Schubiner et al., (Schubiner 2002) methylphenidate was delivered by means of an immediate release formulation in the study by Levin et al. (Levin 2007) it was delivered by means of a sustained release one, which has been associated with lost of efficacy due to tachyphylaxis (Swanson 1999). Conversely, psychostimulants were more efficacious than placebo in achieving sustained cocaine abstinence in cocaine dependent patients without comorbid ADHD.

Five clinical trials were conducted in methadone maintained opioid-cocaine dependent patients, which included a third of the subjects that have been enrolled in RCTs investigating the efficacy of psychostimulants for cocaine dependence. In this population, drugs with CNS stimulating effects (specifically, bupropion and dexamphetamine) showed promising results. Psychostimulants reduced cocaine use, at a trend of statistical significance, and increased sustained cocaine abstinence. Conversely, psychostimulants were not efficacious in non opioid-cocaine dependent patients. Besides, heroin use was lower and sustained heroin abstinence higher with psychostimulants than with placebo, suggesting the existence of an underlying interaction between opioids and psychostimulants (Leri 2003, Castells 2009). These hopeful findings must be interpreted with the utmost care because they were based on 2 out of 5 published clinical trials for which data were available in a way that allowed statistical combination using meta-analytical techniques. Furthermore, psychostimulants did not improve retention in treatment in this population.

The finding that psychostimulants might be efficacious for cocaine dependence in methadone maintained opioid dependent patients and in patients without a comorbid ADHD are coincident with those of other studies that also support the notion that no pharmacological intervention is universally efficacious for cocaine dependence but for specific subgroups of patients (Kosten 2005, McDowell 2005, Kampman 2004).

Psychostimulants were found to be efficacious for achieving sustained cocaine abstinence in single site studies, while they were not in multiple site ones. That most trials investigating the efficacy of bupropion and dexamphetamine as well as all studies enrolling methadone maintained dual heroin-cocaine dependent patients were single site studies could explain the association between number of study sites and efficacy of psychostimulants over sustained cocaine abstinence.

Overall completeness and applicability of evidence

The external validity of this review is limited by the inclusion/exclusion criteria of the included studies. Most studies have been conducted in the US, hampering the generalization of the findings of this review to other regions. Besides, there is an over representation of dual opioid-cocaine dependent patients as well as of patients with comorbid ADHD in comparison to clinical samples. Conversely, patients with a comorbid alcohol dependence or major depressive disorder, which are frequent comorbid disorders, have usually been excluded.

Quality of the evidence

Clinical trial quality must be determined and its influence over meta-analysis results assessed because it is associated with biased

results, with more favourable outcomes to the studied intervention amongst lower quality studies (Jüni 2001). The main findings of this review do not appear to be influenced by sequence generation or blinding, and similar results are obtained with studies with low and high/intermediate risk of bias. However, on the contrary to the expected, the studies with the lowest risk of bias on allocation concealment and other bias showed positive outcomes for psychostimulants on sustained cocaine abstinence whereas those with high/intermediate risk of bias showed no efficacy of psychostimulants. It must be stressed that the quality of this review is limited by the fact that a high attrition was found for most included RCTs, therefore with a high or unclear risk of having biased results because of the incompleteness of the analyzed data.

The findings of this review are limited by the small number of studies included in the meta-analysis of most study outcomes. Therefore the precision of the calculated effects is low. This is particularly true for many subgroup analyses.

Another factor that can affect the quality of the evidence shown by this review is that we have pooled together drugs with different mechanism of action and we have not controlled for the influence of dose because, to our knowledge, no study has determined the pharmacodynamic equivalence between these drugs.

Potential biases in the review process

Reporting bias can jeopardize the validity of any meta-analysis. We have tried to limit the influence of reporting bias by screening several datasets and requesting unpublished results to the contact authors. Proceeding that way has resulted in a substantial increase in the available data. Funnel plots were built in order to determine whether reporting bias has occurred and none of them was suggestive of biased results.

A limitation of this review is that the findings of the subgroup analysis may yield confounded results as a consequence of its bivariate nature. For instance, we found that the achievement of sustained cocaine abstinence was associated with the type of studied psychostimulant (bupropion and dexamphetamine were the only psychostimulants with statistically significant results on this outcome) and with the presence of a comorbid opioid dependence (psychostimulants were efficacious in dual opioid-cocaine dependent patients and were not in patients without a comorbid opioid dependence). Nevertheless, the clinical trials with dual opioid-cocaine dependent patients used bupropion and dexamphetamine as psychostimulants. Thus, we cannot disentangle the effect of a comorbid opioid dependence to that of the studied psychostimulant. To do so more clinical trials would be needed to allow for a multiple subgroups analysis.

Similarly, a confounding effect between the type of cocaine use definition and the studied drug may also explain that psychostimulants were efficacious for achieving sustained cocaine abstinence when cocaine abusers were also included. All clinical trials including cocaine abusers and reporting sustained cocaine abstinence investigated the efficacy of bupropion.

Agreements and disagreements with other studies or reviews

Several reviews using a narrative methodology are available (Moeller 2008, Karila 2008, Grabowski 2004). One systematic review and meta-analysis (Castells 2007) is also available. All in all, these reviews suggest that psychostimulants are promising medications for cocaine dependence. Our review agrees with these previously published studies but adds that bupropion and dexamphetamine are the most promising stimulants and that the patients who would benefit the most from psychostimulant replacement might be those with a comorbid opioid dependence treated with methadone.

One disagreement exists between this and a previously published meta-analysis (Castells 2007) regarding AE induced dropouts. The previous meta-analysis found that AE induced dropouts were more prevalent amongst patients treated with psychostimulants than with placebo, while the present review does not support this finding. Differences regarding the number of included studies (nine RCCT were include in the previous review and 16 in this one) together methodological differences (in the previous review a Fisher test was used while, in the present review, meta-analytical procedures were used to calculate the effects of the intervention over AE induced dropouts) may explain the discrepancy found on this outcome.

AUTHORS' CONCLUSIONS

Implications for practice

Replacement therapy with opiates or nicotine has shown to be efficacious for the treatment of tobacco and heroin dependence, respectively. Though the results of this review are not fully supportive with psychostimulants replacement for cocaine dependence, they give some room for optimism since a trend on improving sustained cocaine abstinence was found. Besides, bupropion and dexamphetamine are the psychostimulants for which more supportive data exist. Finally, dual opioid-cocaine dependent patients seem to be the most suitable candidates for agonist therapy with psychostimulants.

Implications for research

This review shows that some psychostimulants may be promising medications for the treatment of cocaine dependence. This therapeutic approach is called to have an intense research activity in the future. Given the high attrition that features cocaine dependence studies, which hampers the validity of any clinical trial, future studies should address incomplete outcome data with suitable methods.

Some niches for future research have been identified; for instance, psychostimulants should be studied in geographical areas other than the US. The efficacy of psychostimulants should also be assessed in patients with comorbid mood disorders or alcohol dependence. Besides, given the promising results of indirect dopamine drugs like disulfiram (Carroll 2004) or levodopa (Schmitz 2008), the possibility of synergism between two groups of drugs acting on the dopamine system at different levels could also be investigated.

ACKNOWLEDGEMENTS

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Dackis CA, Kampman KM, Lynch KG, Pettinati H, O'Brien CP. A double-blind, placebo-controlled trial of modafinil for cocaine dependence. *Neuropsychopharmacology* 2005;**30**:205–11.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Dackis 2005

Methods	Double-blind, randomised, placebo-controlled clinical trial. Statistical analysis: ITT
Participants	n = 62 cocaine-dependent out-patients (DSM-IV) who had used at least US$ 200 worth of cocaine in the past 30 days. Patients with comorbid alcohol dependence were excluded. Mean age: 44.5 years Gender: 44 men Race: African-American: 50, Caucasian: NR, Other: NR Employed: NR History: days of cocaine use during last month: 10.6, lifetime cocaine use: 12.5 years Route of cocaine use: 54 i.p.
Interventions	Two parallel groups: 1. Modafinil IR 200-400 mg/day q.d. (flexible posology), N = 30 2. Placebo, N = 32 + CBT (16 sessions) Duration: 8 weeks Single site (USA).
Outcomes	Cocaine use assessed with three times weekly UA Sustained cocaine abstinence (defined as at least 3 weeks of continuous abstinence) Retention in treatment Cocaine craving assessed with BSCS and CCQ Depressive symptoms assessed with the BDI and Ham-D
Notes	Author's affiliation: university Study funding: co-funding public and private Assessment of compliance: Blister pack return

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"Computer generated code"
Allocation concealment?	Yes	"Research pharmacist was the only person aware of the medication assignment code"
Blinding? Objective measures	Yes	The outcome or the outcome measurement were not likely to be influenced by lack of blinding

Dackis 2005 (*Continued*)

Blinding? Subjective measures	Yes	Study medication and matched placebo had an identical appearance. Blinding of participants, providers and outcome assessor appears unlikely to have been broken
Incomplete outcome data addressed? Objective outcomes except retention and dropouts	Unclear	One third of the randomised subjects in both study groups did not complete the study in both study groups. Reasons for dropping out were not exhaustively reported and it is unclear whether they differed between active and placebo groups Imputation by means of worst possible scenario
Incomplete outcome data addressed? Subjective outcomes (e.g. craving, depressive symptoms, CGI,...)	Unclear	One third of the randomised subjects in both study groups did not complete the study in both study groups. Reasons for dropping out were not exhaustively reported and it is unclear whether they differed between active and placebo groups Imputation method for subjective outcomes was not reported
Free of other bias?	Unclear	Umbalanced baseline characteristics regarding history of cocaine use. The modafinil group had lower days of cocaine use per week and weekly cocaine cost and longer years of cocaine use than the placebo group, at a statistical trend of significance. These differences could indicate that the sample receiving modafinil had a less severe cocaine addiction, which could result in biased results

Elkashef 2006

Methods	Double-blind, randomised, placebo-controlled clinical trial Statistical analysis: ITT
Participants	n = 300 cocaine-dependent out-patients (DSM-IV). Patients with comorbid alcohol dependence were excluded Mean age: 40.7 years Gender: 234 men Race: African American: 188, Caucasian: 80, Other: 32 Employed: NR History: days of cocaine use during last month: 17.6, lifetime cocaine use: 13.6 years Route of cocaine use: 257 i.p., 12 other

Elkashef 2006 (*Continued*)

Interventions	1. Selegiline patch 20 cm^2, with 6 mg/day q.d. (fixed posology), N = 150 2. Placebo, N = 150 + individualized counselling, 1h session per week Duration: 8 weeks Multi-site trial (USA)
Outcomes	Cocaine use assessed with three times weekly UA Sustained cocaine abstinence (defined as at least 3 weeks of continuous abstinence) Retention in treatment Cocaine craving assessed with BSCS Depressive symptoms assessed with Ham-D Patients withdrawn due to adverse events
Notes	Author's affiliation: university Study funding: co-funding public and private Assessment of compliance: NR

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"Adaptive randomizations using a biased coin procedure"
Allocation concealment?	Unclear	Insufficient information to permit judgement
Blinding? Objective measures	Yes	The outcome or the outcome measurement were not likely to be influenced by lack of blinding
Blinding? Subjective measures	Yes	Study medication and matched placebo had an identical appearance. Blinding of participants, providers and outcome assessor appears unlikely to have been broken
Incomplete outcome data addressed? Objective outcomes except retention and dropouts	Unclear	Almost one third of the randomised subjects in both study groups did not complete the study, most of them due to failure to return to clinic It was not reported whether missing data were imputed or not
Incomplete outcome data addressed? Subjective outcomes (e.g. craving, depressive symptoms, CGI,...)	Unclear	Almost one third of the randomised subjects in both study groups did not complete the study, most of them due to failure to return to clinic It was not reported whether missing data

Elkashef 2006 (*Continued*)

		were imputed or not
Free of other bias?	Unclear	Umbalanced baseline characteristics regarding history of cocaine use. The selegiline group had longer years of cocaine use than the placebo group. This difference could indicate that the sample receiving selegiline had a more severe cocaine addiction, which could result in biased results

Grabowski 1997

Methods	Double-blind, randomised, placebo controlled clinical trial. Patients with comorbid alcohol dependence were excluded. Statistical analysis: non ITT
Participants	n = 49 cocaine-dependent out-patients (DSM-IIIR) Mean age: 34.3 years Gender: 38 male Race: African American:28, Caucasian :17, Other: 4 Employed: 23 History: NR Cocaine route of use: 41 i.p, 4 i.n., 4 i.v
Interventions	1. Methylphenidate 45 mg/day b.i.d. (5mg IR + 20mg SR - 20mg SR) (fixed posology) , N = 25 2. Placebo, N = 24 + Psychosocial therapy (11 sessions) Duration: 13 weeks Single site (USA)
Outcomes	Cocaine use assessed with twice weekly UA Retention in treatment
Notes	Author's affiliation: university Study funding: public Assessment of compliance: MEMS bottles

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Insufficient information to permit judgement
Allocation concealment?	Unclear	Insufficient information to permit judgement

Grabowski 1997 (*Continued*)

Blinding? Objective measures	Yes	The outcome or the outcome measurement were not likely to be influenced by lack of blinding
Blinding? Subjective measures	Yes	The outcome or the outcome measurement were not likely to be influenced by lack of blinding because pills had identical appearance
Incomplete outcome data addressed? Objective outcomes except retention and dropouts	No	High attrition in both study groups. Reasons for dropping out in each study group were not reported Missing data were not imputed
Incomplete outcome data addressed? Subjective outcomes (e.g. craving, depressive symptoms, CGI,...)	No	High attrition in both study groups. Reasons for dropping out in each study group were not reported Missing data were not imputed
Free of other bias?	Yes	The study appears to be free of other sources of biases

Grabowski 2001

Methods	Random allocation;double-blind; 101 days' duration; 3 parallel groups, placebo-controlled. Single site clinical trial (USA) Statistical analysis: ITT and also a post hoc analyses with 112 patients (after exclusion of 16 patients without one urine analysis positive at baseline)
Participants	n = 128 cocaine-dependent patients (DSM-IV). Patients with comorbid alcohol dependence were excluded Mean age: 36+/-6.4 years Gender: 101 male Race: African American: 74, Caucasian: 40, Other: 14 Employed: 49 History: lifetime cocaine use: 12.2 years Route of cocaine use: 103 i.p., 23 i.n., 3 i.v
Interventions	1. Dextroamphetamine SR 15-30mg/day b.i.d. (fixed posology), N = 47 2. Detroamphetamine SR 30-60mg/day b.i.d. (fixed posology), N = 46 3. Placebo, N = 35 + CBT (13 sessions) Single site
Outcomes	Cocaine use assessed with twice weekly UA Retention in treatment Patients dropped out due to adverse events Depressive symptoms assessed with the BDI

Grabowski 2001 (*Continued*)

Notes	Author's affiliation: university Study funding: public Assessment of compliance: Rivoflavin and MEMS bottles

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Insufficient information to permit judgement
Allocation concealment?	Unclear	Insufficient information to permit judgement
Blinding? Objective measures	Yes	The outcome or the outcome measurement were not likely to be influenced by lack of blinding
Blinding? Subjective measures	Unclear	The outcome or the outcome measurement were not likely to be influenced by lack of blinding because pills had identical appearance
Incomplete outcome data addressed? Objective outcomes except retention and dropouts	No	High attrition in all study groups. Reasons for dropping out in each study group were not reported Missing data were not imputed
Incomplete outcome data addressed? Subjective outcomes (e.g. craving, depressive symptoms, CGI,...)	No	High attrition in all study groups. Reasons for dropping out in each study group were not reported Missing data were not imputed
Free of other bias?	Yes	The study appears to be free of other sources of biases

Grabowski 2004

Methods	Double-blind, randomised, placebo controlled clinical trial Statistical analysis: non ITT
Participants	n = 94 dual opioid-cocaine dependent outpatients (DSM-IV). Patients with comorbid alcohol dependence were excluded. Mean age: 36.7+/-7.3 years Geder: 63 male Race: African-American:10, Caucasian: 71, Other: 13 Employed: NR History: NR

Grabowski 2004 (*Continued*)

	Route of cocaine use: 44 i.p., 30 i.n., 20 i.v. (20 speedballs users)
Interventions	1. Dexamphetamine 15-30 mg/day b.i.d. (fixed posology, 4 weeks' induction), N = 26 2. Dexamphetamine 30-60 mg/day b.i.d. (fixed posology, 4 weeks' induction), N = 28 3. Placebo, N = 40 + CBT and relapse prevention (1h each week) + Methadone 1.1mg/kg/day Duration: 24 weeks Single site clinical trial (USA)
Outcomes	Cocaine use assessed with twice a week UA Sustained cocaine abstinence (defined as at least 3 weeks of continuous abstinence) Retention in treatment Depressive symptoms assessed with the BDI
Notes	Author's affiliation: university Study funding: public Assessment of compliance: Riboflavin, MEMS bottles, urine screen drug metabolite

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Insufficient information to permit judgement
Allocation concealment?	Unclear	Insufficient information to permit judgement
Blinding? Objective measures	Yes	The outcome or the outcome measurement were not likely to be influenced by lack of blinding
Blinding? Subjective measures	Unclear	The outcome or the outcome measurement were not likely to be influenced by lack of blinding because pills had identical appearance
Incomplete outcome data addressed? Objective outcomes except retention and dropouts	Unclear	High attrition in both study groups. Reasons for dropping out in each study group were not reported Missing data were not imputed
Incomplete outcome data addressed? Subjective outcomes (e.g. craving, depressive symptoms, CGI,...)	Unclear	High attrition in both study groups. Reasons for dropping out in each study group were not reported Missing data were not imputed

Grabowski 2004 (*Continued*)

Free of other bias?	Yes	The study appears to be free of other sources of biases

Levin 2007

Methods	Double-blind, randomised, placebo controlled clinical trial Statistical analysis: ITT
Participants	n = 106 cocaine-dependent (DSM-IV) patients with adult ADHD. Patients with physiologic dependence on alcohol were excluded Mean age: 37 years (23-52) Sex: 88 male Race: African American: 21, Caucasian: 64, Other: 15 Employed: 80 History: days of cocaine use during last month: 13.5, lifetime cocaine use: 16.5 years Route of cocaine use: 36 i.p., 64 i.n., 5 other
Interventions	1. Methylphenidate SR 40-60mg/day b.i.d. (flexible posology, 2 weeks' induction with IR methylphenidate), N =53 2. Placebo, N = 53 + CBT weekly sessions Duration: 11 weeks Multi-centre clinical trial (USA)
Outcomes	Sustained cocaine abstinence assessed with three times a week UA Cocaine use by means of urine screen (defined as at least 2 weeks of continuous abstinence) Retention in treatment Craving assessed with a VAS ADHD severity assessed with AARS Number of patients withdrawn due to adverse events
Notes	Author's affiliation: university Study funding: public Assessment of compliance: riboflavin

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Insufficient information to permit judgement
Allocation concealment?	Unclear	Insufficient information to permit judgement

Levin 2007 (*Continued*)

Blinding? Objective measures	Yes	The outcome or the outcome measurement were not likely to be influenced by lack of blinding
Blinding? Subjective measures	Unclear	Methods to ensure blinding were not described
Incomplete outcome data addressed? Objective outcomes except retention and dropouts	Unclear	High attrition. Most patients in both groups dropped out due to lack of interest Imputation method was not specified
Incomplete outcome data addressed? Subjective outcomes (e.g. craving, depressive symptoms, CGI,...)	Unclear	High attrition. Most patients in both groups dropped out due to lack of interest Imputation method was not specified
Free of other bias?	Yes	The study appears to be free of other sources of biases

Margolin 1995 a

Methods	Double-blind, randomised, placebo controlled clinical trial Allocation stratified by the presence of antisocial personality disorder Statistical analysis: unspecified
Participants	n = 149 methadone maintained dual heroin-cocaine dependent out-patients (DSM-IIIR).Patients with comorbid alcohol dependence were excluded. Mean age: 37.2+/-6.9 years Sex: 93 male Race: Afro-American: 64, Caucasian: 67, Other: 18 Employed: 10 History: lifetime cocaine use: 7.7+/-6.5 years Route of cocaine use: unspecified
Interventions	1. Bupropion 200-300 mg/day t.i.d. (3 days medication induction, flexible posology), N = 74 2. Placebo, N = 75 + Methadone + Counseling Duration: 12 weeks Multi-centre clinical trial (USA)
Outcomes	Cocaine use assessed with three times weekly UA Retention in treatment Cocaine craving assessed with a VAS Depressive symptoms assessed with Ham-D Patients withdrawn due to adverse events

Margolin 1995 a (*Continued*)

Notes	Author's affiliation: university Study funding: co-funding public and private Assessment of compliance: bupropion and metabolites every 2 weeks

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Insufficient information to permit judgement
Allocation concealment?	Unclear	Insufficient information to permit judgement
Blinding? Objective measures	Yes	The outcome or the outcome measurement were not likely to be influenced by lack of blinding
Blinding? Subjective measures	Yes	Study medication and matched placebo had an identical appearance. Blinding of participants, providers and outcome assessor appears unlikely to have been broken
Incomplete outcome data addressed? Objective outcomes except retention and dropouts	Yes	Low attrition Missing urine were coded as positive
Incomplete outcome data addressed? Subjective outcomes (e.g. craving, depressive symptoms, CGI,...)	Unclear	Low attrition Omissions were assumed to be completely random
Free of other bias?	Yes	The study appears to be free of other sources of biases

Margolin 1995 b

Methods	Double-blind, randomised, placebo controlled clinical trial Statistical analysis: unspecified
Participants	n = 37 methadone maintained dual heroin-cocaine dependent outpatients who were cocaine abstinent for 2 weeks. Patients with comorbid alcohol dependence were excluded Mean age: 34.1+/-6.9 years Gender: 16 men Race: African American: 9, Caucasian: 25, Other: 3 History: lifetime cocaine use: 11+/-6.6 years, amount of cocaine use: 2.51+/-3.84 g/week Route of cocaine use: 7 i.p., 7 i.n., 23 i.v.

Margolin 1995 b (*Continued*)

Interventions	1. Mazindol IR 1mg/day q.d. (fixed posology), N = 18 2. Placebo, N = 19 + Methadone + Case management, behavioural contingency and weekly psychotherapy group Duration: 12 weeks Single site clinical trial (USA)
Outcomes	Cocaine use assessed with three times weekly UA Retention in treatment Cocaine craving assessed with VAS Depressive symptoms assessed with BDI Patients dropped out due to adverse events
Notes	Author's affiliation: university Study funding: co-funding public and private Assessment of compliance: unspecified

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Insufficient information to permit judgement
Allocation concealment?	Yes	Pharmacy controlled. "All study personnel were blind to subject assignment"
Blinding? Objective measures	Yes	The outcome or the outcome measurement were not likely to be influenced by lack of blinding
Blinding? Subjective measures	Yes	The outcome or the outcome measurement were not likely to be influenced by lack of blinding because active medication and matching placebo were identical
Incomplete outcome data addressed? Objective outcomes except retention and dropouts	Yes	Low attrition Imputation by means of worst possible scenario
Incomplete outcome data addressed? Subjective outcomes (e.g. craving, depressive symptoms, CGI,...)	Unclear	Low attrition Imputation method for subjective outcomes was not described
Free of other bias?	Yes	The study appears to be free of other sources of biases

Margolin 1997

Methods	Double-blind, randomised, placebo controlled clinical trial Statistical analysis: unspecified
Participants	n = 17 methadone maintained dual heroin-cocaine (DSM-IIIR) dependent outpatients Mean age: 36+/-5.1 years Gender: 9 men Race: African American:4, Caucasian: 11, Other: 2 Employed: 2 History: lifetime cocaine use: 9.6+/-5 years. Route of cocaine use: 11 i.p., 1 i.n., 5 i.v.
Interventions	1. Mazindol IR 8mg/day q.d. (4 weeks' medication induction, flexible posology), N = 6 2. Mazindol IR 1mg/day q.d. (fixed posology), N = 7 3. Placebo, N = 4 + Methadone + Counseling session weekly Duration: 12 weeks Single site clinical trial (USA)
Outcomes	Cocaine use by means of three times weekly UA Retention in treatment Cocaine craving assessed with VAS Patients dropped out due to adverse events
Notes	Author's affiliation: university Study funding: public Assessment of compliance: Unspecified

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Insufficient information to permit judgement
Allocation concealment?	Yes	"All study personnel, with exception of the pharmacist were blind to treatment assignment"
Blinding? Objective measures	Yes	The outcome or the outcome measurement were not likely to be influenced by lack of blinding
Blinding? Subjective measures	Unclear	Insufficient information to permit judgement
Incomplete outcome data addressed? Objective outcomes except retention and dropouts	Unclear	Low attrition The study did not report how incomplete data were addressed

Margolin 1997 (*Continued*)

Incomplete outcome data addressed? Subjective outcomes (e.g. craving, depressive symptoms, CGI,...)	Unclear	Low attrition The study did not report how incomplete data were addressed
Free of other bias?	Yes	The study appears to be free of other sources of biases

Mooney 2009

Methods	Double-blind, randomized, placebo controlled clinical trial Analysis: ITT *Post hoc* analysis focused on 25 patients finishing the trial
Participants	n = 82 cocaine dependent out-patients (DSM-IV). Patients with comorbid alcohol dependence were excluded. Mean age: 36.4 years Gender: 54 men Race: African-American: 49, Caucasian: 23, Other: 10 Employed: 39 History: days of cocaine use during last month: 11.7, lifetime cocaine use: 10.1 years. Route of cocaine use: 58 i.p.
Interventions	1. Methamphetamine IR 30 mg, 6 times a day (5-7 days induction, fixed posology), N = 30 2. Methamphetamine SR 30mg q.d. (5-7 days induction, fixed posology), N = 25 3. Placebo, N = 27 + CBT (1h session weekly) + CM (implemented in weeks 6-9, fixed-ratio schedule with BE negative urine samples reinforced with a US$20 payment) Duration: 9 weeks Single site clinical trial (USA)
Outcomes	Cocaine use by means of with three times weekly UA Retention in treatment Cocaine craving assessed with VAS Depressive symptoms assessed with BDI Patients dropped out due to adverse events
Notes	Author's affiliation: university Study funding: public Assessment of compliance: MEMS bottles, riboflavin

Risk of bias

Item	**Authors' judgement**	**Description**

Mooney 2009 (*Continued*)

Adequate sequence generation?	Unclear	Insufficient information to permit judgement
Allocation concealment?	Unclear	Insufficient information to permit judgement
Blinding? Objective measures	Yes	The outcome or the outcome measurement were not likely to be influenced by lack of blinding
Blinding? Subjective measures	Yes	The outcome or the outcome measurement were not likely to be influenced by lack of blinding because active medication and matching placebo were identical
Incomplete outcome data addressed? Objective outcomes except retention and dropouts	No	Attrition was very high. Protocol violations followed by lost to follow-up were the most frequent reasons for dropping out in all study groups The study did not input missing data
Incomplete outcome data addressed? Subjective outcomes (e.g. craving, depressive symptoms, CGI,...)	No	Attrition was very high. Protocol violations followed by lost to follow-up were the most frequent reasons for dropping out in all study groups The study did not input missing data
Free of other bias?	Yes	The study appears to be free of other sources of biases

Perry 2004

Methods	Double-blind, randomized, placebo controlled clinical trial Statistical analysis: unspecified
Participants	n = 24 cocaine dependent/abuser out-patients (DSM III-R) with schizophrenia. It was unclear whether patients with comorbid alcohol dependence were excluded. Mean age: 37.8+/-7.6 years Gender: 23 men Race: African-American:19, Caucasian: 4, Other: 1 Employed: unspecified History: unspecified Route of cocaine use: unspecified
Interventions	1. Mazindol IR 6 mg/day t.i.d. (1 week induction, fixed posology), N = 11 2. Placebo, N = 13 + Antipsychotics (933+/-764 mg/day chlorpromazine equivalent dose) + Limited CBT

Perry 2004 (*Continued*)

	+ Motivational enhancement Duration: 6 weeks Single site clinical trial (USA)
Outcomes	Cocaine use assessed with once a week UA Retention in treatment Cocaine craving assessed with VAS Patients dropped out due to adverse events
Notes	Author's affiliation:university Study funding: co-funding public and private Assessment of compliance: Unspecified

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Insufficient information to permit judgement
Allocation concealment?	Unclear	Insufficient information to permit judgement
Blinding? Objective measures	Yes	The outcome or the outcome measurement were not likely to be influenced by lack of blinding
Blinding? Subjective measures	Yes	The outcome or the outcome measurement were not likely to be influenced by lack of blinding because active medication and matching placebo were identical
Incomplete outcome data addressed? Objective outcomes except retention and dropouts	Unclear	Attrition was high. Reasons for dropping out were not reported Imputation methods, if any, were not reported
Incomplete outcome data addressed? Subjective outcomes (e.g. craving, depressive symptoms, CGI,...)	Unclear	Attrition was high. Reasons for dropping out were not reported Imputation methods, if any, were not reported
Free of other bias?	Unclear	Insufficient information to permit judgement because the study did not describe patients' baseline characteristics

Poling 2006

Methods	Double-blind, randomised, placebo controlled clinical trial Randomization was stratified by gender and race. Statistical analysis: unspecified
Participants	n = 106 methadone-maintained patients dual heroin-cocaine dependent/abusers (DSM IV). Patients with comorbid alcohol dependence were excluded. Major depressive disorder was found in 30 patients. Mean age: 34.6+/-9 years Gender: 74 men Race: African-American: 11, Caucasian: 80, Other: 15 Employed: unspecified History: days of cocaine use during last month: 16.6, lifetime cocaine dependence: 94 Route of cocaine use: unspecified
Interventions	1. Bupropion SR 300 mg/day b.i.d. (one week induction, fixed posology) + CM, N = 27 2. Bupropion SR 300 mg/day b.i.d. (one week induction, fixed posology) + VC, N = 30 3. Placebo + CM, N = 25 4. Placebo + VC, N = 24 CM (vouchers for submitting urine samples negative, max US$ 15 per sample) VC (vouchers regardless of results, US$ 3 per sample submitted) + CBT (once weekly individual session) + Methadone 60mg/day (30 mg first week) Duration: 24 weeks Single site clinical trial (USA)
Outcomes	Cocaine use by means of tree times weekly UA Sustained cocaine abstinence (defined as at least 3 weeks of continuous abstinence) Retention in treatment Depressive symptoms assessed with Ham-D and CES-D
Notes	Author's affiliation: university Study funding: public Assessment of compliance: Check mouth

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	"Urn randomisation technique"
Allocation concealment?	Yes	"Only research pharmacist was aware of the medication condition"
Blinding? Objective measures	Yes	The outcome or the outcome measurement were not likely to be influenced by lack of blinding

Poling 2006 (*Continued*)

Blinding? Subjective measures	Yes	Study medication and placebo were encapsulated to have an identical appearance. Blinding of participants, providers and outcome assessor appears unlikely to have been broken.
Incomplete outcome data addressed? Objective outcomes except retention and dropouts	Unclear	Attrition was rather high. Reasons for dropping out were not reported No imputation of missing data
Incomplete outcome data addressed? Subjective outcomes (e.g. craving, depressive symptoms, CGI,...)	Unclear	Attrition was rather high. Reasons for dropping out were not reported No imputation of missing data
Free of other bias?	Yes	The study appears to be free of other sources of biases

Schubiner 2002

Methods	Double-blind, randomised, placebo controlled clinical trial Stratified by gender, men were further stratified by APD and women by BPD. Statistical analysis: ITT
Participants	n = 59 cocaine-dependent patients with comorbid ADHD (DSM-IV). it was unclear wether patients with comorbid alcohol dependence were excluded. Mean age:37.1 years Gender: 43 men Race: Caucasian :34 Employed: unspecified History: days of cocaine use during last month: 13.5 Route of cocaine use: unspecified
Interventions	1. Methylphenidate IR 30-90 mg/day t.i.d. (mean 26 mg t.i.d., one week induction, flexible posology), N = 24 2. Pemoline 3. Placebo, N = 24 + CBT (24 session group for cocaine dependence and individual for ADHD with comorbid SUD) Duration: 12 weeks Single site clinical trial (USA)
Outcomes	Cocaine use by means of three times weekly UA Retention in treatment Craving assessed with the Tiffany Cocaine Craving Scale ADHD symptoms assessed with ADHD Symptom Checklist Depressive symptoms assessed with BDI Patients dropped out due to adverse events

Schubiner 2002 (*Continued*)

Notes	Author's affiliation: university Study funding: public Assessment of compliance: Computerized questionnaire on the number of pills taken The group of patients randomised to Pemoline was withdrawn while the study was conducted because of recruitment problems. Thus only 48 patients were included in the statistical analysis

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Insufficient information to permit judgement
Allocation concealment?	Unclear	Insufficient information to permit judgement
Blinding? Objective measures	Yes	The outcome or the outcome measurement were not likely to be influenced by lack of blinding
Blinding? Subjective measures	Yes	Research pharmacist compounded study medication and placebo, which had an identical appearance. Blinding of participants, providers and outcome assessor appears unlikely to have been broken.
Incomplete outcome data addressed? Objective outcomes except retention and dropouts	No	Attrition was high and reasons for dropping out were not reported for any study group. Imputation methods, if any, were not reported
Incomplete outcome data addressed? Subjective outcomes (e.g. craving, depressive symptoms, CGI,...)	No	Attrition was high and reasons for dropping out were not reported for any study group. Imputation methods, if any, were not reported
Free of other bias?	Unclear	One study group (Pemoline) was withdrawn during the course of the study because of recruitment difficulties

Shearer 2003

Methods	Double-blind, randomised, placebo controlled clinical trial Stratification by gender Analysis: ITT
Participants	n = 30 cocaine-dependent (DSM IV). 24 patients had a comorbid opioid dependence. It was unclear whether patients with alcohol dependence were excluded. Mean age: 28+/6 years Gender: 16 men Race: unspecified Employed: unspecified History: frequency of cocaine use: 6+/-5 times a day Route of cocaine use: 30 i.v.
Interventions	1. Dexamphetamine IR 20-60 mg (mean 41mg) q.d. (9 days induction, flexible posology) , N = 16 2. Placebo, N =14 + Drug and alcohol counselling + Methadone (24 subjects) Duration: 14 weeks Multi-centre trial (Australia)
Outcomes	Cocaine use by means of UA every 2 weeks Sustained cocaine abstinence (defined as at least 3 weeks of continuous abstinence) Retention in treatment Cocaine craving assessed with VAS Self-reported cocaine use Depressive symptoms assessed with the Brief Symptom Inventory
Notes	Author's affiliation: university Study funding: co-funding private and public Assessment of compliance: Unspecified

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"Using randomisation schedules"
Allocation concealment?	Yes	"Pharmacy controlled"
Blinding? Objective measures	Yes	The outcome or the outcome measurement were not likely to be influenced by lack of blinding
Blinding? Subjective measures	Unclear	Insufficient information to permit judgement

Shearer 2003 (*Continued*)

Incomplete outcome data addressed? Objective outcomes except retention and dropouts	Unclear	Attrition was very high and reasons for dropping out were not described for each study group Missing urine were deemed positive
Incomplete outcome data addressed? Subjective outcomes (e.g. craving, depressive symptoms, CGI,...)	Unclear	Attrition was very high and reasons for dropping out were not described for each study group Data for included subjects subsequently lost to follow-up were imputed from baseline data using a "worst case scenario" assumption of no change
Free of other bias?	Yes	The study appears to be free of other sources of biases

Shoptaw 2008

Methods	Double-blind, randomised, placebo controlled clinical trial Stratification by gender Statistical analysis: ITT
Participants	n = 70 cocaine-dependent out-patients (DSM IV). Patients with alcohol dependence were excluded. Mean age: 36.9+/-8 years Gender: 59 men Race: African-American 38, Caucasian 2, Other 30 Employed:unspecified History: last month cocaine use: 11.1 days, lifetime cocaine use: 8.2 years Route of cocaine use: 59 i.p., 7 i.n., 1 i.v., 2 oral, 1 unspecified
Interventions	1. Bupropion 300 mg b.i.d. (3 days induction,flexible posology), N = 37 2. Placebo, N = 33 + CBT (3 sessions a week) + Counseling (once a week) Duration: 16 weeks Single site (USA)
Outcomes	Cocaine use by means of three times weekly UA Sustained cocaine abstinence (defined as at least 3 weeks of continuous abstinence) Retention in treatment Cocaine craving assessed with VAS Depressive symptoms assessed with BDI
Notes	Author's affiliation: university Study funding: public Assessment of compliance: Pill count

Shoptaw 2008 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Insufficient information to permit judgement
Allocation concealment?	Unclear	Insufficient information to permit judgement
Blinding? Objective measures	Yes	The outcome or the outcome measurement were not likely to be influenced by lack of blinding
Blinding? Subjective measures	Yes	Study medication and matched placebo had an identical appearance. Blinding of participants, providers and outcome assessor appears unlikely to have been broken
Incomplete outcome data addressed? Objective outcomes except retention and dropouts	No	Attrition was very high. Failure to return was the most frequent reason for dropping out in both study groups Missing data were not imputed
Incomplete outcome data addressed? Subjective outcomes (e.g. craving, depressive symptoms, CGI,...)	No	Attrition was very high. Failure to return was the most frequent reason for dropping out in both study groups Missing data were not imputed
Free of other bias?	Yes	The study appears to be free of other sources of biases

Stine 1995

Methods	Double-blind, randomised, placebo controlled clinical trial. Analysis: ITT
Participants	n = 43 cocaine-dependent (DSM-IIIR) out-patients, reporting cocaine use of at least 12g in the 3 months prior to entering the study. Fiveteen patients had a comorbid major depressive disorder and 4 an antisocial personality disorder. Patients with alcohol dependence were excluded. Mean age: 34.5 years Gender: 37 men Race: African-American: 22, Caucasian: 34, Other: 4 Employed: unspecified History: unspecified Route of cocaine use: unspecified

Stine 1995 (*Continued*)

Interventions	1. Mazindol 2 mg q.d. (fixed posology), N = 22 2. Placebo, N = 21 + Counseling (6 sessions) Duration: 6 weeks Multi-centre trial (USA)
Outcomes	Cocaine use by means of once weekly UA Sustained cocaine abstinence (defined as at least 3 weeks of continuous abstinence) Retention in treatment Self-reported cocaine use Cocaine craving assessed with a 5-point Analog Scale Depressive symptoms severity assessed with Ham-D and BDI Patients dropped out due to adverse events
Notes	Author's affiliation: university Study funding: co-funding public and private Assessment of compliance: Self-report or failure to pick up

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Insufficient information to permit judgement
Allocation concealment?	Unclear	Insufficient information to permit judgement
Blinding? Objective measures	Yes	The outcome or the outcome measurement were not likely to be influenced by lack of blinding
Blinding? Subjective measures	Unclear	Insufficient information to permit judgement
Incomplete outcome data addressed? Objective outcomes except retention and dropouts	Unclear	Attrition was high in both study groups Missing urine were considered positive
Incomplete outcome data addressed? Subjective outcomes (e.g. craving, depressive symptoms, CGI,...)	Unclear	Attrition was high in both study groups LOCF was used to impute missing data of continuous measures
Free of other bias?	Yes	The study appears to be free of other sources of biases

Abreviations: ADHD: attention deficit/hyperactivity disorder, ASRS: adult ADHD self reported scale BDI: Beck depression inventory, b.i.d.: twice a day, BSCS: brief substance craving scale, CBT: cognitive behavioural therapy, CCQ: cocaine craving questionnaire, CES-D: centre for epidemiologic studies depression scale, CM: contingency management, Ham-D: Hamilton depression scale, i.n.: intranasal, i.p.: intrapulmonary, i.v..: intravenous, ITT: intention to treat, LOCF: last observation carried forward, NR: not reported, q.d.: once a day, t.i.d.: three times a day, UA: urinalysis, VAS: visual analogue scale, VC: voucher control

Characteristics of excluded studies *[ordered by study ID]*

Aharonovich 2006	Subanalyisis of an included study (Levin 2007)
Avants 1998	Not a randomised placebo controlled clinical trial
Berger 1989	Not a randomised placebo controlled clinical trial
Downey 2000	Preliminar results of an included study (Schubiner 2002)
Grabowski 1994	Preliminar results of an included study (Grabowski 1997)
Kampman 1997	Not a randomised placebo controlled clinical trial
Levin 1999	Not a randomised placebo controlled clinical trial
Levin 2002	Not a randomised placebo controlled clinical trial
Levin 2006	Cocaine dependence or abuse was not an inclusion criteria
Margolin 1991	Not a randomised placebo controlled clinical trial
Montoya 1994	Not a randomised placebo controlled clinical trial
Mooney 2008 II	Cocaine abuse or dependence was not an inclusion criteria
Ollo 1996	Laboratory study without an outpatient follow up
Seibyl 1992	Not a randomised placebo controlled clinical trial
Starosta 2006	Subanalysis of an included study (Dackis 2005)
Tennant 1990	Not a randomised placebo controlled clinical trial

Characteristics of ongoing studies *[ordered by study ID]*

Aharonovich

Trial name or title	A placebo-controlled double-blind combined treatment of modafinil and CBT for cocaine dependence
Methods	Random allocation; double-blind; 12 weeks' duration; two parallel groups, placebo-controlled. Phase II.
Participants	Cocaine-dependent out-patients (DSM-IV) that used cocaine at least 8 days in the last month or report episodic binges of large amounts of cocaine
Interventions	1.Modafinil 2.Placebo + CBT-RP
Outcomes	Treatment retention outcome Cocaine use Cognitive functioning Cocaine withdrawal symptoms throughout the study
Starting date	2006
Contact information	Efrat Aharonovich 212 923 3031
Notes	

Casas

Trial name or title	Efficacy of caffeine, with and without biperiden,as a maintenance treatment for cocaine dependence
Methods	Random allocation;double-blind; 22 weeks' duration; three parallel groups, placebo-controlled. Phase IV
Participants	Cocaine-dependent out-patients (DSM-IV-TR)
Interventions	1.Caffeine 300-1200 mg t.i.d. and biperide 8 mg b.i.d 2.Caffeine 300-1200 mg t.i.d. and placebo 3.Placebo (During 10 days in an inhospital setting)
Outcomes	Cocaine use Survival
Starting date	July 2008
Contact information	Miquel Casas mcasas@vhebron.net
Notes	

Dackis a

Trial name or title	Modafinil treatment for cocaine-dependent individuals
Methods	Random allocation;double-blind; 24 weeks' duration; three parallel groups, placebo-controlled. Phase II
Participants	n=120 Cocaine-dependent patients (DSM-IV)
Interventions	1.Modafinil 200 mg /day 2.Modafinil 400 mg/ day 3.Placebo (Treatment during 8 weeks) +CBT
Outcomes	Urine toxicology Retention Cocaine craving
Starting date	July 2004
Contact information	Charles Dackis
Notes	Completed

Dackis b

Trial name or title	Community-based modafinil treatment of women with cocaine dependence and HIV-High risk behaviour
Methods	Random allocation;double-blind; 8 weeks' duration; two parallel groups, placebo-controlled. Phase II
Participants	Cocaine-dependent patients (DSM-IV) using at least 8 days moth
Interventions	1.Modafinil 300 mg /day 2.Placebo +Behavioural:Telephone monitoring and Adaptive Counselling
Outcomes	Cocaine use High risk behaviour
Starting date	September 2006
Contact information	Thea L Gallis gallis˙t@mail.trc.upenn.edu
Notes	

Herin

Trial name or title	Pilot study examining effect for dextroamphetamine to treat cocaine dependence plus attention-deficit hyperactivity disorder (ADHD)
Methods	Random allocation;double-blind; 12 weeks' duration; two parallel groups, placebo-controlled. Phase II
Participants	Cocaine-dependent and ADHD patients
Interventions	1.Dextroamphetamine SR 60mg /day 2.Placebo +CBT
Outcomes	Substance use ADHD symptoms Treatment retention Cocaine Craving
Starting date	August 2007
Contact information	
Notes	Terminated

Levin a

Trial name or title	Free treatment for cocaine dependence:A placebo-controlled study of mixed amphetamine salts (Adderall-XR) and topiramate for the treatment of cocaine dependence
Methods	Random allocation;double-blind; 14 weeks' duration; two parallel groups, placebo-controlled. Phase II. Mesures of interest: -BE presence in urine three times a week
Participants	n=120 cocaine-dependent out-patients that used cocaine at least 4 days in the past month, with at least weekly cocaine use.
Interventions	1.Adderall-XR and topiramate 2.Placebo
Outcomes	Sustained cocaine abstinence Pattern of cocaine use Cocaine craving
Starting date	February 2007
Contact information	David J Brooks brooksd@pi.cpmc.columbia.edu
Notes	

Levin b

Trial name or title	Randomized, double-blind, placebo-controlled study of mixed amphetamine salts (Adderall-XR) for the treatment of adult attention deficit hyperactivity disorder (ADHD) and cocaine dependence
Methods	Random allocation;double-blind; 14 weeks' duration; three parallel groups, placebo-controlled. Phase II/Phase III
Participants	n=75 Cocaine-dependent (DSM-IV) and ADHD out-patients (DSM-IV-TR)
Interventions	1.Adderall-XR 80 mg/day 2.Adderall-XR 60 mg/day 3.Placebo
Outcomes	Cocaine urine toxicology ADHD symptoms (AARS; CGI)
Starting date	December 2007
Contact information	Amy Mahony mahonya@pi.cpmc.columbia.edu
Notes	

Malcolm

Trial name or title	Modafinil combined with cognitive behavior therapy to treat cocaine addiction
Methods	Random allocation;double-blind; 8 weeks' duration; three parallel groups, placebo-controlled. Phase II. Mesures of interest: -BE presence in urine three times a week
Participants	Cocaine-dependent patients (DSM-IV)
Interventions	1. Modafinil 200 mg/day 2. Modafinil 400 mg/day 3. Placebo + CBT
Outcomes	Number of cocaine non-use days Consecutive cocaine non-use days
Starting date	April 2004
Contact information	Kristi Huebner huebnerk@musc.edu
Notes	

Mattick

Trial name or title	Randomised placebo-controlled trial of modafinil for cocaine dependence
Methods	Random allocation;double-blind; 10 weeks' duration; two parallel groups, placebo-controlled. Phase II.
Participants	Cocaine-dependent patients (DSM-IV)
Interventions	1. Modafinil 200 mg/day 2. Placebo + Tailored CBT
Outcomes	Urinalysis negative for cocaine over 10 weeks Adverse events Compliance Retention
Starting date	July 2005
Contact information	
Notes	

Moeller

Trial name or title	Caffeine and cocaine
Methods	Random allocation;double-blind; 3 weeks' duration; two parallel groups, placebo-controlled. Phase I/II.
Participants	Cocaine-dependent patients (DSM-IV)
Interventions	1. Caffeine 600-900 mg/day 2. Placebo
Outcomes	Cocaine positive urine 3 weeks of treatment Cue reactivity 3 weeks of treatment
Starting date	April 2008
Contact information	Ann D Garcia Ann.D.Garcia@uth.tmc.edu
Notes	

Schmitz a

Trial name or title	Treatment of cocaine dependence:comparison of three doses of dextro-amphetamine sulphate and placebo
Methods	Random allocation;double-blind; 25 weeks' duration; four parallel groups, placebo-controlled. Phase II.

Schmitz a (*Continued*)

Participants	Cocaine dependent patients (DSM-IV)
Interventions	1. Dextro-Amphetamine sulphate 0 mg (placebo) 2. Dextro-Amphetamine sulphate 40 mg/day 3. Dextro-Amphetamine sulphate 60 mg/day 4. Dextro-Amphetamine sulphate 80 mg/day
Outcomes	Substance use Retention
Starting date	September 2003
Contact information	
Notes	Completed

Schmitz b

Trial name or title	Medications for stopping cocaine dependence and preventing relapse
Methods	Random allocation;double-blind; 12 weeks' duration; four parallel groups, placebo-controlled. Phase II.
Participants	Cocaine dependent patients (DSM-IV)
Interventions	1. Naltrexone 50 mg/day 2. Levodopa/carbidopa 800/200 mg/day 3. Modafinil 400 mg/day 4. Placebo
Outcomes	Medication compliance Medication side effects
Starting date	March 2006
Contact information	Ann Garcia Ann.D.Garcia@uth.tmc.edu
Notes	

Schmitz c

Trial name or title	Pharmacotherapy dosing regimen in cocaine and opiate dependent individuals
Methods	Random allocation;double-blind; 24 weeks' duration; five parallel groups, placebo-controlled. Phase II.
Participants	Cocaine abuse or dependence patient (SCID) and opiate dependence (SCID)

Schmitz c (*Continued*)

Interventions	1.Modafinil 200 mg/day 2.Modafinil 400 mg/day 3. Citalopram 20 mg/day 4. Citalopram 40 mg/day 5. Placebo + Methadone
Outcomes	Confirmed abstinence of cocaine Retention Medication compliance
Starting date	July 2006
Contact information	Jan Lindsay jan.a.lindsay@uth.tmc.edu
Notes	

Schmitz d

Trial name or title	Effectiveness of modafinil and D-amphetamine in treating cocaine dependent individuals
Methods	Random allocation;double-blind; 16 weeks' duration; four parallel groups, placebo-controlled. Phase II.
Participants	Cocaine abuse or dependence patient (SCID)
Interventions	1. Modafinil 200 mg/day 2. Modafinil 400 mg/day 3. Modafinil 200 mg/day and D-amphetamine 30 mg/day 4. Placebo
Outcomes	Medication compliance Medication side effects
Starting date	March 2006
Contact information	Jan Lindsay jan.a.lindsay@uth.tmc.edu
Notes	

Abreviations: ADHD: attention deficit/hyperactivity disorder, ASRS: adult ADHD self reported scale, b.i.d.: twice a day, CBT: cognitive behavioural therapy, CBT-RP: cognitive behavioural therapy and relapse prevention, CGI: clinical global impression, SCID: structured clinical interview for DSM-IV, t.i.d.: three times a day.

CBT-RP

DATA AND ANALYSES

Comparison 1. Psychostimulants vs. Placebo: Primary analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cocaine use assessed by the mean (SD) of the proportion of cocaine-free UA across the study per patient	7	469	Std. Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.07, 0.29]
2 Sustained cocaine abstinence	8	811	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.98, 2.02]
3 Number of patients who finished the study	16	1345	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.89, 1.07]
4 Self-reported cocaine use	1	28	Std. Mean Difference (IV, Random, 95% CI)	Not estimable
5 Cocaine craving	3	340	Std. Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.15, 0.27]
6 Patient-rated CGI-severity scale	1	300	Std. Mean Difference (IV, Random, 95% CI)	0.28 [0.05, 0.50]
7 Investigator-rated CGI-severity scale	1	300	Std. Mean Difference (IV, Random, 95% CI)	0.07 [-0.15, 0.30]
8 Patient-rated CGI-improvement scale	1	300	Std. Mean Difference (IV, Random, 95% CI)	0.27 [0.04, 0.50]
9 CGI investigator change	1	300	Std. Mean Difference (IV, Random, 95% CI)	Not estimable
10 CGI investigator improvement =1or 2	1	106	Risk Ratio (IV, Random, 95% CI)	0.81 [0.57, 1.15]
11 Depressive symptoms severity	2	90	Std. Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.48, 0.35]
12 Patients dropped out due to any adverse events	11	964	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.02, 0.03]
13 Patients dropped out due to cardiovascular adverse events	7	417	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.03, 0.02]
14 Heroin use assessed by the mean (SD) of the proportion of heroin-free UA across the study per patient	2	167	Std. Mean Difference (IV, Fixed, 95% CI)	0.29 [-0.02, 0.61]
15 Sustained heroin abstinence	2	199	Risk Ratio (M-H, Fixed, 95% CI)	1.77 [1.31, 2.39]
16 ADHD severity	2	121	Std. Mean Difference (IV, Random, 95% CI)	-0.36 [-1.11, 0.38]

Comparison 2. Subgroup analysis 1: Sustained cocaine abstinence

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Type of drug	8	811	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.98, 2.02]
1.1 Bupropion	2	176	Risk Ratio (M-H, Random, 95% CI)	1.64 [1.09, 2.45]
1.2 Dexamphetamine	2	124	Risk Ratio (M-H, Random, 95% CI)	2.12 [1.18, 3.84]
1.3 Mazindol	1	43	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.29, 2.22]
1.4 Methylphenidate	1	106	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.37, 2.13]
1.5 Modafinil	1	62	Risk Ratio (M-H, Random, 95% CI)	2.67 [0.94, 7.60]

1.6 Selegiline	1	300	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.24, 1.44]
2 Definition of cocaine use disorder	8	811	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.98, 2.02]
2.1 Cocaine abuse or dependence	2	176	Risk Ratio (M-H, Random, 95% CI)	1.64 [1.09, 2.45]
2.2 Cocaine dependence	6	635	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.76, 2.17]
3 Comorbid ADHD as inclusion criterion	8	811	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.98, 2.02]
3.1 With comorbid ADHD	1	106	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.37, 2.13]
3.2 Without comorbid ADHD	7	705	Risk Ratio (M-H, Random, 95% CI)	1.50 [1.01, 2.21]
4 Comorbid opioid dependence as inclusion criterion	8	811	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.98, 2.02]
4.1 With a comorbid opioid dependence	2	200	Risk Ratio (M-H, Random, 95% CI)	1.84 [1.23, 2.74]
4.2 Without a comorbid opioid dependence	6	611	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.71, 1.78]
5 Clinical trial reporting quality: Sequence generation	8	811	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.98, 2.02]
5.1 Low risk of bias	4	498	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.82, 2.42]
5.2 Intermediate or high risk of bias	4	313	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.75, 2.52]
6 Clinical trial reporting quality: Allocation concealment	8	811	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.98, 2.02]
6.1 Low risk of bias	3	198	Risk Ratio (M-H, Random, 95% CI)	1.71 [1.19, 2.47]
6.2 Intermediate or high risk of bias	5	613	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.63, 2.06]
7 Clinical trial reporting quality: Blinding	8	811	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.98, 2.02]
7.1 Low risk of bias	8	811	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.98, 2.02]
7.2 Intermediate or high risk of bias	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
8 Clinical trial reporting quality: Incomplete outcome data	8	811	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.98, 2.02]
8.1 Low risk of bias	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
8.2 Intermediate or high risk of bias	8	811	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.98, 2.02]
9 Clinical trial reporting quality: Other bias	8	811	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.98, 2.02]
9.1 Low risk of bias	6	449	Risk Ratio (M-H, Random, 95% CI)	1.53 [1.14, 2.07]
9.2 Intermediate or high risk of bias	2	362	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.27, 5.40]
10 Single vs. Multiple sites	8	811	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.98, 2.02]
10.1 Single site	4	332	Risk Ratio (M-H, Random, 95% CI)	1.89 [1.35, 2.64]
10.2 Multiple sites	4	479	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.55, 1.40]

Comparison 3. Subgroup analysis 2: Type of drug

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cocaine use assessed by the mean (SD) of the proportion of cocaine-free UA across the study per patient	7	469	Std. Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.07, 0.29]
1.1 Bupropion	2	176	Std. Mean Difference (IV, Fixed, 95% CI)	0.25 [-0.05, 0.55]
1.2 Dexamphetamine	2	90	Std. Mean Difference (IV, Fixed, 95% CI)	0.31 [-0.13, 0.74]
1.3 Methylphenidate	3	203	Std. Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.36, 0.19]
2 Number of patients who finished the study	16	1345	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.89, 1.07]
2.1 Bupropion	3	325	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.87, 1.16]
2.2 Dexamphetamine	3	252	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.90, 2.05]
2.3 Mazindol	4	121	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.71, 1.24]
2.4 Methamphetamine	1	82	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.52, 2.11]
2.5 Methylphenidate	3	203	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.68, 1.22]
2.6 Modafinil	1	62	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.67, 1.40]
2.7 Selegiline	1	300	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.76, 1.03]
3 Cocaine craving	3	340	Std. Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.15, 0.27]
3.1 Bupropion	1	12	Std. Mean Difference (IV, Fixed, 95% CI)	-0.51 [-1.68, 0.67]
3.2 Mazindol	1	28	Std. Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.76, 0.73]
3.3 Selegiline	1	300	Std. Mean Difference (IV, Fixed, 95% CI)	0.09 [-0.14, 0.31]
4 Depressive symptoms severity	2	90	Std. Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.48, 0.35]
4.1 Bupropion	1	62	Std. Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.53, 0.47]
4.2 Mazindol	1	28	Std. Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.87, 0.61]
5 Patients dropped out due to any adverse events	11	964	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.02, 0.03]
5.1 Bupropion	1	149	Risk Difference (M-H, Random, 95% CI)	Not estimable
5.2 Dexamphetamine	2	158	Risk Difference (M-H, Random, 95% CI)	0.12 [-0.06, 0.30]
5.3 Mazindol	4	121	Risk Difference (M-H, Random, 95% CI)	-0.01 [-0.09, 0.07]
5.4 Methamphetamine	1	82	Risk Difference (M-H, Random, 95% CI)	0.02 [-0.05, 0.08]
5.5 Methylphenidate	2	154	Risk Difference (M-H, Random, 95% CI)	-0.01 [-0.05, 0.04]
5.6 Selegiline	1	300	Risk Difference (M-H, Random, 95% CI)	Not estimable
6 Patients dropped out due to cardiovascular adverse events	7	417	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.03, 0.02]
6.1 Bupropion	1	149	Risk Difference (M-H, Fixed, 95% CI)	Not estimable
6.2 Dexamphetamine	1	30	Risk Difference (M-H, Fixed, 95% CI)	Not estimable
6.3 Mazindol	3	84	Risk Difference (M-H, Fixed, 95% CI)	Not estimable
6.4 Methylphenidate	2	154	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.06, 0.03]
7 Heroin use assessed by the mean (SD) of the proportion of heroin-free UA across the study per patient	2	167	Std. Mean Difference (IV, Fixed, 95% CI)	0.29 [-0.02, 0.61]
7.1 Bupropion	1	105	Std. Mean Difference (IV, Fixed, 95% CI)	0.28 [-0.10, 0.67]
7.2 Dexamphetamine	1	62	Std. Mean Difference (IV, Fixed, 95% CI)	0.31 [-0.24, 0.85]
8 Sustained heroin abstinence	2	199	Risk Ratio (M-H, Fixed, 95% CI)	1.77 [1.31, 2.39]
8.1 Bupropion	1	105	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [1.04, 2.43]
8.2 Dexamphetamine	1	94	Risk Ratio (M-H, Fixed, 95% CI)	1.98 [1.28, 3.04]
9 ADHD severity	2	121	Std. Mean Difference (IV, Random, 95% CI)	-0.36 [-1.11, 0.38]

9.1 Methylphenidate	2	121	Std. Mean Difference (IV, Random, 95% CI)	-0.36 [-1.11, 0.38]

Comparison 4. Subgroup analysis 3: Definition of cocaine use disorder

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cocaine use assessed by the mean (SD) of the proportion of cocaine-free UA across the study per patient	7	469	Std. Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.07, 0.29]
1.1 Cocaine abuse or dependence	2	176	Std. Mean Difference (IV, Fixed, 95% CI)	0.25 [-0.05, 0.55]
1.2 Cocaine dependence	5	293	Std. Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.21, 0.26]
2 Number of patients who finished the study	16	1345	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.89, 1.07]
2.1 Cocaine abuse or dependence	3	200	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.69, 1.27]
2.2 Cocaine dependence	13	1145	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.89, 1.08]
3 Cocaine craving	3	340	Std. Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.15, 0.27]
3.1 Cocaine abuse or dependence	1	12	Std. Mean Difference (IV, Fixed, 95% CI)	-0.51 [-1.68, 0.67]
3.2 Cocaine dependence	2	328	Std. Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.14, 0.29]
4 Depressive symptoms severity	2	90	Std. Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.48, 0.35]
4.1 Cocaine abuse or dependence	1	62	Std. Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.53, 0.47]
4.2 Cocaine dependence	1	28	Std. Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.87, 0.61]
5 Patients dropped out due to any adverse events	11	964	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.02, 0.03]
5.1 Cocaine abuse or dependence	1	24	Risk Difference (M-H, Random, 95% CI)	Not estimable
5.2 Cocaine dependence	10	940	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.02, 0.04]
6 Patients dropped out due to cardiovascular adverse events	7	417	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.03, 0.02]
6.1 Cocaine abuse or dependence	1	24	Risk Difference (M-H, Fixed, 95% CI)	Not estimable
6.2 Cocaine dependence	6	393	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.03, 0.02]
7 Heroin use assessed by the mean (SD) of the proportion of heroin-free UA across the study per patient	2	167	Std. Mean Difference (IV, Fixed, 95% CI)	0.29 [-0.02, 0.61]
7.1 Cocaine abuse or dependence	1	105	Std. Mean Difference (IV, Fixed, 95% CI)	0.28 [-0.10, 0.67]
7.2 Cocaine dependence	1	62	Std. Mean Difference (IV, Fixed, 95% CI)	0.31 [-0.24, 0.85]
8 Sustained heroin abstinence	2	199	Risk Ratio (M-H, Fixed, 95% CI)	1.77 [1.31, 2.39]
8.1 Cocaine abuse or dependence	2	199	Risk Ratio (M-H, Fixed, 95% CI)	1.77 [1.31, 2.39]
8.2 Cocaine dependence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9 ADHD severity	2	121	Std. Mean Difference (IV, Random, 95% CI)	-0.36 [-1.11, 0.38]

9.1 Cocaine abuse or dependence	0	0	Std. Mean Difference (IV, Random, 95% CI)	Not estimable
9.2 Cocaine dependence	2	121	Std. Mean Difference (IV, Random, 95% CI)	-0.36 [-1.11, 0.38]

Comparison 5. Subgroup analysis 4: Comorbid ADHD as inclusion criterion

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cocaine use assessed by the mean (SD) of the proportion of cocaine-free UA across the study per patient	7	469	Std. Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.07, 0.29]
1.1 With comorbid ADHD	2	154	Std. Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.33, 0.30]
1.2 Without comorbid ADHD	5	315	Std. Mean Difference (IV, Fixed, 95% CI)	0.17 [-0.05, 0.40]
2 Number of patients who finished the study	16	1345	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.89, 1.07]
2.1 With comorbid ADHD	2	154	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.64, 1.25]
2.2 Without comorbid ADHD	14	1191	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.89, 1.08]
3 Cocaine craving	3	340	Std. Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.15, 0.27]
3.1 With comorbid ADHD	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable
3.2 Without comorbid ADHD	3	340	Std. Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.15, 0.27]
4 Depressive symptoms severity	2	90	Std. Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.48, 0.35]
4.1 With comorbid ADHD	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable
4.2 Without comorbid ADHD	2	90	Std. Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.48, 0.35]
5 Patients dropped out due to any adverse events	11	964	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.02, 0.03]
5.1 With comorbid ADHD	2	154	Risk Difference (M-H, Random, 95% CI)	-0.01 [-0.05, 0.04]
5.2 Without comorbid ADHD	9	810	Risk Difference (M-H, Random, 95% CI)	0.02 [-0.02, 0.06]
6 Patients dropped out due to cardiovascular adverse events	7	417	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.03, 0.02]
6.1 With comorbid ADHD	2	154	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.06, 0.03]
6.2 Without comorbid ADHD	5	263	Risk Difference (M-H, Fixed, 95% CI)	Not estimable
7 Heroin use assessed by the mean (SD) of the proportion of heroin-free UA across the study per patient	2	167	Std. Mean Difference (IV, Fixed, 95% CI)	0.29 [-0.02, 0.61]
7.1 With comorbid ADHD	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable
7.2 Without comorbid ADHD	2	167	Std. Mean Difference (IV, Fixed, 95% CI)	0.29 [-0.02, 0.61]
8 Sustained heroin abstinence	2	199	Risk Ratio (M-H, Fixed, 95% CI)	1.77 [1.31, 2.39]
8.1 With comorbid ADHD	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8.2 Withou comorbid ADHD	2	199	Risk Ratio (M-H, Fixed, 95% CI)	1.77 [1.31, 2.39]

9 ADHD severity	2	121	Std. Mean Difference (IV, Random, 95% CI)	-0.36 [-1.11, 0.38]
9.1 With comorbid ADHD	2	121	Std. Mean Difference (IV, Random, 95% CI)	-0.36 [-1.11, 0.38]
9.2 Without comorbid ADHD	0	0	Std. Mean Difference (IV, Random, 95% CI)	Not estimable

Comparison 6. Subgroup analysis 5: Comorbid opioid dependence as inclusion criterion

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cocaine use assessed by the mean (SD) of the proportion of cocaine-free UA across the study per patient	7	469	Std. Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.07, 0.29]
1.1 With a comorbid opioid dependence	2	166	Std. Mean Difference (IV, Fixed, 95% CI)	0.28 [-0.04, 0.59]
1.2 Without a comorbid opioid dependence	5	303	Std. Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.20, 0.25]
2 Number of patients who finished the study	16	1345	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.89, 1.05]
2.1 With a comorbid opioid dependence	5	403	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.88, 1.18]
2.2 Without a comorbid opioid dependence	11	942	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.81, 1.03]
3 Cocaine craving	3	340	Std. Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.15, 0.27]
3.1 With a comorbid opioid dependence	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable
3.2 Without a comorbid opioid dependence	3	340	Std. Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.15, 0.27]
4 Depressive symptoms severity	2	90	Std. Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.48, 0.35]
4.1 With a comorbid opioid dependence	1	62	Std. Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.53, 0.47]
4.2 Without a comorbid opioid dependence	1	28	Std. Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.87, 0.61]
5 Patients dropped out due to any adverse events	11	964	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.02, 0.03]
5.1 With a comorbid opioid dependence	3	203	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.04, 0.05]
5.2 Without a comorbid opioid dependence	8	761	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.02, 0.05]
6 Patients dropped out due to cardiovascular adverse events	7	417	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.03, 0.02]
6.1 With a comorbid opioid dependence	2	166	Risk Difference (M-H, Fixed, 95% CI)	Not estimable
6.2 Without a comorbid opioid dependence	5	251	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.05, 0.03]

7 Heroin use assessed by the mean (SD) of the proportion of heroin-free UA across the study per patient	2	167	Std. Mean Difference (IV, Fixed, 95% CI)	0.29 [-0.02, 0.61]
7.1 With a comorbid opioid dependence	2	167	Std. Mean Difference (IV, Fixed, 95% CI)	0.29 [-0.02, 0.61]
7.2 Without a comorbid opioid dependence	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable
8 Sustained heroin abstinence	2	199	Risk Ratio (M-H, Fixed, 95% CI)	1.77 [1.31, 2.39]
8.1 With a comorbid opioid dependence	2	199	Risk Ratio (M-H, Fixed, 95% CI)	1.77 [1.31, 2.39]
8.2 Without a comorbid opioid dependence	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9 ADHD severity	2	121	Std. Mean Difference (IV, Random, 95% CI)	-0.36 [-1.11, 0.38]
9.1 With a comorbid opioid dependence	0	0	Std. Mean Difference (IV, Random, 95% CI)	Not estimable
9.2 Without a comorbid opioid dependence	2	121	Std. Mean Difference (IV, Random, 95% CI)	-0.36 [-1.11, 0.38]

Comparison 7. Subgroup analysis 6: Clinical trial reporting quality: Sequence generation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cocaine use assessed by the mean (SD) of the proportion of cocaine-free UA across the study per patient	7	469	Std. Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.07, 0.29]
1.1 Low risk of bias	2	136	Std. Mean Difference (IV, Fixed, 95% CI)	0.29 [-0.05, 0.63]
1.2 Intermediate or high risk of bias	5	333	Std. Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.18, 0.26]
2 Number of patients who finished the study	16	1345	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.89, 1.07]
2.1 Low risk of bias	4	498	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.79, 1.03]
2.2 Intermediate or high risk of bias	12	847	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.91, 1.18]
3 Cocaine craving	3	340	Std. Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.15, 0.27]
3.1 Low risk of bias	1	300	Std. Mean Difference (IV, Fixed, 95% CI)	0.09 [-0.14, 0.31]
3.2 High risk of bias	2	40	Std. Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.78, 0.47]
4 Depressive symptoms severity	2	90	Std. Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.48, 0.35]
4.1 Low risk of bias	1	62	Std. Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.53, 0.47]
4.2 Intermediate or high risk of bias	1	28	Std. Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.87, 0.61]
5 Patients dropped out due to any adverse events	11	964	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.02, 0.03]
5.1 Low risk of bias	2	330	Risk Difference (M-H, Random, 95% CI)	0.11 [-0.37, 0.60]
5.2 Intermediate or high risk of bias	9	634	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.01, 0.04]

6 Patients dropped out due to cardiovascular adverse events	7	417	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.03, 0.02]
6.1 Low risk of bias	1	30	Risk Difference (M-H, Fixed, 95% CI)	Not estimable
6.2 Intermediate or high risk of bias	6	387	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.03, 0.02]
7 Heroin use assessed by the mean (SD) of the proportion of heroin-free UA across the study per patient	2	167	Std. Mean Difference (IV, Fixed, 95% CI)	0.29 [-0.02, 0.61]
7.1 Low risk of bias	1	105	Std. Mean Difference (IV, Fixed, 95% CI)	0.28 [-0.10, 0.67]
7.2 Intermediate or high risk of bias	1	62	Std. Mean Difference (IV, Fixed, 95% CI)	0.31 [-0.24, 0.85]
8 Sustained heroin abstinence	2	199	Risk Ratio (M-H, Fixed, 95% CI)	1.77 [1.31, 2.39]
8.1 Low risk of bias	1	105	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [1.04, 2.43]
8.2 Intermediate or high risk of bias	1	94	Risk Ratio (M-H, Fixed, 95% CI)	1.98 [1.28, 3.04]
9 ADHD severity	2	121	Std. Mean Difference (IV, Random, 95% CI)	-0.36 [-1.11, 0.38]
9.1 Low risk of bias	0	0	Std. Mean Difference (IV, Random, 95% CI)	Not estimable
9.2 Intermediate or low risk of bias	2	121	Std. Mean Difference (IV, Random, 95% CI)	-0.36 [-1.11, 0.38]

Comparison 8. Subgroup analysis 7: Clinical trial reporting quality: Blinding

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cocaine use assessed by the mean (SD) of the proportion of cocaine-free UA across the study per patient	7	469	Std. Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.07, 0.29]
1.1 Low risk of bias	7	469	Std. Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.07, 0.29]
1.2 Intermediate or high risk of bias	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable
2 Number of patients who finished the study (retention)	16	1345	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.89, 1.07]
2.1 Low risk of bias	5	459	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.86, 1.38]
2.2 Intermediate or high risk of bias	11	886	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.85, 1.04]
3 Cocaine craving	3	340	Std. Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.15, 0.27]
3.1 Low risk of bias	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable
3.2 High risk of bias	3	340	Std. Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.15, 0.27]
4 Depressive symptoms severity	2	90	Std. Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.48, 0.35]
4.1 Low risk of bias	1	62	Std. Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.53, 0.47]
4.2 Intermediate or high risk of bias	1	28	Std. Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.87, 0.61]
5 Patients dropped out due to any adverse events	11	964	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.02, 0.03]
5.1 Low risk of bias	2	210	Risk Difference (M-H, Random, 95% CI)	0.05 [-0.01, 0.10]

5.2 Intermediate or high risk of bias	9	754	Risk Difference (M-H, Random, 95% CI)	Not estimable
6 Patients dropped out due to cardiovascular adverse events	7	417	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.03, 0.02]
6.1 Low risk of bias	0	0	Risk Difference (M-H, Fixed, 95% CI)	Not estimable
6.2 Intermediate or high risk of bias	7	417	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.03, 0.02]
7 Heroin use assessed by the mean (SD) of the proportion of heroin-free UA across the study per patient	2	167	Std. Mean Difference (IV, Fixed, 95% CI)	0.29 [-0.02, 0.61]
7.1 Low risk of bias	2	167	Std. Mean Difference (IV, Fixed, 95% CI)	0.29 [-0.02, 0.61]
7.2 Intermediate or high risk of bias	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable
8 Sustained heroin abstinence	2	199	Risk Ratio (M-H, Fixed, 95% CI)	1.77 [1.31, 2.39]
8.1 Low risk of bias	2	199	Risk Ratio (M-H, Fixed, 95% CI)	1.77 [1.31, 2.39]
8.2 Intermediate or high risk of bias	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9 ADHD severity	2	121	Std. Mean Difference (IV, Random, 95% CI)	-0.36 [-1.11, 0.38]
9.1 Low risk of bias	0	0	Std. Mean Difference (IV, Random, 95% CI)	Not estimable
9.2 Intermediate or low risk of bias	2	121	Std. Mean Difference (IV, Random, 95% CI)	-0.36 [-1.11, 0.38]

Comparison 9. Subgroup analysis 8: Clinical trial reporting quality: Allocation concealment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cocaine use assessed by the mean (SD) of the proportion of cocaine-free UA across the study per patient	7	469	Std. Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.07, 0.29]
1.1 Low risk of bias	2	136	Std. Mean Difference (IV, Fixed, 95% CI)	0.29 [-0.05, 0.63]
1.2 Intermediate or high risk of bias	5	333	Std. Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.18, 0.26]
2 Number of patients who finished the study	16	1345	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.89, 1.07]
2.1 Low risk of bias	5	252	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.79, 1.15]
2.2 Intermediate or high risk of bias	11	1093	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.88, 1.09]
3 Cocaine craving	3	340	Std. Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.15, 0.27]
3.1 Low risk of bias	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable
3.2 Intermediate or high risk of bias	3	340	Std. Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.15, 0.27]
4 Depressive symptoms severity	2	90	Std. Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.48, 0.35]
4.1 Low risk of bias	1	62	Std. Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.53, 0.47]
4.2 Intermediate or high risk of bias	1	28	Std. Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.87, 0.61]

5 Patients dropped out due to any adverse events	11	964	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.02, 0.03]
5.1 Low risk of bias	3	84	Risk Difference (M-H, Random, 95% CI)	0.09 [-0.04, 0.22]
5.2 Intermediate or high risk of bias	8	880	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.01, 0.01]
6 Patients dropped out due to cardiovascular adverse events	7	417	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.03, 0.02]
6.1 Low risk of bias	2	47	Risk Difference (M-H, Fixed, 95% CI)	Not estimable
6.2 Intermediate or high risk of bias	5	370	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.03, 0.02]
7 Heroin use assessed by the mean (SD) of the proportion of heroin-free UA across the study per patient	2	167	Std. Mean Difference (IV, Fixed, 95% CI)	0.29 [-0.02, 0.61]
7.1 Low risk of bias	1	105	Std. Mean Difference (IV, Fixed, 95% CI)	0.28 [-0.10, 0.67]
7.2 Intermediate or high risk of bias	1	62	Std. Mean Difference (IV, Fixed, 95% CI)	0.31 [-0.24, 0.85]
8 Sustained heroin abstinence	2	199	Risk Ratio (M-H, Fixed, 95% CI)	1.77 [1.31, 2.39]
8.1 Low risk of bias	1	105	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [1.04, 2.43]
8.2 Intermediate or high risk of bias	1	94	Risk Ratio (M-H, Fixed, 95% CI)	1.98 [1.28, 3.04]
9 ADHD severity	2	121	Std. Mean Difference (IV, Random, 95% CI)	-0.36 [-1.11, 0.38]
9.1 Low risk of bias	0	0	Std. Mean Difference (IV, Random, 95% CI)	Not estimable
9.2 Intermediate or low risk of bias	2	121	Std. Mean Difference (IV, Random, 95% CI)	-0.36 [-1.11, 0.38]

Comparison 10. Subgroup analysis 9: Clinical trial reporting quality: Incomplete outcome data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cocaine use assessed by the mean (SD) of the proportion of cocaine-free UA across the study per patient	7	469	Std. Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.07, 0.29]
1.1 Low risk of bias	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.2 Intermediate or high risk of bias	7	469	Std. Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.07, 0.29]
2 Number of patients who finished the study	16	1345	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.89, 1.07]
2.1 Low risk of bias	16	1345	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.89, 1.07]
2.2 Intermediate or high risk of bias	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3 Cocaine craving	3	340	Std. Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.15, 0.27]
3.1 Low risk of bias	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable
3.2 Intermediate or high risk of bias	3	340	Std. Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.15, 0.27]
4 Depressive symptoms severity	2	90	Std. Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.48, 0.35]
4.1 Low risk of bias	1	62	Std. Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.53, 0.47]

4.2 Intermediate or high risk of bias	1	28	Std. Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.87, 0.61]
5 Patients dropped out due to any adverse events	11	964	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.02, 0.03]
5.1 Low risk of bias	3	84	Risk Difference (M-H, Random, 95% CI)	0.09 [-0.04, 0.22]
5.2 Intermediate or high risk of bias	8	880	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.01, 0.01]
6 Patients dropped out due to cardiovascular adverse events	7	417	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.03, 0.02]
6.1 Low risk of bias	2	47	Risk Difference (M-H, Fixed, 95% CI)	Not estimable
6.2 Intermediate or high risk of bias	5	370	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.03, 0.02]
7 Heroin use assessed by the mean (SD) of the proportion of heroin-free UA across the study per patient	2	167	Std. Mean Difference (IV, Fixed, 95% CI)	0.29 [-0.02, 0.61]
7.1 Low risk of bias	1	105	Std. Mean Difference (IV, Fixed, 95% CI)	0.28 [-0.10, 0.67]
7.2 Intermediate or high risk of bias	1	62	Std. Mean Difference (IV, Fixed, 95% CI)	0.31 [-0.24, 0.85]
8 Sustained heroin abstinence	2	199	Risk Ratio (M-H, Fixed, 95% CI)	1.77 [1.31, 2.39]
8.1 Low risk of bias	1	105	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [1.04, 2.43]
8.2 Intermediate or high risk of bias	1	94	Risk Ratio (M-H, Fixed, 95% CI)	1.98 [1.28, 3.04]
9 ADHD severity	2	121	Std. Mean Difference (IV, Random, 95% CI)	-0.36 [-1.11, 0.38]
9.1 Low risk of bias	0	0	Std. Mean Difference (IV, Random, 95% CI)	Not estimable
9.2 Intermediate or low risk of bias	2	121	Std. Mean Difference (IV, Random, 95% CI)	-0.36 [-1.11, 0.38]

Comparison 11. Subgroup analysis 10: Clinical trial reporting quality: Other bias

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cocaine use assessed by the mean (SD) of the proportion of cocaine-free UA across the study per patient	7	469	Std. Mean Difference (IV, Random, 95% CI)	0.11 [-0.07, 0.29]
1.1 Low risk of bias	6	421	Std. Mean Difference (IV, Random, 95% CI)	0.10 [-0.09, 0.30]
1.2 Intermediate or high risk of bias	1	48	Std. Mean Difference (IV, Random, 95% CI)	0.19 [-0.38, 0.75]
2 Number of patients who finished the study	16	1345	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.89, 1.07]
2.1 Low risk of bias	12	911	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.92, 1.18]
2.2 Intermediate or high risk of bias	4	434	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.77, 1.01]
3 Cocaine craving	3	340	Std. Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.15, 0.27]
3.1 Low risk of bias	2	40	Std. Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.78, 0.47]
3.2 Intermediate or high risk of bias	1	300	Std. Mean Difference (IV, Fixed, 95% CI)	0.09 [-0.14, 0.31]

4 Depressive symptoms severity	2	90	Std. Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.48, 0.35]
4.1 Low risk of bias	2	90	Std. Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.48, 0.35]
4.2 Intermediate or high risk of bias	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable
5 Patients dropped out due to any adverse events	11	964	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.02, 0.03]
5.1 Low risk of bias	8	592	Risk Difference (M-H, Random, 95% CI)	0.02 [-0.01, 0.05]
5.2 Intermediate or high risk of bias	3	372	Risk Difference (M-H, Random, 95% CI)	Not estimable
6 Patients dropped out due to cardiovascular adverse events	7	417	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.03, 0.02]
6.1 Low risk of bias	5	345	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.03, 0.02]
6.2 Intermediate or high risk of bias	2	72	Risk Difference (M-H, Fixed, 95% CI)	Not estimable
7 Heroin use assessed by the mean (SD) of the proportion of heroin-free UA across the study per patient	2	167	Std. Mean Difference (IV, Fixed, 95% CI)	0.29 [-0.02, 0.61]
7.1 Low risk of bias	2	167	Std. Mean Difference (IV, Fixed, 95% CI)	0.29 [-0.02, 0.61]
7.2 Intermediate or high risk of bias	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable
8 Sustained heroin abstinence	2	199	Risk Ratio (M-H, Fixed, 95% CI)	1.77 [1.31, 2.39]
8.1 Low risk of bias	2	199	Risk Ratio (M-H, Fixed, 95% CI)	1.77 [1.31, 2.39]
8.2 Intermediate or high risk of bias	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9 ADHD severity	2	121	Std. Mean Difference (IV, Random, 95% CI)	-0.36 [-1.11, 0.38]
9.1 Low risk of bias	1	96	Std. Mean Difference (IV, Random, 95% CI)	-0.06 [-0.46, 0.34]
9.2 Intermediate or low risk of bias	1	25	Std. Mean Difference (IV, Random, 95% CI)	-0.84 [-1.67, -0.01]

Comparison 12. Subgroup analysis 11: Single vs. Multiple sites

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cocaine use assessed by the mean (SD) of the proportion of cocaine-free UA across the study per patient	7	469	Std. Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.07, 0.29]
1.1 Single site	5	333	Std. Mean Difference (IV, Fixed, 95% CI)	0.16 [-0.06, 0.38]
1.2 Multiple sites	2	136	Std. Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.34, 0.33]
2 Number of patients who finished the study (retention)	16	1345	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.89, 1.07]
2.1 Single site	11	717	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.87, 1.20]
2.2 Multiple sites	5	628	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.84, 1.05]
3 Cocaine craving	3	340	Std. Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.15, 0.27]
3.1 Low risk of bias	1	12	Std. Mean Difference (IV, Fixed, 95% CI)	-0.51 [-1.68, 0.67]
3.2 Intermediate or high risk of bias	2	328	Std. Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.14, 0.29]

4 Depressive symptoms severity	2	90	Std. Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.48, 0.35]
4.1 Low risk of bias	1	62	Std. Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.53, 0.47]
4.2 Intermediate or high risk of bias	1	28	Std. Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.87, 0.61]
5 Patients dropped out due to any adverse events	11	964	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.02, 0.03]
5.1 Low risk of bias	6	336	Risk Difference (M-H, Random, 95% CI)	0.03 [-0.01, 0.07]
5.2 Intermediate or high risk of bias	5	628	Risk Difference (M-H, Random, 95% CI)	Not estimable
6 Patients dropped out due to cardiovascular adverse events	7	417	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.03, 0.02]
6.1 Low risk of bias	3	89	Risk Difference (M-H, Fixed, 95% CI)	Not estimable
6.2 Intermediate or high risk of bias	4	328	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.03, 0.02]
7 Heroin use assessed by the mean (SD) of the proportion of heroin-free UA across the study per patient	2	167	Std. Mean Difference (IV, Fixed, 95% CI)	0.29 [-0.02, 0.61]
7.1 Low risk of bias	2	167	Std. Mean Difference (IV, Fixed, 95% CI)	0.29 [-0.02, 0.61]
7.2 Intermediate or high risk of bias	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable
8 Sustained heroin abstinence	2	199	Risk Ratio (M-H, Fixed, 95% CI)	1.77 [1.31, 2.39]
8.1 Low risk of bias	2	199	Risk Ratio (M-H, Fixed, 95% CI)	1.77 [1.31, 2.39]
8.2 Intermediate or high risk of bias	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9 ADHD severity	2	121	Std. Mean Difference (IV, Random, 95% CI)	-0.36 [-1.11, 0.38]
9.1 Low risk of bias	1	25	Std. Mean Difference (IV, Random, 95% CI)	-0.84 [-1.67, -0.01]
9.2 Intermediate or low risk of bias	1	96	Std. Mean Difference (IV, Random, 95% CI)	-0.06 [-0.46, 0.34]

Comparison 13. Psychostimulants vs. Placebo: Sensitivity analyses of the safety measures

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Patients dropped out due to any adverse events	8	623	Risk Ratio (M-H, Fixed, 95% CI)	1.68 [0.74, 3.79]
2 Patients dropped out due to cardiovascular adverse events	1	106	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 8.00]

Analysis 1.1. Comparison 1 Psychostimulants vs. Placebo: Primary analysis, Outcome 1 Cocaine use assessed by the mean (SD) of the proportion of cocaine-free UA across the study per patient.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 1 Psychostimulants vs. Placebo: Primary analysis

Outcome: 1 Cocaine use assessed by the mean (SD) of the proportion of cocaine-free UA across the study per patient

Study or subgroup	Favours placebo N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Grabowski 1997	25	30.7 (40)	24	43.8 (41)		10.6 %	-0.32 [-0.88, 0.25]
Grabowski 2004	41	21 (16.8)	19	16.1 (16.9)		11.3 %	0.29 [-0.26, 0.83]
Levin 2007	53	27 (29)	53	30 (29)		23.2 %	-0.10 [-0.48, 0.28]
Poling 2006	57	52.2 (32.1)	49	43 (35.8)		22.9 %	0.27 [-0.11, 0.65]
Schubiner 2002	24	50 (50)	24	42 (32)		10.5 %	0.19 [-0.38, 0.75]
Shearer 2003	16	38.6 (34.3)	14	27.1 (30)		6.4 %	0.35 [-0.38, 1.07]
Shoptaw 2008	37	13.1 (14.2)	33	10.3 (11.2)		15.2 %	0.22 [-0.26, 0.69]
Total (95% CI)	**253**		**216**			**100.0 %**	**0.11 [-0.07, 0.29]**

Heterogeneity: $Chi^2 = 5.15$, df = 6 (P = 0.52); $I^2 = 0.0\%$

Test for overall effect: Z = 1.19 (P = 0.24)

Analysis 1.2. Comparison 1 Psychostimulants vs. Placebo: Primary analysis, Outcome 2 Sustained cocaine abstinence.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 1 Psychostimulants vs. Placebo: Primary analysis

Outcome: 2 Sustained cocaine abstinence

Study or subgroup	Psychostimulants n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Dackis 2005	10/30	4/32		9.2 %	2.67 [0.94, 7.60]
Elkashef 2006	7/150	12/150		11.5 %	0.58 [0.24, 1.44]
Grabowski 2004	24/54	7/40		15.2 %	2.54 [1.22, 5.30]
Levin 2007	8/53	9/53		12.1 %	0.89 [0.37, 2.13]
Poling 2006	34/57	18/49		26.0 %	1.62 [1.06, 2.48]
Shearer 2003	7/16	4/14		10.0 %	1.53 [0.56, 4.15]
Shoptaw 2008	6/37	3/33		6.5 %	1.78 [0.48, 6.57]
Stine 1995	5/22	6/21		9.5 %	0.80 [0.29, 2.22]
Total (95% CI)	**419**	**392**		**100.0 %**	**1.41 [0.98, 2.02]**

Total events: 101 (Psychostimulants), 63 (Placebo)

Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 10.34$, df = 7 (P = 0.17); $I^2 = 32\%$

Test for overall effect: Z = 1.84 (P = 0.066)

Analysis 1.3. Comparison 1 Psychostimulants vs. Placebo: Primary analysis, Outcome 3 Number of patients who finished the study.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 1 Psychostimulants vs. Placebo: Primary analysis

Outcome: 3 Number of patients who finished the study

Study or subgroup	Psychostimulants n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dackis 2005	19/30	21/32		5.7 %	0.97 [0.67, 1.40]
Elkashef 2006	97/150	110/150		31.1 %	0.88 [0.76, 1.03]
Grabowski 1997	12/25	12/24		3.5 %	0.96 [0.54, 1.70]
Grabowski 2001	23/93	8/35		3.3 %	1.08 [0.53, 2.19]
Grabowski 2004	24/54	10/40		3.2 %	1.78 [0.96, 3.29]
Levin 2007	23/53	24/53		6.8 %	0.96 [0.63, 1.47]
Margolin 1995 a	63/74	62/75		17.4 %	1.03 [0.89, 1.19]
Margolin 1995 b	15/18	15/19		4.1 %	1.06 [0.77, 1.44]
Margolin 1997	10/13	4/4		1.9 %	0.83 [0.55, 1.27]
Mooney 2009	17/55	8/27		3.0 %	1.04 [0.52, 2.11]
Perry 2004	3/11	5/13		1.3 %	0.71 [0.22, 2.32]
Poling 2006	32/57	30/49		9.1 %	0.92 [0.67, 1.26]
Schubiner 2002	11/24	14/24		4.0 %	0.79 [0.45, 1.36]
Shearer 2003	6/16	5/14		1.5 %	1.05 [0.41, 2.70]
Shoptaw 2008	7/37	5/33		1.5 %	1.25 [0.44, 3.56]
Stine 1995	9/22	9/21		2.6 %	0.95 [0.47, 1.93]
Total (95% CI)	**732**	**613**		**100.0 %**	**0.97 [0.89, 1.07]**

Total events: 371 (Psychostimulants), 342 (Placebo)

Heterogeneity: Chi^2 = 8.08, df = 15 (P = 0.92); I^2 =0.0%

Test for overall effect: Z = 0.55 (P = 0.58)

Analysis 1.4. Comparison 1 Psychostimulants vs. Placebo: Primary analysis, Outcome 4 Self-reported cocaine use.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

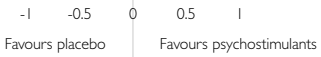
Comparison: 1 Psychostimulants vs. Placebo: Primary analysis

Outcome: 4 Self-reported cocaine use

Study or subgroup	Psychostimulants N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Stine 1995	15	0.6 (0.2)	13	0.6 (0.7)		100.0 %	0.0 [-0.74, 0.74]
Total (95% CI)	**15**		**13**			**100.0 %**	**0.0 [-0.74, 0.74]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P = 1.0)



Analysis 1.5. Comparison 1 Psychostimulants vs. Placebo: Primary analysis, Outcome 5 Cocaine craving.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

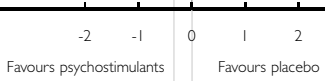
Comparison: 1 Psychostimulants vs. Placebo: Primary analysis

Outcome: 5 Cocaine craving

Study or subgroup	Favours psychostimulants N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Elkashef 2006	150	3.6 (3.1)	150	3.3 (3.8)		88.5 %	0.09 [-0.14, 0.31]
Shoptaw 2008	7	0.5 (1.1)	5	1.8 (3.5)		3.3 %	-0.51 [-1.68, 0.67]
Stine 1995	15	4.2 (6.2)	13	4.3 (7.6)		8.2 %	-0.01 [-0.76, 0.73]
Total (95% CI)	**172**		**168**			**100.0 %**	**0.06 [-0.15, 0.27]**

Heterogeneity: Chi^2 = 0.98, df = 2 (P = 0.61); I^2 =0.0%

Test for overall effect: Z = 0.54 (P = 0.59)



Analysis 1.6. Comparison 1 Psychostimulants vs. Placebo: Primary analysis, Outcome 6 Patient-rated CGI-severity scale.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 1 Psychostimulants vs. Placebo: Primary analysis

Outcome: 6 Patient-rated CGI-severity scale

Study or subgroup	Psychostimulants N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Elkashef 2006	150	3.2 (1.5)	150	2.8 (1.4)		100.0 %	0.28 [0.05, 0.50]
Total (95% CI)	**150**		**150**			**100.0 %**	**0.28 [0.05, 0.50]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.37 (P = 0.018)

Analysis 1.7. Comparison 1 Psychostimulants vs. Placebo: Primary analysis, Outcome 7 Investigator-rated CGI-severity scale.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

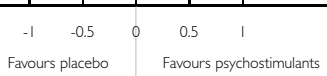
Comparison: 1 Psychostimulants vs. Placebo: Primary analysis

Outcome: 7 Investigator-rated CGI-severity scale

Study or subgroup	Psychostimulants N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Elkashef 2006	150	3.4 (1.4)	150	3.3 (1.3)		100.0 %	0.07 [-0.15, 0.30]
Total (95% CI)	**150**		**150**			**100.0 %**	**0.07 [-0.15, 0.30]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.64 (P = 0.52)



Analysis 1.8. Comparison 1 Psychostimulants vs. Placebo: Primary analysis, Outcome 8 Patient-rated CGI-improvement scale.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

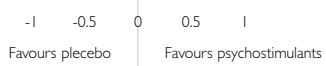
Comparison: 1 Psychostimulants vs. Placebo: Primary analysis

Outcome: 8 Patient-rated CGI-improvement scale

Study or subgroup	Psychostimulants N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Elkashef 2006	150	2.4 (1.1)	150	2.1 (1.1)		100.0 %	0.27 [0.04, 0.50]
Total (95% CI)	**150**		**150**			**100.0 %**	**0.27 [0.04, 0.50]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.34 (P = 0.019)



Analysis 1.9. Comparison 1 Psychostimulants vs. Placebo: Primary analysis, Outcome 9 CGI investigator change.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 1 Psychostimulants vs. Placebo: Primary analysis

Outcome: 9 CGI investigator change

Study or subgroup	Psychostimulants N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Elkashef 2006	150	2.5 (1.2)	150	2.5 (1.1)		100.0 %	0.0 [-0.23, 0.23]
Total (95% CI)	**150**		**150**			**100.0 %**	**0.0 [-0.23, 0.23]**

Heterogeneity: not applicable

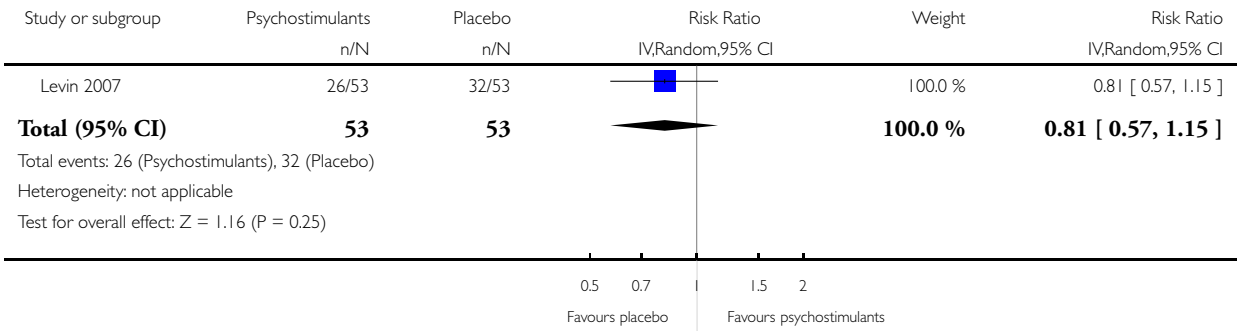
Test for overall effect: Z = 0.0 (P = 1.0)

Analysis 1.10. Comparison 1 Psychostimulants vs. Placebo: Primary analysis, Outcome 10 CGI investigator improvement =1or 2.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 1 Psychostimulants vs. Placebo: Primary analysis

Outcome: 10 CGI investigator improvement =1or 2

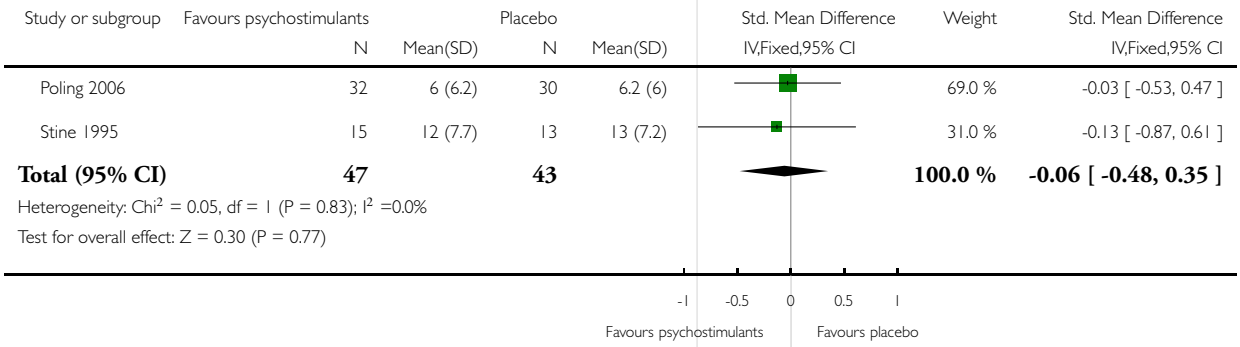


Analysis 1.11. Comparison 1 Psychostimulants vs. Placebo: Primary analysis, Outcome 11 Depressive symptoms severity.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 1 Psychostimulants vs. Placebo: Primary analysis

Outcome: 11 Depressive symptoms severity



Analysis 1.12. Comparison 1 Psychostimulants vs. Placebo: Primary analysis, Outcome 12 Patients dropped out due to any adverse events.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 1 Psychostimulants vs. Placebo: Primary analysis

Outcome: 12 Patients dropped out due to any adverse events

Study or subgroup	Favours psychostimulants n/N	Placebo n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
Elkashef 2006	0/150	0/150		34.1 %	0.0 [-0.01, 0.01]
Grabowski 2001	7/93	0/35		10.5 %	0.08 [0.01, 0.14]
Levin 2007	1/53	1/53		14.7 %	0.0 [-0.05, 0.05]
Margolin 1995 a	2/74	2/75		14.6 %	0.00 [-0.05, 0.05]
Margolin 1995 b	2/18	1/19		2.0 %	0.06 [-0.12, 0.23]
Margolin 1997	0/13	0/4		0.8 %	0.0 [-0.28, 0.28]
Mooney 2009	1/55	0/27		10.9 %	0.02 [-0.05, 0.08]
Perry 2004	0/11	0/13		2.7 %	0.0 [-0.15, 0.15]
Schubiner 2002	0/24	1/24		4.8 %	-0.04 [-0.15, 0.07]
Shearer 2003	5/16	1/14		0.9 %	0.24 [-0.02, 0.51]
Stine 1995	0/22	1/21		4.0 %	-0.05 [-0.17, 0.07]
Total (95% CI)	**529**	**435**		**100.0 %**	**0.01 [-0.02, 0.03]**

Total events: 18 (Favours psychostimulants), 7 (Placebo)

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 14.48$, df = 10 (P = 0.15); $I^2 = 31\%$

Test for overall effect: Z = 0.72 (P = 0.47)

Analysis 1.13. Comparison 1 Psychostimulants vs. Placebo: Primary analysis, Outcome 13 Patients dropped out due to cardiovascular adverse events.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 1 Psychostimulants vs. Placebo: Primary analysis

Outcome: 13 Patients dropped out due to cardiovascular adverse events

Study or subgroup	Favours psychostimulants n/N	Control n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
Levin 2007	0/53	1/53		25.7 %	-0.02 [-0.07, 0.03]
Margolin 1995 a	0/74	0/75		36.2 %	0.0 [-0.03, 0.03]
Margolin 1997	0/13	0/4		3.0 %	0.0 [-0.28, 0.28]
Perry 2004	0/11	0/13		5.8 %	0.0 [-0.15, 0.15]
Schubiner 2002	0/24	0/24		11.7 %	0.0 [-0.08, 0.08]
Shearer 2003	0/16	0/14		7.3 %	0.0 [-0.12, 0.12]
Stine 1995	0/22	0/21		10.4 %	0.0 [-0.09, 0.09]
Total (95% CI)	**213**	**204**		**100.0 %**	**0.00 [-0.03, 0.02]**

Total events: 0 (Favours psychostimulants), 1 (Control)

Heterogeneity: $Chi^2 = 0.47$, df = 6 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 0.35 (P = 0.72)

Analysis 1.14. Comparison 1 Psychostimulants vs. Placebo: Primary analysis, Outcome 14 Heroin use assessed by the mean (SD) of the proportion of heroin-free UA across the study per patient.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 1 Psychostimulants vs. Placebo: Primary analysis

Outcome: 14 Heroin use assessed by the mean (SD) of the proportion of heroin-free UA across the study per patient

Study or subgroup	Favours placebo N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Grabowski 2004	43	37.9 (15.2)	19	33 (17)		33.6 %	0.31 [-0.24, 0.85]
Poling 2006	57	52.2 (32.1)	48	42.9 (33.1)		66.4 %	0.28 [-0.10, 0.67]
Total (95% CI)	**100**		**67**			**100.0 %**	**0.29 [-0.02, 0.61]**

Heterogeneity: $Chi^2 = 0.00$, df = 1 (P = 0.95); $I^2 = 0.0\%$

Test for overall effect: Z = 1.82 (P = 0.069)

Analysis 1.15. Comparison 1 Psychostimulants vs. Placebo: Primary analysis, Outcome 15 Sustained heroin abstinence.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 1 Psychostimulants vs. Placebo: Primary analysis

Outcome: 15 Sustained heroin abstinence

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Grabowski 2004	40/54	15/40		46.9 %	1.98 [1.28, 3.04]
Poling 2006	34/57	18/48		53.1 %	1.59 [1.04, 2.43]
Total (95% CI)	**111**	**88**		**100.0 %**	**1.77 [1.31, 2.39]**

Total events: 74 (Experimental), 33 (Control)

Heterogeneity: Chi^2 = 0.50, df = 1 (P = 0.48); I^2 =0.0%

Test for overall effect: Z = 3.72 (P = 0.00020)

Analysis 1.16. Comparison 1 Psychostimulants vs. Placebo: Primary analysis, Outcome 16 ADHD severity.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

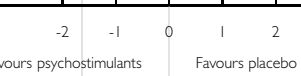
Comparison: 1 Psychostimulants vs. Placebo: Primary analysis

Outcome: 16 ADHD severity

Study or subgroup	Psychostimulants N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Levin 2007	46	18.8 (10.8)	50	19.6 (14.3)		61.3 %	-0.06 [-0.46, 0.34]
Schubiner 2002	11	1.9 (0.8)	14	2.7 (1)		38.7 %	-0.84 [-1.67, -0.01]
Total (95% CI)	**57**		**64**			**100.0 %**	**-0.36 [-1.11, 0.38]**

Heterogeneity: Tau^2 = 0.19; Chi^2 = 2.75, df = 1 (P = 0.10); I^2 =64%

Test for overall effect: Z = 0.96 (P = 0.34)



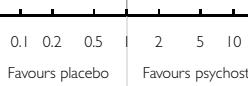
Analysis 2.1. Comparison 2 Subgroup analysis 1: Sustained cocaine abstinence, Outcome 1 Type of drug.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 2 Subgroup analysis 1: Sustained cocaine abstinence

Outcome: 1 Type of drug

Study or subgroup	Psychostimulants n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Bupropion					
Poling 2006	34/57	18/49		26.0 %	1.62 [1.06, 2.48]
Shoptaw 2008	6/37	3/33		6.5 %	1.78 [0.48, 6.57]
Subtotal (95% CI)	**94**	**82**		**32.5 %**	**1.64 [1.09, 2.45]**
Total events: 40 (Psychostimulants), 21 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.02, df = 1 (P = 0.89); I^2 =0.0%					
Test for overall effect: Z = 2.40 (P = 0.017)					
2 Dexamphetamine					
Grabowski 2004	24/54	7/40		15.2 %	2.54 [1.22, 5.30]
Shearer 2003	7/16	4/14		10.0 %	1.53 [0.56, 4.15]
Subtotal (95% CI)	**70**	**54**		**25.1 %**	**2.12 [1.18, 3.84]**
Total events: 31 (Psychostimulants), 11 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.65, df = 1 (P = 0.42); I^2 =0.0%					
Test for overall effect: Z = 2.49 (P = 0.013)					
3 Mazindol					
Stine 1995	5/22	6/21		9.5 %	0.80 [0.29, 2.22]
Subtotal (95% CI)	**22**	**21**		**9.5 %**	**0.80 [0.29, 2.22]**
Total events: 5 (Psychostimulants), 6 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.44 (P = 0.66)					
4 Methylphenidate					
Levin 2007	8/53	9/53		12.1 %	0.89 [0.37, 2.13]
Subtotal (95% CI)	**53**	**53**		**12.1 %**	**0.89 [0.37, 2.13]**
Total events: 8 (Psychostimulants), 9 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.26 (P = 0.79)					
5 Modafinil					
Dackis 2005	10/30	4/32		9.2 %	2.67 [0.94, 7.60]
Subtotal (95% CI)	**30**	**32**		**9.2 %**	**2.67 [0.94, 7.60]**
Total events: 10 (Psychostimulants), 4 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.84 (P = 0.066)					
6 Selegiline					



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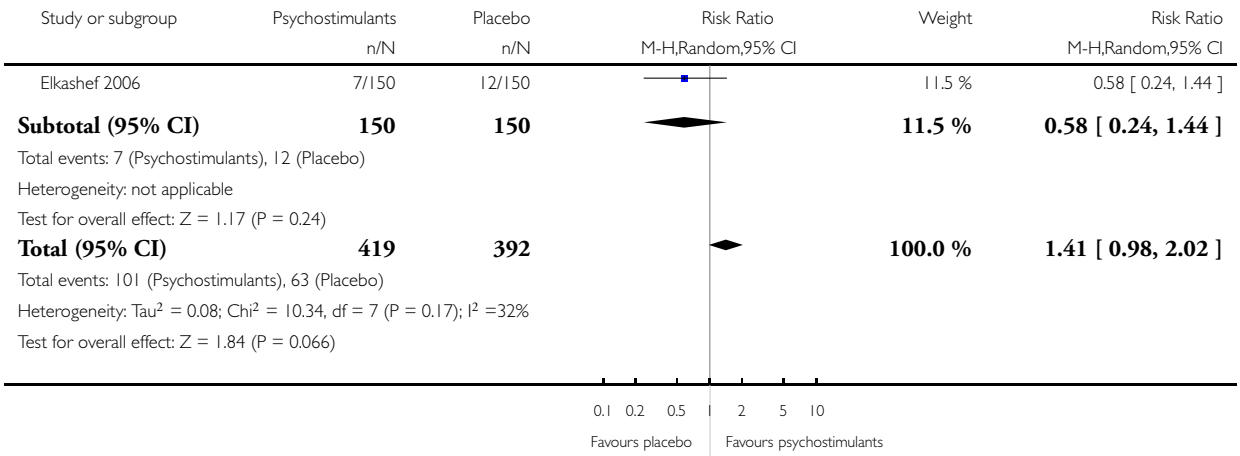
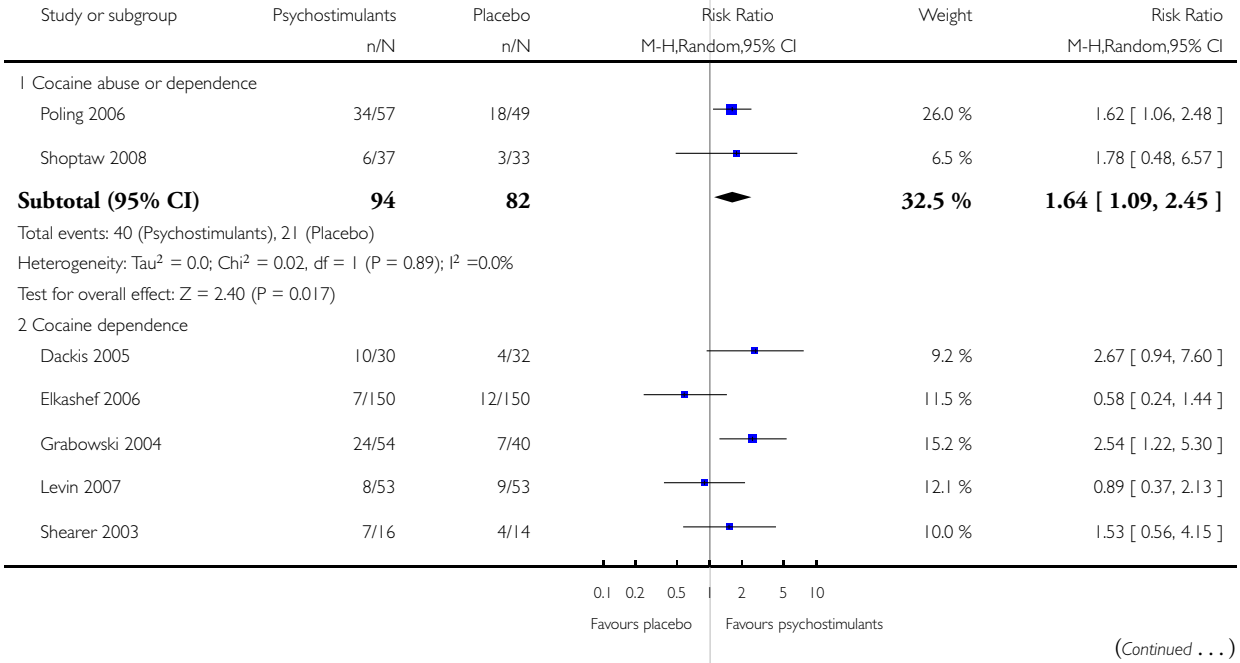


Analysis 2.2. Comparison 2 Subgroup analysis 1: Sustained cocaine abstinence, Outcome 2 Definition of cocaine use disorder.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 2 Subgroup analysis 1: Sustained cocaine abstinence

Outcome: 2 Definition of cocaine use disorder



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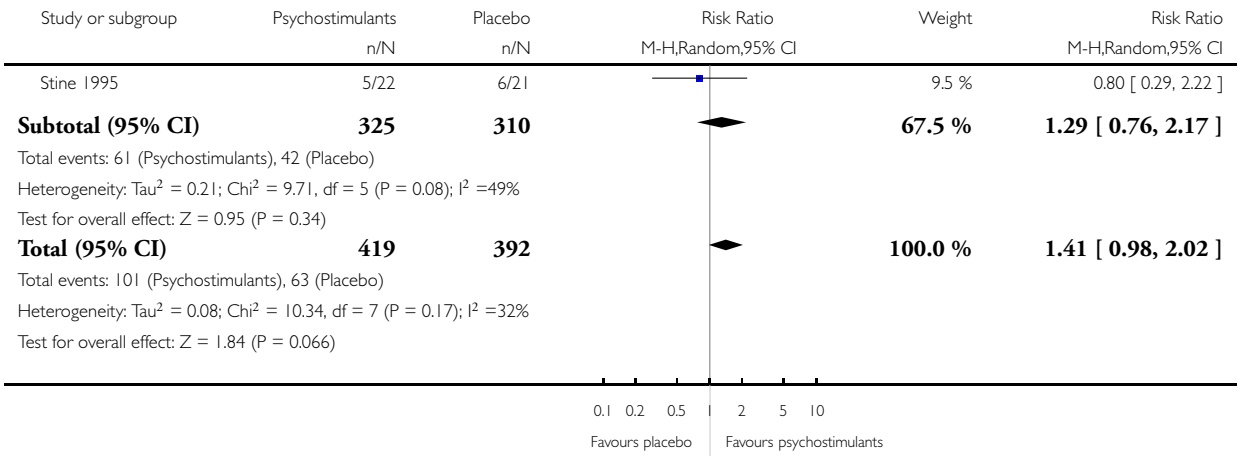
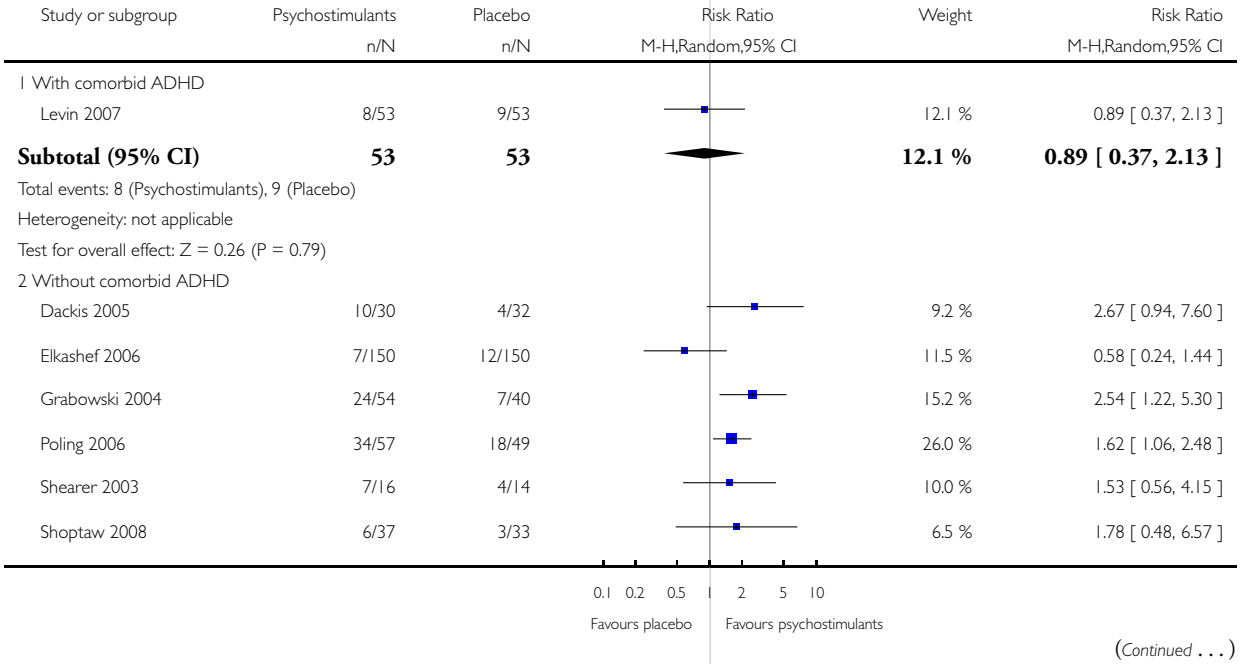


Analysis 2.3. Comparison 2 Subgroup analysis 1: Sustained cocaine abstinence, Outcome 3 Comorbid ADHD as inclusion criterion.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 2 Subgroup analysis 1: Sustained cocaine abstinence

Outcome: 3 Comorbid ADHD as inclusion criterion



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Study or subgroup	Psychostimulants n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Stine 1995	5/22	6/21		9.5 %	0.80 [0.29, 2.22]
Subtotal (95% CI)	**366**	**339**		**87.9 %**	**1.50 [1.01, 2.21]**
Total events: 93 (Psychostimulants), 54 (Placebo)					
Heterogeneity: Tau^2 = 0.09; Chi^2 = 8.97, df = 6 (P = 0.18); I^2 =33%					
Test for overall effect: Z = 2.03 (P = 0.043)					
Total (95% CI)	**419**	**392**		**100.0 %**	**1.41 [0.98, 2.02]**
Total events: 101 (Psychostimulants), 63 (Placebo)					
Heterogeneity: Tau^2 = 0.08; Chi^2 = 10.34, df = 7 (P = 0.17); I^2 =32%					
Test for overall effect: Z = 1.84 (P = 0.066)					

Analysis 2.4. Comparison 2 Subgroup analysis 1: Sustained cocaine abstinence, Outcome 4 Comorbid opioid dependence as inclusion criterion.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 2 Subgroup analysis 1: Sustained cocaine abstinence

Outcome: 4 Comorbid opioid dependence as inclusion criterion

Study or subgroup	Psychostimulants n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 With a comorbid opioid dependence					
Grabowski 2004	24/54	7/40		15.2 %	2.54 [1.22, 5.30]
Poling 2006	34/57	18/49		26.0 %	1.62 [1.06, 2.48]
Subtotal (95% CI)	**111**	**89**		**41.2 %**	**1.84 [1.23, 2.74]**
Total events: 58 (Psychostimulants), 25 (Placebo)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 1.11, df = 1 (P = 0.29); I^2 =10%					
Test for overall effect: Z = 2.98 (P = 0.0029)					
2 Without a comorbid opioid dependence					
Dackis 2005	10/30	4/32		9.2 %	2.67 [0.94, 7.60]
Elkashef 2006	7/150	12/150		11.5 %	0.58 [0.24, 1.44]
Levin 2007	8/53	9/53		12.1 %	0.89 [0.37, 2.13]
Shearer 2003	7/16	4/14		10.0 %	1.53 [0.56, 4.15]
Shoptaw 2008	6/37	3/33		6.5 %	1.78 [0.48, 6.57]

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Study or subgroup	Psychostimulants n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Stine 1995	5/22	6/21		9.5 %	0.80 [0.29, 2.22]
Subtotal (95% CI)	**308**	**303**		**58.8 %**	**1.13 [0.71, 1.78]**
Total events: 43 (Psychostimulants), 38 (Placebo)					
Heterogeneity: Tau^2 = 0.06; Chi^2 = 6.20, df = 5 (P = 0.29); I^2 =19%					
Test for overall effect: Z = 0.51 (P = 0.61)					
Total (95% CI)	**419**	**392**		**100.0 %**	**1.41 [0.98, 2.02]**
Total events: 101 (Psychostimulants), 63 (Placebo)					
Heterogeneity: Tau^2 = 0.08; Chi^2 = 10.34, df = 7 (P = 0.17); I^2 =32%					
Test for overall effect: Z = 1.84 (P = 0.066)					

Analysis 2.5. Comparison 2 Subgroup analysis 1: Sustained cocaine abstinence, Outcome 5 Clinical trial reporting quality: Sequence generation.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 2 Subgroup analysis 1: Sustained cocaine abstinence

Outcome: 5 Clinical trial reporting quality: Sequence generation

Study or subgroup	Psychostimulants n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Low risk of bias					
Dackis 2005	10/30	4/32		9.2 %	2.67 [0.94, 7.60]
Elkashef 2006	7/150	12/150		11.5 %	0.58 [0.24, 1.44]
Poling 2006	34/57	18/49		26.0 %	1.62 [1.06, 2.48]
Shearer 2003	7/16	4/14		10.0 %	1.53 [0.56, 4.15]
Subtotal (95% CI)	**253**	**245**		**56.7 %**	**1.41 [0.82, 2.42]**
Total events: 58 (Psychostimulants), 38 (Placebo)					
Heterogeneity: Tau^2 = 0.14; Chi^2 = 5.55, df = 3 (P = 0.14); I^2 =46%					
Test for overall effect: Z = 1.23 (P = 0.22)					
2 Intermediate or high risk of bias					
Grabowski 2004	24/54	7/40		15.2 %	2.54 [1.22, 5.30]
Levin 2007	8/53	9/53		12.1 %	0.89 [0.37, 2.13]
Shoptaw 2008	6/37	3/33		6.5 %	1.78 [0.48, 6.57]

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Study or subgroup	Psychostimulants n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Stine 1995	5/22	6/21		9.5 %	0.80 [0.29, 2.22]
Subtotal (95% CI)	**166**	**147**		**43.3 %**	**1.38 [0.75, 2.52]**
Total events: 43 (Psychostimulants), 25 (Placebo)					
Heterogeneity: Tau^2 = 0.15; Chi^2 = 4.86, df = 3 (P = 0.18); I^2 =38%					
Test for overall effect: Z = 1.03 (P = 0.30)					
Total (95% CI)	**419**	**392**		**100.0 %**	**1.41 [0.98, 2.02]**
Total events: 101 (Psychostimulants), 63 (Placebo)					
Heterogeneity: Tau^2 = 0.08; Chi^2 = 10.34, df = 7 (P = 0.17); I^2 =32%					
Test for overall effect: Z = 1.84 (P = 0.066)					

Analysis 2.6. Comparison 2 Subgroup analysis 1: Sustained cocaine abstinence, Outcome 6 Clinical trial reporting quality: Allocation concealment.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 2 Subgroup analysis 1: Sustained cocaine abstinence

Outcome: 6 Clinical trial reporting quality: Allocation concealment

Study or subgroup	Psychostimulants n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Low risk of bias					
Dackis 2005	10/30	4/32		9.2 %	2.67 [0.94, 7.60]
Poling 2006	34/57	18/49		26.0 %	1.62 [1.06, 2.48]
Shearer 2003	7/16	4/14		10.0 %	1.53 [0.56, 4.15]
Subtotal (95% CI)	**103**	**95**		**45.2 %**	**1.71 [1.19, 2.47]**
Total events: 51 (Psychostimulants), 26 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.81, df = 2 (P = 0.67); I^2 =0.0%					
Test for overall effect: Z = 2.88 (P = 0.0040)					
2 Intermediate or high risk of bias					
Elkashef 2006	7/150	12/150		11.5 %	0.58 [0.24, 1.44]
Grabowski 2004	24/54	7/40		15.2 %	2.54 [1.22, 5.30]
Levin 2007	8/53	9/53		12.1 %	0.89 [0.37, 2.13]
Shoptaw 2008	6/37	3/33		6.5 %	1.78 [0.48, 6.57]

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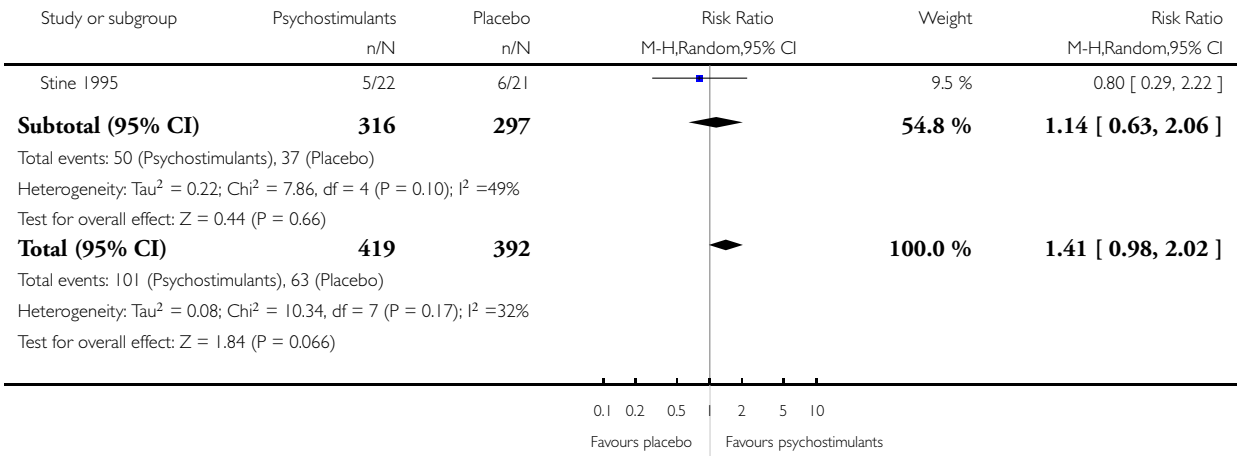
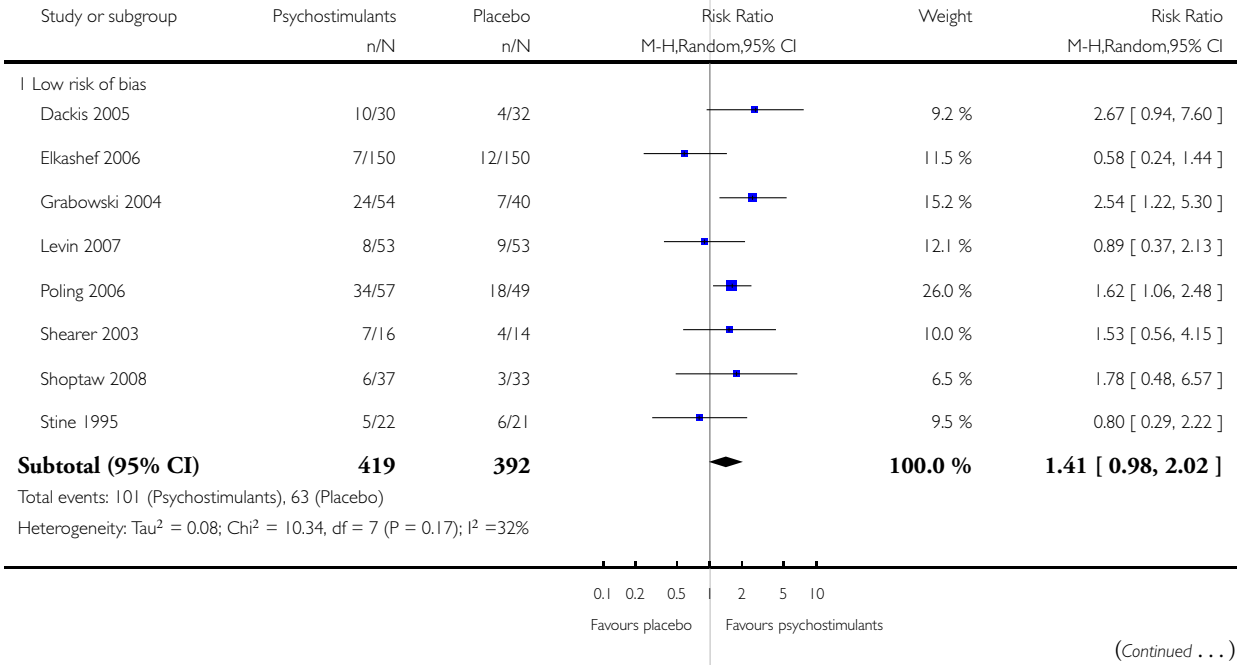


Analysis 2.7. Comparison 2 Subgroup analysis 1: Sustained cocaine abstinence, Outcome 7 Clinical trial reporting quality: Blinding.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 2 Subgroup analysis 1: Sustained cocaine abstinence

Outcome: 7 Clinical trial reporting quality: Blinding



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Study or subgroup	Psychostimulants n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Test for overall effect: Z = 1.84 (P = 0.066)					
2 Intermediate or high risk of bias					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Psychostimulants), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**419**	**392**		**100.0 %**	**1.41 [0.98, 2.02]**
Total events: 101 (Psychostimulants), 63 (Placebo)					
Heterogeneity: Tau^2 = 0.08; Chi^2 = 10.34, df = 7 (P = 0.17); I^2 =32%					
Test for overall effect: Z = 1.84 (P = 0.066)					

Analysis 2.8. Comparison 2 Subgroup analysis 1: Sustained cocaine abstinence, Outcome 8 Clinical trial reporting quality: Incomplete outcome data.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 2 Subgroup analysis 1: Sustained cocaine abstinence

Outcome: 8 Clinical trial reporting quality: Incomplete outcome data

Study or subgroup	Psychostimulants n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Low risk of bias					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Psychostimulants), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Intermediate or high risk of bias					
Dackis 2005	10/30	4/32		9.2 %	2.67 [0.94, 7.60]
Elkashef 2006	7/150	12/150		11.5 %	0.58 [0.24, 1.44]
Grabowski 2004	24/54	7/40		15.2 %	2.54 [1.22, 5.30]
Levin 2007	8/53	9/53		12.1 %	0.89 [0.37, 2.13]
Poling 2006	34/57	18/49		26.0 %	1.62 [1.06, 2.48]
Shearer 2003	7/16	4/14		10.0 %	1.53 [0.56, 4.15]
Shoptaw 2008	6/37	3/33		6.5 %	1.78 [0.48, 6.57]

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Study or subgroup	Psychostimulants n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Stine 1995	5/22	6/21		9.5 %	0.80 [0.29, 2.22]
Subtotal (95% CI)	**419**	**392**		**100.0 %**	**1.41 [0.98, 2.02]**
Total events: 101 (Psychostimulants), 63 (Placebo)					
Heterogeneity: Tau^2 = 0.08; Chi^2 = 10.34, df = 7 (P = 0.17); I^2 =32%					
Test for overall effect: Z = 1.84 (P = 0.066)					
Total (95% CI)	**419**	**392**		**100.0 %**	**1.41 [0.98, 2.02]**
Total events: 101 (Psychostimulants), 63 (Placebo)					
Heterogeneity: Tau^2 = 0.08; Chi^2 = 10.34, df = 7 (P = 0.17); I^2 =32%					
Test for overall effect: Z = 1.84 (P = 0.066)					

Analysis 2.9. Comparison 2 Subgroup analysis 1: Sustained cocaine abstinence, Outcome 9 Clinical trial reporting quality: Other bias.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 2 Subgroup analysis 1: Sustained cocaine abstinence

Outcome: 9 Clinical trial reporting quality: Other bias

Study or subgroup	Psychostimulants n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Low risk of bias					
Grabowski 2004	24/54	7/40		15.2 %	2.54 [1.22, 5.30]
Levin 2007	8/53	9/53		12.1 %	0.89 [0.37, 2.13]
Poling 2006	34/57	18/49		26.0 %	1.62 [1.06, 2.48]
Shearer 2003	7/16	4/14		10.0 %	1.53 [0.56, 4.15]
Shoptaw 2008	6/37	3/33		6.5 %	1.78 [0.48, 6.57]
Stine 1995	5/22	6/21		9.5 %	0.80 [0.29, 2.22]
Subtotal (95% CI)	**239**	**210**		**79.3 %**	**1.53 [1.14, 2.07]**
Total events: 84 (Psychostimulants), 47 (Placebo)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 5.00, df = 5 (P = 0.42); I^2 =0%					
Test for overall effect: Z = 2.81 (P = 0.0050)					
2 Intermediate or high risk of bias					
Dackis 2005	10/30	4/32		9.2 %	2.67 [0.94, 7.60]

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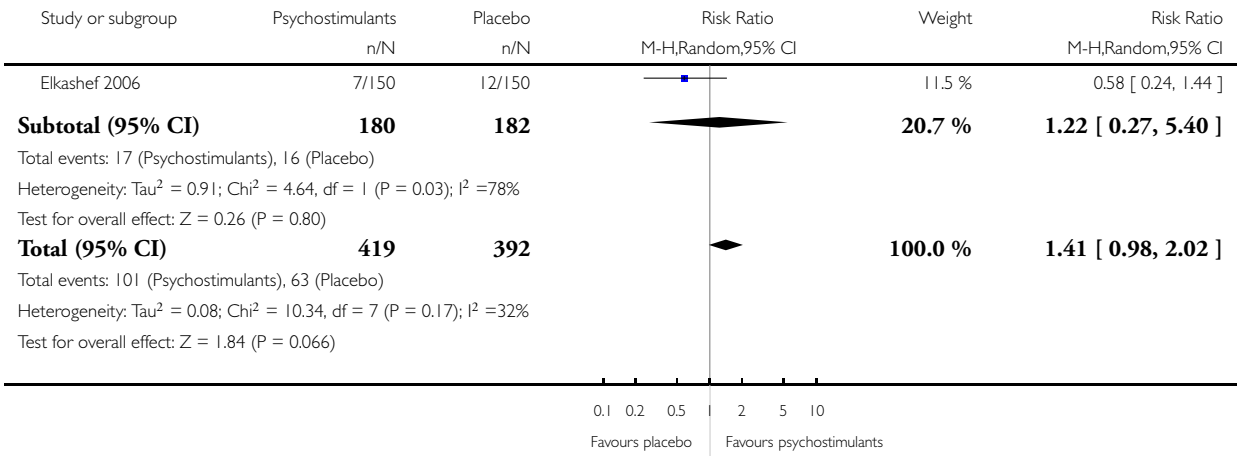
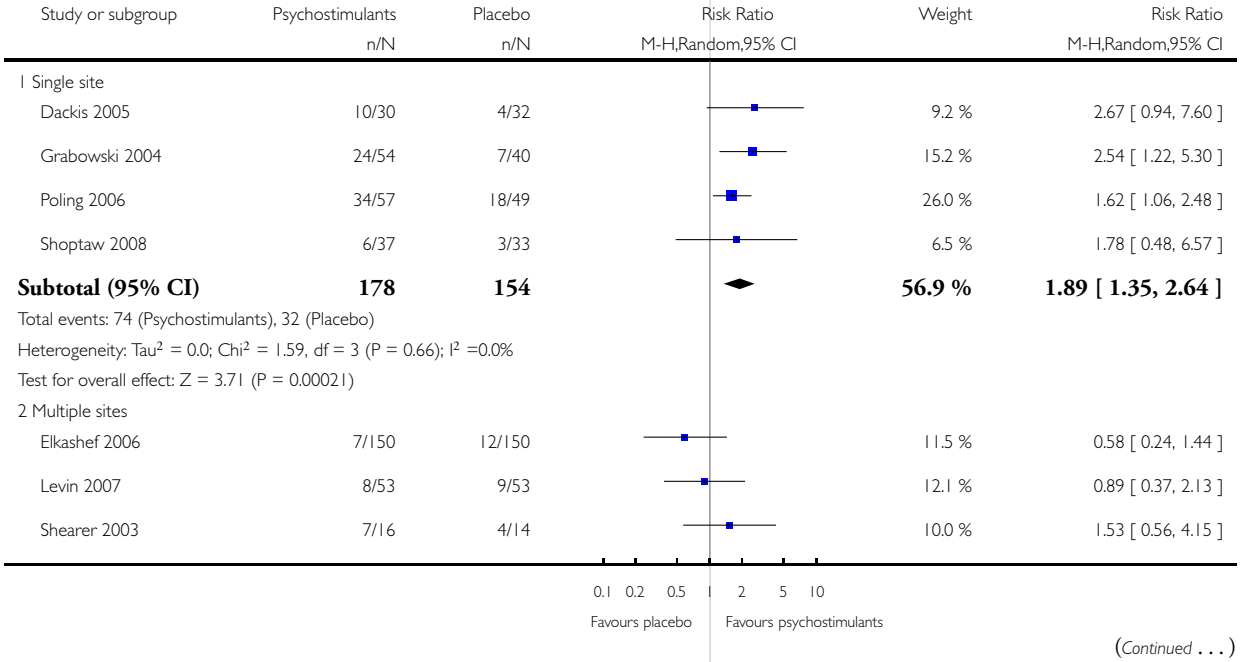


Analysis 2.10. Comparison 2 Subgroup analysis 1: Sustained cocaine abstinence, Outcome 10 Single vs. Multiple sites.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 2 Subgroup analysis 1: Sustained cocaine abstinence

Outcome: 10 Single vs. Multiple sites



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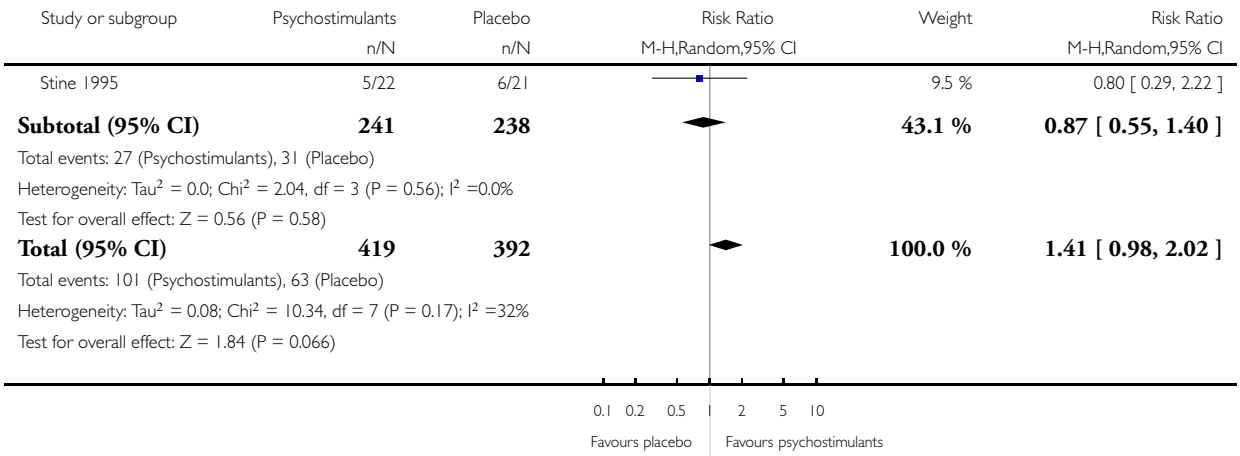
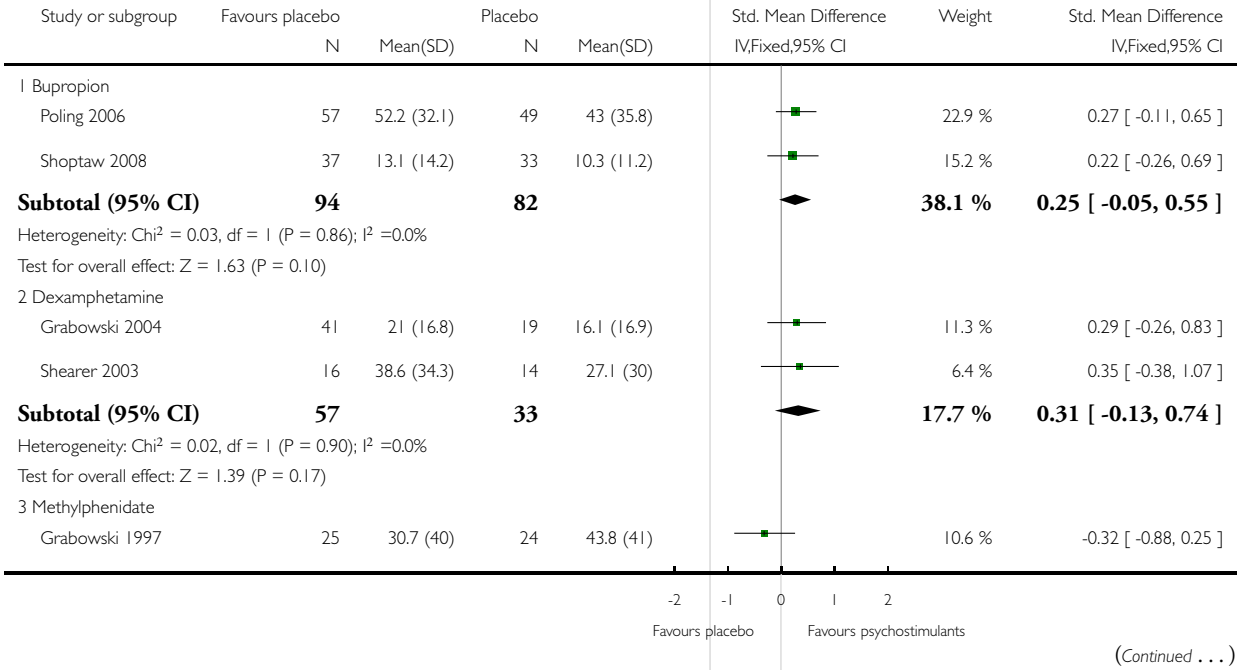


Analysis 3.1. Comparison 3 Subgroup analysis 2: Type of drug, Outcome 1 Cocaine use assessed by the mean (SD) of the proportion of cocaine-free UA across the study per patient.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 3 Subgroup analysis 2: Type of drug

Outcome: 1 Cocaine use assessed by the mean (SD) of the proportion of cocaine-free UA across the study per patient



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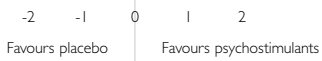
Study or subgroup	Favours placebo N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Levin 2007	53	27 (29)	53	30 (29)		23.2 %	-0.10 [-0.48, 0.28]
Schubiner 2002	24	50 (50)	24	42 (32)		10.5 %	0.19 [-0.38, 0.75]
Subtotal (95% CI)	**102**		**101**			**44.2 %**	**-0.09 [-0.36, 0.19]**
Heterogeneity: Chi² = 1.55, df = 2 (P = 0.46); I² =0.0%							
Test for overall effect: Z = 0.61 (P = 0.54)							
Total (95% CI)	**253**		**216**			**100.0 %**	**0.11 [-0.07, 0.29]**
Heterogeneity: Chi² = 5.15, df = 6 (P = 0.52); I² =0.0%							
Test for overall effect: Z = 1.19 (P = 0.24)							
Test for subgroup differences: Chi² = 3.55, df = 2 (P = 0.17), I² =44%							



Analysis 3.2. Comparison 3 Subgroup analysis 2: Type of drug, Outcome 2 Number of patients who finished the study.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 3 Subgroup analysis 2: Type of drug

Outcome: 2 Number of patients who finished the study

Study or subgroup	Favours placebo n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Bupropion					
Margolin 1995 a	63/74	62/75		17.4 %	1.03 [0.89, 1.19]
Poling 2006	32/57	30/49		9.1 %	0.92 [0.67, 1.26]
Shoptaw 2008	7/37	5/33		1.5 %	1.25 [0.44, 3.56]
Subtotal (95% CI)	**168**	**157**		**28.0 %**	**1.00 [0.87, 1.16]**
Total events: 102 (Favours placebo), 97 (Placebo)					
Heterogeneity: Chi² = 0.60, df = 2 (P = 0.74); I² =0.0%					
Test for overall effect: Z = 0.06 (P = 0.95)					
2 Dexamphetamine					
Grabowski 2001	23/93	8/35		3.3 %	1.08 [0.53, 2.19]
Grabowski 2004	24/54	10/40		3.2 %	1.78 [0.96, 3.29]
Shearer 2003	6/16	5/14		1.5 %	1.05 [0.41, 2.70]
Subtotal (95% CI)	**163**	**89**		**8.0 %**	**1.36 [0.90, 2.05]**

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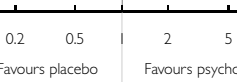
Study or subgroup	Favours placebo n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 53 (Favours placebo), 23 (Placebo)					
Heterogeneity: Chi² = 1.42, df = 2 (P = 0.49); I² =0.0%					
Test for overall effect: Z = 1.45 (P = 0.15)					
3 Mazindol					
Margolin 1995 b	15/18	15/19		4.1 %	1.06 [0.77, 1.44]
Margolin 1997	10/13	4/4		1.9 %	0.83 [0.55, 1.27]
Perry 2004	3/11	5/13		1.3 %	0.71 [0.22, 2.32]
Stine 1995	9/22	9/21		2.6 %	0.95 [0.47, 1.93]
Subtotal (95% CI)	**64**	**57**		**9.9 %**	**0.94 [0.71, 1.24]**
Total events: 37 (Favours placebo), 33 (Placebo)					
Heterogeneity: Chi² = 1.06, df = 3 (P = 0.79); I² =0.0%					
Test for overall effect: Z = 0.42 (P = 0.67)					
4 Methamphetamine					
Mooney 2009	17/55	8/27		3.0 %	1.04 [0.52, 2.11]
Subtotal (95% CI)	**55**	**27**		**3.0 %**	**1.04 [0.52, 2.11]**
Total events: 17 (Favours placebo), 8 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.12 (P = 0.91)					
5 Methylphenidate					
Grabowski 1997	12/25	12/24		3.5 %	0.96 [0.54, 1.70]
Levin 2007	23/53	24/53		6.8 %	0.96 [0.63, 1.47]
Schubiner 2002	11/24	14/24		4.0 %	0.79 [0.45, 1.36]
Subtotal (95% CI)	**102**	**101**		**14.2 %**	**0.91 [0.68, 1.22]**
Total events: 46 (Favours placebo), 50 (Placebo)					
Heterogeneity: Chi² = 0.36, df = 2 (P = 0.83); I² =0.0%					
Test for overall effect: Z = 0.63 (P = 0.53)					
6 Modafinil					
Dackis 2005	19/30	21/32		5.7 %	0.97 [0.67, 1.40]
Subtotal (95% CI)	**30**	**32**		**5.7 %**	**0.97 [0.67, 1.40]**
Total events: 19 (Favours placebo), 21 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.19 (P = 0.85)					
7 Selegiline					
Elkashef 2006	97/150	110/150		31.1 %	0.88 [0.76, 1.03]
Subtotal (95% CI)	**150**	**150**		**31.1 %**	**0.88 [0.76, 1.03]**
Total events: 97 (Favours placebo), 110 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.61 (P = 0.11)					
Total (95% CI)	**732**	**613**		**100.0 %**	**0.97 [0.89, 1.07]**
Total events: 371 (Favours placebo), 342 (Placebo)					
Heterogeneity: Chi² = 8.08, df = 15 (P = 0.92); I² =0.0%					



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Study or subgroup	Favours placebo n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI

Test for overall effect: Z = 0.55 (P = 0.58)

Analysis 3.3. Comparison 3 Subgroup analysis 2: Type of drug, Outcome 3 Cocaine craving.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 3 Subgroup analysis 2: Type of drug

Outcome: 3 Cocaine craving

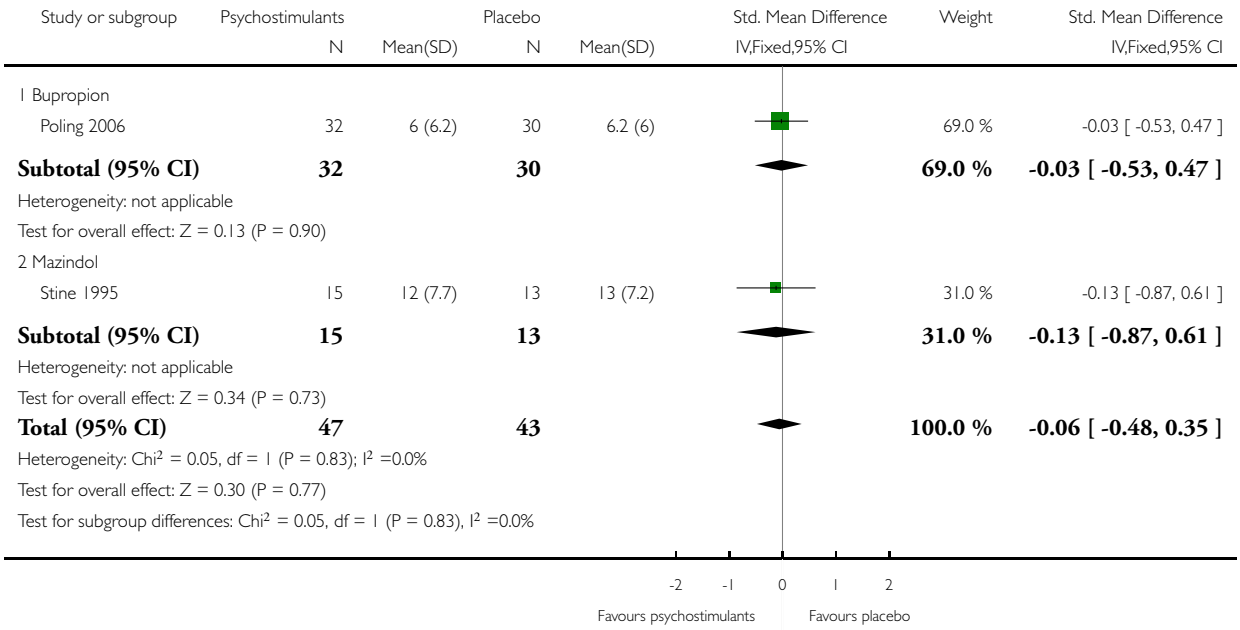
Study or subgroup	Psychostimulants N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 Bupropion							
Shoptaw 2008	7	0.5 (1.1)	5	1.8 (3.5)		3.3 %	-0.51 [-1.68, 0.67]
Subtotal (95% CI)	**7**		**5**			**3.3 %**	**-0.51 [-1.68, 0.67]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.84 (P = 0.40)							
2 Mazindol							
Stine 1995	15	4.2 (6.2)	13	4.3 (7.6)		8.2 %	-0.01 [-0.76, 0.73]
Subtotal (95% CI)	**15**		**13**			**8.2 %**	**-0.01 [-0.76, 0.73]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.04 (P = 0.97)							
3 Selegiline							
Elkashef 2006	150	3.6 (3.1)	150	3.3 (3.8)		88.5 %	0.09 [-0.14, 0.31]
Subtotal (95% CI)	**150**		**150**			**88.5 %**	**0.09 [-0.14, 0.31]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.75 (P = 0.46)							
Total (95% CI)	**172**		**168**			**100.0 %**	**0.06 [-0.15, 0.27]**
Heterogeneity: Chi^2 = 0.98, df = 2 (P = 0.61); I^2 =0.0%							
Test for overall effect: Z = 0.54 (P = 0.59)							
Test for subgroup differences: Chi^2 = 0.98, df = 2 (P = 0.61), I^2 =0.0%							

Analysis 3.4. Comparison 3 Subgroup analysis 2: Type of drug, Outcome 4 Depressive symptoms severity.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 3 Subgroup analysis 2: Type of drug

Outcome: 4 Depressive symptoms severity



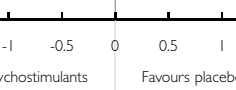
Analysis 3.5. Comparison 3 Subgroup analysis 2: Type of drug, Outcome 5 Patients dropped out due to any adverse events.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 3 Subgroup analysis 2: Type of drug

Outcome: 5 Patients dropped out due to any adverse events

Study or subgroup	Psychostimulants n/N	Placebo n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
1 Bupropion					
Margolin 1995 a	2/74	2/75		14.6 %	0.00 [-0.05, 0.05]
Subtotal (95% CI)	**74**	**75**		**14.6 %**	**0.00 [-0.05, 0.05]**
Total events: 2 (Psychostimulants), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.01 (P = 0.99)					
2 Dexamphetamine					
Grabowski 2001	7/93	0/35		10.5 %	0.08 [0.01, 0.14]
Shearer 2003	5/16	1/14		0.9 %	0.24 [-0.02, 0.51]
Subtotal (95% CI)	**109**	**49**		**11.4 %**	**0.12 [-0.06, 0.30]**
Total events: 12 (Psychostimulants), 1 (Placebo)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 2.12, df = 1 (P = 0.15); I^2 =53%					
Test for overall effect: Z = 1.34 (P = 0.18)					
3 Mazindol					
Margolin 1995 b	2/18	1/19		2.0 %	0.06 [-0.12, 0.23]
Margolin 1997	0/13	0/4		0.8 %	0.0 [-0.28, 0.28]
Perry 2004	0/11	0/13		2.7 %	0.0 [-0.15, 0.15]
Stine 1995	0/22	1/21		4.0 %	-0.05 [-0.17, 0.07]
Subtotal (95% CI)	**64**	**57**		**9.4 %**	**-0.01 [-0.09, 0.07]**
Total events: 2 (Psychostimulants), 2 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.03, df = 3 (P = 0.79); I^2 =0.0%					
Test for overall effect: Z = 0.21 (P = 0.83)					
4 Methamphetamine					
Mooney 2009	1/55	0/27		10.9 %	0.02 [-0.05, 0.08]
Subtotal (95% CI)	**55**	**27**		**10.9 %**	**0.02 [-0.05, 0.08]**
Total events: 1 (Psychostimulants), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.55 (P = 0.58)					
5 Methylphenidate					
Levin 2007	1/53	1/53		14.7 %	0.0 [-0.05, 0.05]
Schubiner 2002	0/24	1/24		4.8 %	-0.04 [-0.15, 0.07]



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Study or subgroup	Psychostimulants n/N	Placebo n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
Subtotal (95% CI)	**77**	**77**		**19.5 %**	**-0.01 [-0.05, 0.04]**
Total events: 1 (Psychostimulants), 2 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.51$, df = 1 (P = 0.47); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.33 (P = 0.74)					
6 Selegiline					
Elkashef 2006	0/150	0/150		34.1 %	0.0 [-0.01, 0.01]
Subtotal (95% CI)	**150**	**150**		**34.1 %**	**0.0 [-0.01, 0.01]**
Total events: 0 (Psychostimulants), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
Total (95% CI)	**529**	**435**		**100.0 %**	**0.01 [-0.02, 0.03]**
Total events: 18 (Psychostimulants), 7 (Placebo)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 14.48$, df = 10 (P = 0.15); $I^2 = 31\%$					
Test for overall effect: Z = 0.72 (P = 0.47)					

-1 -0.5 0 0.5 1

Favours psychostimulants Favours placebo

Analysis 3.6. Comparison 3 Subgroup analysis 2: Type of drug, Outcome 6 Patients dropped out due to cardiovascular adverse events.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 3 Subgroup analysis 2: Type of drug

Outcome: 6 Patients dropped out due to cardiovascular adverse events

Study or subgroup	Experimental n/N	Control n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
1 Bupropion					
Margolin 1995 a	0/74	0/75		36.2 %	0.0 [-0.03, 0.03]
Subtotal (95% CI)	**74**	**75**		**36.2 %**	**0.0 [-0.03, 0.03]**
Total events: 0 (Experimental), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
2 Dexamphetamine					
Shearer 2003	0/16	0/14		7.3 %	0.0 [-0.12, 0.12]
Subtotal (95% CI)	**16**	**14**		**7.3 %**	**0.0 [-0.12, 0.12]**
Total events: 0 (Experimental), 0 (Control)					

-0.5 -0.25 0 0.25 0.5

Favours psychostimulants Favours placebo

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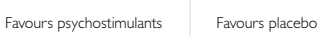
Study or subgroup	Experimental n/N	Control n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
3 Mazindol					
Margolin 1997	0/13	0/4		3.0 %	0.0 [-0.28, 0.28]
Perry 2004	0/11	0/13		5.8 %	0.0 [-0.15, 0.15]
Stine 1995	0/22	0/21		10.4 %	0.0 [-0.09, 0.09]
Subtotal (95% CI)	**46**	**38**		**19.2 %**	**0.0 [-0.09, 0.09]**
Total events: 0 (Experimental), 0 (Control)					
Heterogeneity: Chi^2 = 0.0, df = 2 (P = 1.00); I^2 =0.0%					
Test for overall effect: Z = 0.0 (P = 1.0)					
4 Methylphenidate					
Levin 2007	0/53	1/53		25.7 %	-0.02 [-0.07, 0.03]
Schubiner 2002	0/24	0/24		11.7 %	0.0 [-0.08, 0.08]
Subtotal (95% CI)	**77**	**77**		**37.4 %**	**-0.01 [-0.06, 0.03]**
Total events: 0 (Experimental), 1 (Control)					
Heterogeneity: Chi^2 = 0.16, df = 1 (P = 0.69); I^2 =0.0%					
Test for overall effect: Z = 0.58 (P = 0.56)					
Total (95% CI)	**213**	**204**		**100.0 %**	**0.00 [-0.03, 0.02]**
Total events: 0 (Experimental), 1 (Control)					
Heterogeneity: Chi^2 = 0.47, df = 6 (P = 1.00); I^2 =0.0%					
Test for overall effect: Z = 0.35 (P = 0.72)					



Analysis 3.7. Comparison 3 Subgroup analysis 2: Type of drug, Outcome 7 Heroin use assessed by the mean (SD) of the proportion of heroin-free UA across the study per patient.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 3 Subgroup analysis 2: Type of drug

Outcome: 7 Heroin use assessed by the mean (SD) of the proportion of heroin-free UA across the study per patient

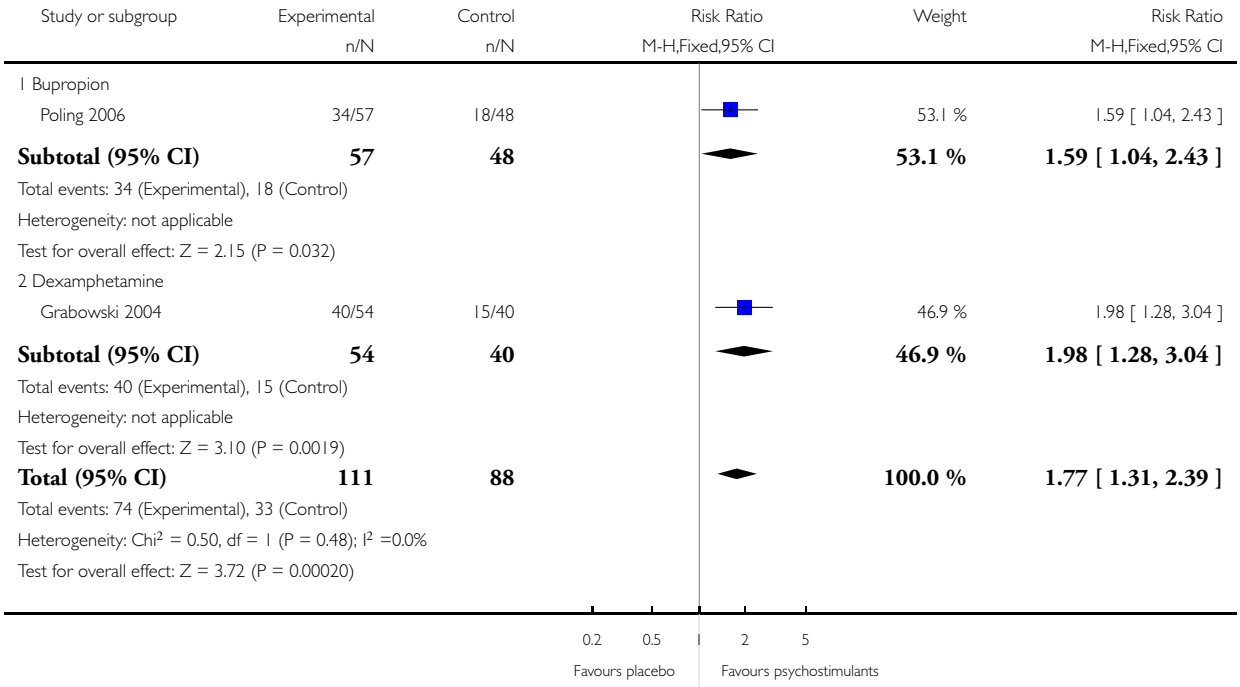
Study or subgroup	Psychostimulants N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 Bupropion							
Poling 2006	57	52.2 (32.1)	48	42.9 (33.1)		66.4 %	0.28 [-0.10, 0.67]
Subtotal (95% CI)	**57**		**48**			**66.4 %**	**0.28 [-0.10, 0.67]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.44 (P = 0.15)							
2 Dexamphetamine							
Grabowski 2004	43	37.9 (15.2)	19	33 (17)		33.6 %	0.31 [-0.24, 0.85]
Subtotal (95% CI)	**43**		**19**			**33.6 %**	**0.31 [-0.24, 0.85]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.11 (P = 0.27)							
Total (95% CI)	**100**		**67**			**100.0 %**	**0.29 [-0.02, 0.61]**
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.95); I^2 =0.0%							
Test for overall effect: Z = 1.82 (P = 0.069)							
Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 0.95), I^2 =0.0%							

Analysis 3.8. Comparison 3 Subgroup analysis 2: Type of drug, Outcome 8 Sustained heroin abstinence.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 3 Subgroup analysis 2: Type of drug

Outcome: 8 Sustained heroin abstinence



Analysis 3.9. Comparison 3 Subgroup analysis 2: Type of drug, Outcome 9 ADHD severity.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 3 Subgroup analysis 2: Type of drug

Outcome: 9 ADHD severity

Study or subgroup	Psychostimulants N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Methylphenidate							
Levin 2007	46	18.8 (10.8)	50	19.6 (14.3)		61.3 %	-0.06 [-0.46, 0.34]
Schubiner 2002	11	1.9 (0.8)	14	2.7 (1)		38.7 %	-0.84 [-1.67, -0.01]
Total (95% CI)	**57**		**64**			**100.0 %**	**-0.36 [-1.11, 0.38]**
Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 2.75$, df = 1 (P = 0.10); I^2 =64%							
Test for overall effect: Z = 0.96 (P = 0.34)							

Analysis 4.1. Comparison 4 Subgroup analysis 3: Definition of cocaine use disorder, Outcome 1 Cocaine use assessed by the mean (SD) of the proportion of cocaine-free UA across the study per patient.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 4 Subgroup analysis 3: Definition of cocaine use disorder

Outcome: 1 Cocaine use assessed by the mean (SD) of the proportion of cocaine-free UA across the study per patient

Study or subgroup	Psychostimulants N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 Cocaine abuse or dependence							
Poling 2006	57	52.2 (32.1)	49	43 (35.8)		22.9 %	0.27 [-0.11, 0.65]
Shoptaw 2008	37	13.1 (14.2)	33	10.3 (11.2)		15.2 %	0.22 [-0.26, 0.69]
Subtotal (95% CI)	**94**		**82**			**38.1 %**	**0.25 [-0.05, 0.55]**
Heterogeneity: $Chi^2 = 0.03$, df = 1 (P = 0.86); I^2 =0.0%							
Test for overall effect: Z = 1.63 (P = 0.10)							
2 Cocaine dependence							
Grabowski 1997	25	30.7 (40)	24	43.8 (41)		10.6 %	-0.32 [-0.88, 0.25]
Grabowski 2004	41	21 (16.8)	19	16.1 (16.9)		11.3 %	0.29 [-0.26, 0.83]
Levin 2007	53	27 (29)	53	30 (29)		23.2 %	-0.10 [-0.48, 0.28]

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Study or subgroup	Psychostimulants N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Schubiner 2002	24	50 (50)	24	42 (32)		10.5 %	0.19 [-0.38, 0.75]
Shearer 2003	16	38.6 (34.3)	14	27.1 (30)		6.4 %	0.35 [-0.38, 1.07]
Subtotal (95% CI)	**159**		**134**			**61.9 %**	**0.03 [-0.21, 0.26]**
Heterogeneity: Chi² = 3.81, df = 4 (P = 0.43); I² =0.0%							
Test for overall effect: Z = 0.23 (P = 0.82)							
Total (95% CI)	**253**		**216**			**100.0 %**	**0.11 [-0.07, 0.29]**
Heterogeneity: Chi² = 5.15, df = 6 (P = 0.52); I² =0.0%							
Test for overall effect: Z = 1.19 (P = 0.24)							
Test for subgroup differences: Chi² = 1.31, df = 1 (P = 0.25), I² =24%							

Analysis 4.2. Comparison 4 Subgroup analysis 3: Definition of cocaine use disorder, Outcome 2 Number of patients who finished the study.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 4 Subgroup analysis 3: Definition of cocaine use disorder

Outcome: 2 Number of patients who finished the study

Study or subgroup	Psychostimulants n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Cocaine abuse or dependence					
Perry 2004	3/11	5/13		1.3 %	0.71 [0.22, 2.32]
Poling 2006	32/57	30/49		9.1 %	0.92 [0.67, 1.26]
Shoptaw 2008	7/37	5/33		1.5 %	1.25 [0.44, 3.56]
Subtotal (95% CI)	**105**	**95**		**11.9 %**	**0.94 [0.69, 1.27]**
Total events: 42 (Psychostimulants), 40 (Placebo)					
Heterogeneity: Chi² = 0.52, df = 2 (P = 0.77); I² =0.0%					
Test for overall effect: Z = 0.42 (P = 0.67)					
2 Cocaine dependence					
Dackis 2005	19/30	21/32		5.7 %	0.97 [0.67, 1.40]
Elkashef 2006	97/150	110/150		31.1 %	0.88 [0.76, 1.03]
Grabowski 1997	12/25	12/24		3.5 %	0.96 [0.54, 1.70]
Grabowski 2001	23/93	8/35		3.3 %	1.08 [0.53, 2.19]

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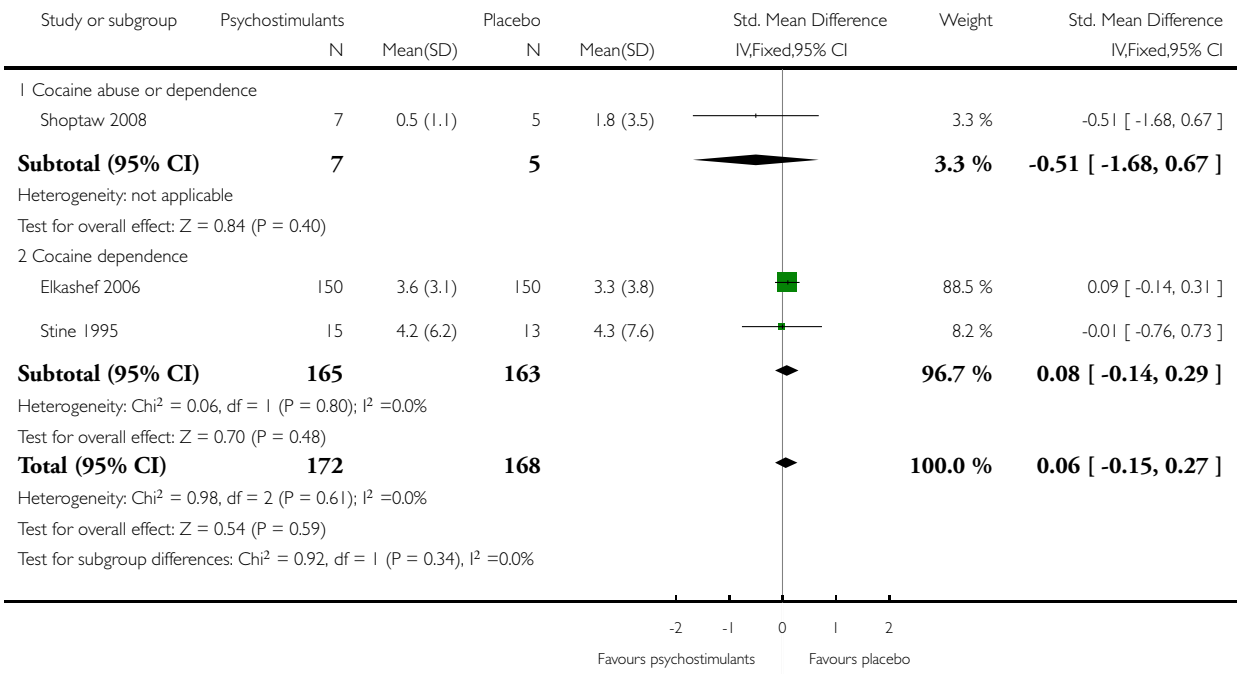
Study or subgroup	Psychostimulants n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Grabowski 2004	24/54	10/40		3.2 %	1.78 [0.96, 3.29]
Levin 2007	23/53	24/53		6.8 %	0.96 [0.63, 1.47]
Margolin 1995 a	63/74	62/75		17.4 %	1.03 [0.89, 1.19]
Margolin 1995 b	15/18	15/19		4.1 %	1.06 [0.77, 1.44]
Margolin 1997	10/13	4/4		1.9 %	0.83 [0.55, 1.27]
Mooney 2009	17/55	8/27		3.0 %	1.04 [0.52, 2.11]
Schubiner 2002	11/24	14/24		4.0 %	0.79 [0.45, 1.36]
Shearer 2003	6/16	5/14		1.5 %	1.05 [0.41, 2.70]
Stine 1995	9/22	9/21		2.6 %	0.95 [0.47, 1.93]
Subtotal (95% CI)	**627**	**518**		**88.1 %**	**0.98 [0.89, 1.08]**
Total events: 329 (Psychostimulants), 302 (Placebo)					
Heterogeneity: Chi^2 = 7.48, df = 12 (P = 0.82); I^2 =0.0%					
Test for overall effect: Z = 0.42 (P = 0.67)					
Total (95% CI)	**732**	**613**		**100.0 %**	**0.97 [0.89, 1.07]**
Total events: 371 (Psychostimulants), 342 (Placebo)					
Heterogeneity: Chi^2 = 8.08, df = 15 (P = 0.92); I^2 =0.0%					
Test for overall effect: Z = 0.55 (P = 0.58)					

Analysis 4.3. Comparison 4 Subgroup analysis 3: Definition of cocaine use disorder, Outcome 3 Cocaine craving.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 4 Subgroup analysis 3: Definition of cocaine use disorder

Outcome: 3 Cocaine craving

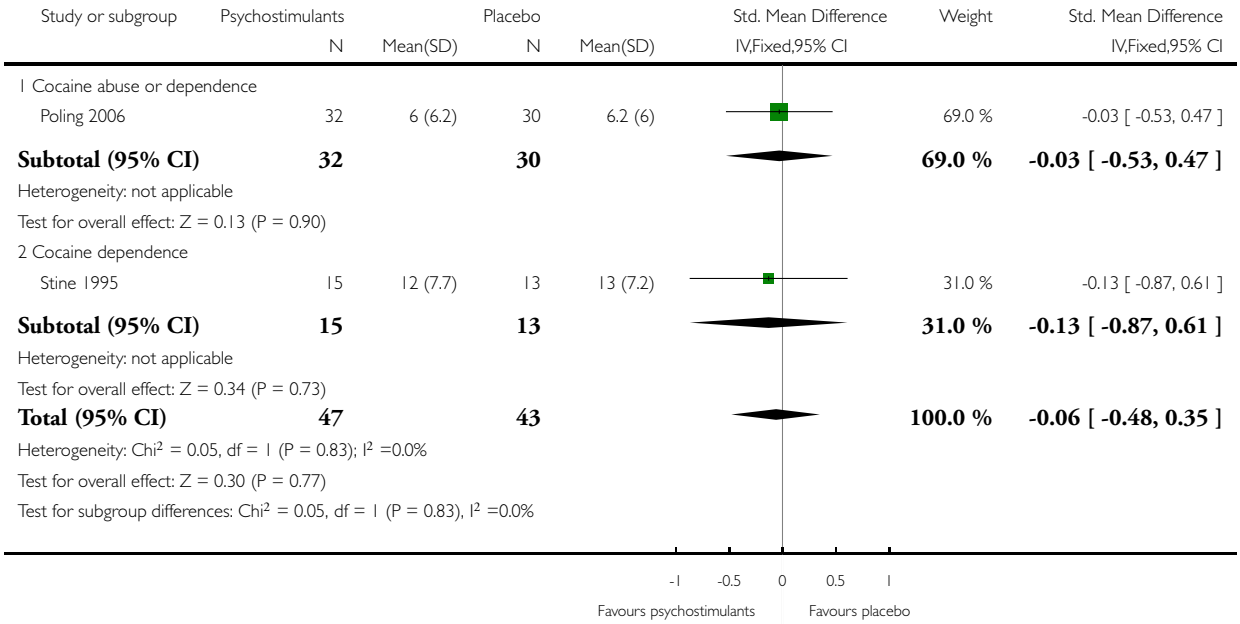


Analysis 4.4. Comparison 4 Subgroup analysis 3: Definition of cocaine use disorder, Outcome 4 Depressive symptoms severity.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 4 Subgroup analysis 3: Definition of cocaine use disorder

Outcome: 4 Depressive symptoms severity



Analysis 4.5. Comparison 4 Subgroup analysis 3: Definition of cocaine use disorder, Outcome 5 Patients dropped out due to any adverse events.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 4 Subgroup analysis 3: Definition of cocaine use disorder

Outcome: 5 Patients dropped out due to any adverse events

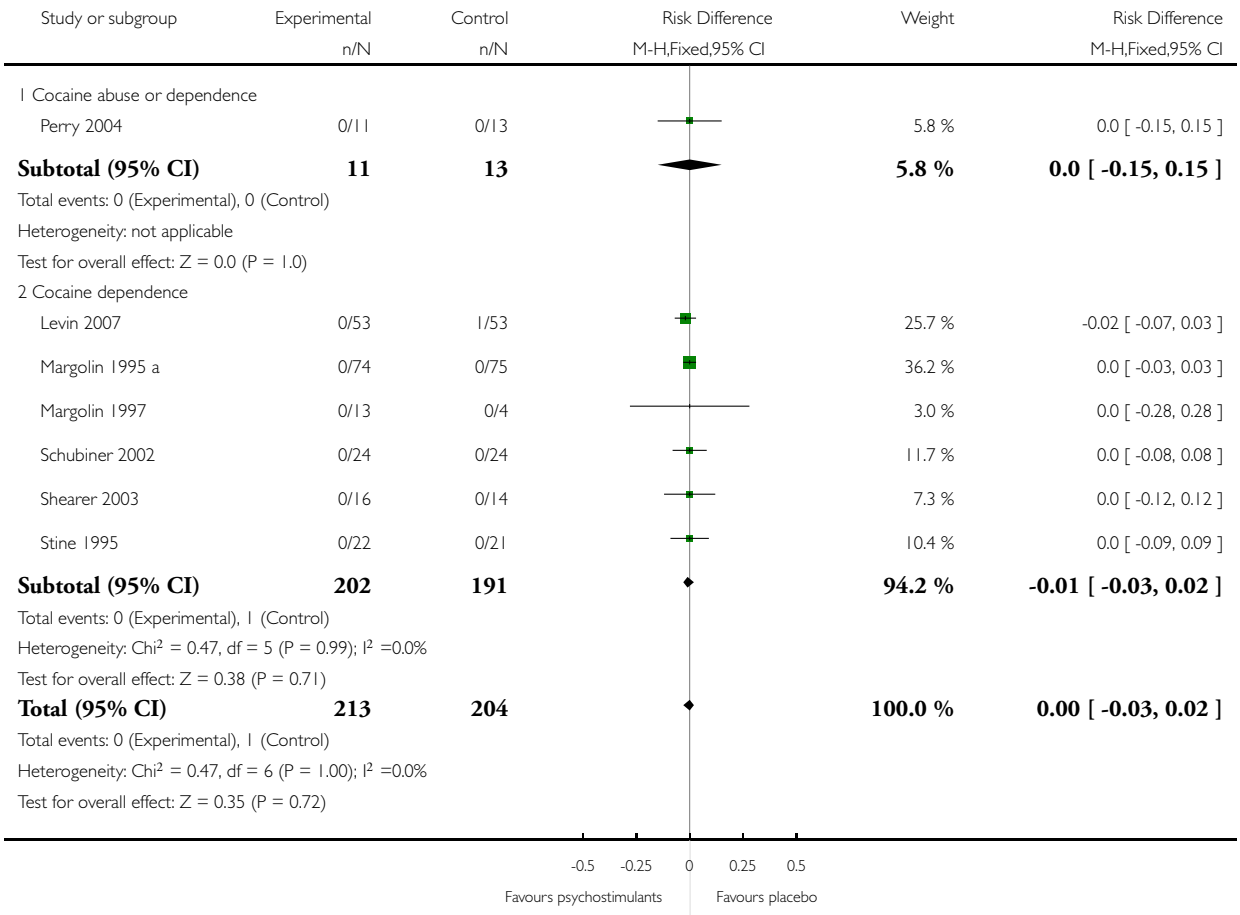
Study or subgroup	Psychostimulants n/N	Placebo n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
1 Cocaine abuse or dependence					
Perry 2004	0/11	0/13		2.7 %	0.0 [-0.15, 0.15]
Subtotal (95% CI)	**11**	**13**		**2.7 %**	**0.0 [-0.15, 0.15]**
Total events: 0 (Psychostimulants), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
2 Cocaine dependence					
Elkashef 2006	0/150	0/150		34.1 %	0.0 [-0.01, 0.01]
Grabowski 2001	7/93	0/35		10.5 %	0.08 [0.01, 0.14]
Levin 2007	1/53	1/53		14.7 %	0.0 [-0.05, 0.05]
Margolin 1995 a	2/74	2/75		14.6 %	0.00 [-0.05, 0.05]
Margolin 1995 b	2/18	1/19		2.0 %	0.06 [-0.12, 0.23]
Margolin 1997	0/13	0/4		0.8 %	0.0 [-0.28, 0.28]
Mooney 2009	1/55	0/27		10.9 %	0.02 [-0.05, 0.08]
Schubiner 2002	0/24	1/24		4.8 %	-0.04 [-0.15, 0.07]
Shearer 2003	5/16	1/14		0.9 %	0.24 [-0.02, 0.51]
Stine 1995	0/22	1/21		4.0 %	-0.05 [-0.17, 0.07]
Subtotal (95% CI)	**518**	**422**		**97.3 %**	**0.01 [-0.02, 0.04]**
Total events: 18 (Psychostimulants), 7 (Placebo)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 14.74, df = 9 (P = 0.10); I^2 =39%					
Test for overall effect: Z = 0.72 (P = 0.47)					
Total (95% CI)	**529**	**435**		**100.0 %**	**0.01 [-0.02, 0.03]**
Total events: 18 (Psychostimulants), 7 (Placebo)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 14.48, df = 10 (P = 0.15); I^2 =31%					
Test for overall effect: Z = 0.72 (P = 0.47)					

Analysis 4.6. Comparison 4 Subgroup analysis 3: Definition of cocaine use disorder, Outcome 6 Patients dropped out due to cardiovascular adverse events.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 4 Subgroup analysis 3: Definition of cocaine use disorder

Outcome: 6 Patients dropped out due to cardiovascular adverse events

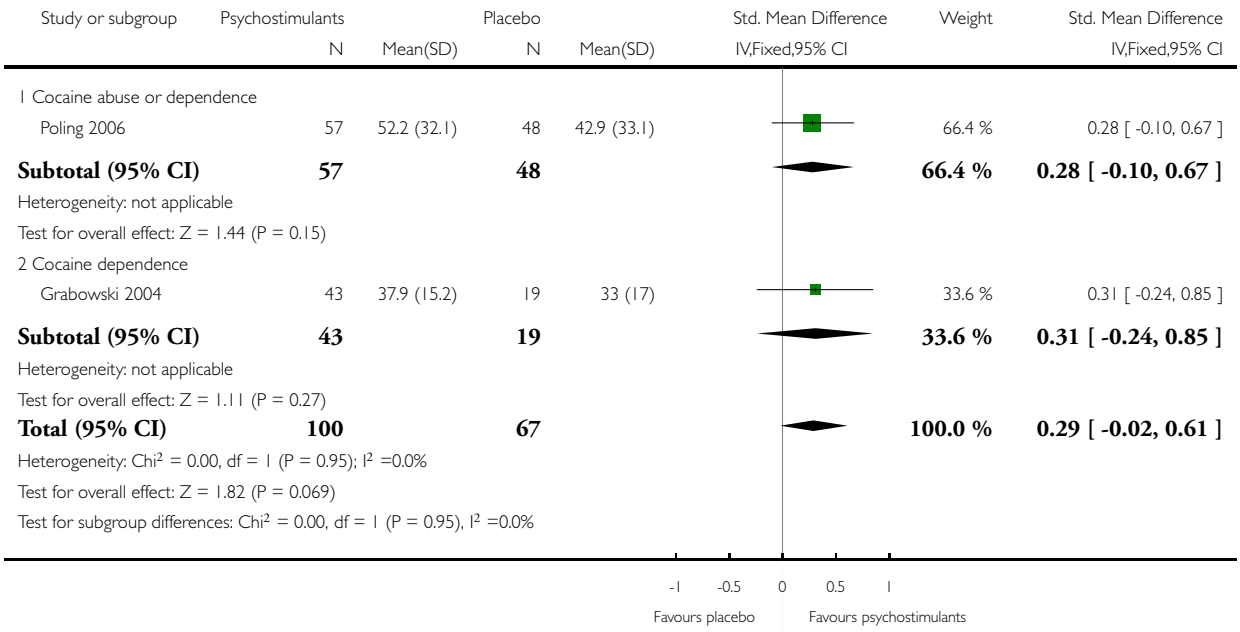


Analysis 4.7. Comparison 4 Subgroup analysis 3: Definition of cocaine use disorder, Outcome 7 Heroin use assessed by the mean (SD) of the proportion of heroin-free UA across the study per patient.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 4 Subgroup analysis 3: Definition of cocaine use disorder

Outcome: 7 Heroin use assessed by the mean (SD) of the proportion of heroin-free UA across the study per patient



Analysis 4.8. Comparison 4 Subgroup analysis 3: Definition of cocaine use disorder, Outcome 8 Sustained heroin abstinence.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 4 Subgroup analysis 3: Definition of cocaine use disorder

Outcome: 8 Sustained heroin abstinence

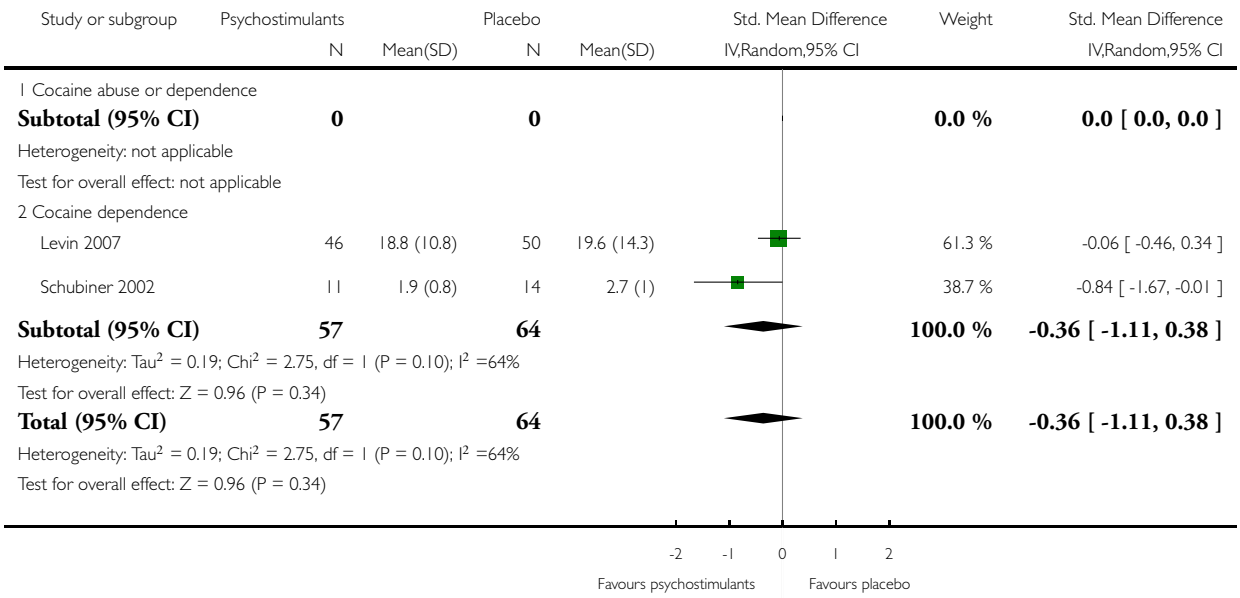
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Cocaine abuse or dependence					
Grabowski 2004	40/54	15/40		46.9 %	1.98 [1.28, 3.04]
Poling 2006	34/57	18/48		53.1 %	1.59 [1.04, 2.43]
Subtotal (95% CI)	**111**	**88**		**100.0 %**	**1.77 [1.31, 2.39]**
Total events: 74 (Experimental), 33 (Control)					
Heterogeneity: Chi^2 = 0.50, df = 1 (P = 0.48); I^2 =0.0%					
Test for overall effect: Z = 3.72 (P = 0.00020)					
2 Cocaine dependence					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Experimental), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**111**	**88**		**100.0 %**	**1.77 [1.31, 2.39]**
Total events: 74 (Experimental), 33 (Control)					
Heterogeneity: Chi^2 = 0.50, df = 1 (P = 0.48); I^2 =0.0%					
Test for overall effect: Z = 3.72 (P = 0.00020)					

Analysis 4.9. Comparison 4 Subgroup analysis 3: Definition of cocaine use disorder, Outcome 9 ADHD severity.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 4 Subgroup analysis 3: Definition of cocaine use disorder

Outcome: 9 ADHD severity

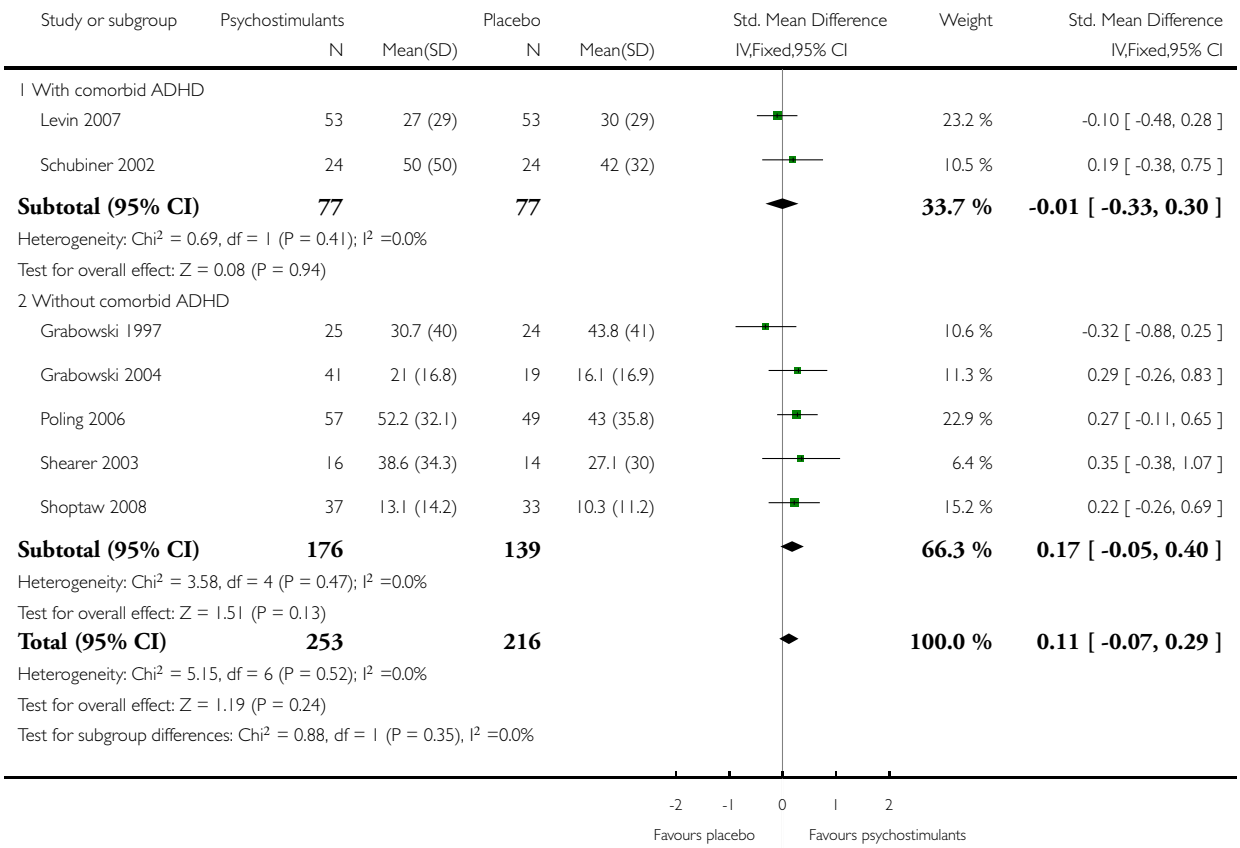


Analysis 5.1. Comparison 5 Subgroup analysis 4: Comorbid ADHD as inclusion criterion, Outcome 1 Cocaine use assessed by the mean (SD) of the proportion of cocaine-free UA across the study per patient.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 5 Subgroup analysis 4: Comorbid ADHD as inclusion criterion

Outcome: 1 Cocaine use assessed by the mean (SD) of the proportion of cocaine-free UA across the study per patient



Analysis 5.2. Comparison 5 Subgroup analysis 4: Comorbid ADHD as inclusion criterion, Outcome 2 Number of patients who finished the study.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 5 Subgroup analysis 4: Comorbid ADHD as inclusion criterion

Outcome: 2 Number of patients who finished the study

Study or subgroup	Psychostimulants n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 With comorbid ADHD					
Levin 2007	23/53	24/53		6.8 %	0.96 [0.63, 1.47]
Schubiner 2002	11/24	14/24		4.0 %	0.79 [0.45, 1.36]
Subtotal (95% CI)	**77**	**77**		**10.7 %**	**0.89 [0.64, 1.25]**
Total events: 34 (Psychostimulants), 38 (Placebo)					
Heterogeneity: Chi^2 = 0.31, df = 1 (P = 0.58); I^2 =0.0%					
Test for overall effect: Z = 0.65 (P = 0.52)					
2 Without comorbid ADHD					
Dackis 2005	19/30	21/32		5.7 %	0.97 [0.67, 1.40]
Elkashef 2006	97/150	110/150		31.1 %	0.88 [0.76, 1.03]
Grabowski 1997	12/25	12/24		3.5 %	0.96 [0.54, 1.70]
Grabowski 2001	23/93	8/35		3.3 %	1.08 [0.53, 2.19]
Grabowski 2004	24/54	10/40		3.2 %	1.78 [0.96, 3.29]
Margolin 1995 a	63/74	62/75		17.4 %	1.03 [0.89, 1.19]
Margolin 1995 b	15/18	15/19		4.1 %	1.06 [0.77, 1.44]
Margolin 1997	10/13	4/4		1.9 %	0.83 [0.55, 1.27]
Mooney 2009	17/55	8/27		3.0 %	1.04 [0.52, 2.11]
Perry 2004	3/11	5/13		1.3 %	0.71 [0.22, 2.32]
Poling 2006	32/57	30/49		9.1 %	0.92 [0.67, 1.26]
Shearer 2003	6/16	5/14		1.5 %	1.05 [0.41, 2.70]
Shoptaw 2008	7/37	5/33		1.5 %	1.25 [0.44, 3.56]
Stine 1995	9/22	9/21		2.6 %	0.95 [0.47, 1.93]
Subtotal (95% CI)	**655**	**536**		**89.3 %**	**0.98 [0.89, 1.08]**
Total events: 337 (Psychostimulants), 304 (Placebo)					
Heterogeneity: Chi^2 = 7.56, df = 13 (P = 0.87); I^2 =0.0%					
Test for overall effect: Z = 0.34 (P = 0.74)					
Total (95% CI)	**732**	**613**		**100.0 %**	**0.97 [0.89, 1.07]**
Total events: 371 (Psychostimulants), 342 (Placebo)					
Heterogeneity: Chi^2 = 8.08, df = 15 (P = 0.92); I^2 =0.0%					
Test for overall effect: Z = 0.55 (P = 0.58)					

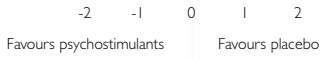
Analysis 5.3. Comparison 5 Subgroup analysis 4: Comorbid ADHD as inclusion criterion, Outcome 3 Cocaine craving.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 5 Subgroup analysis 4: Comorbid ADHD as inclusion criterion

Outcome: 3 Cocaine craving

Study or subgroup	Psychostimulants N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 With comorbid ADHD							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Without comorbid ADHD							
Elkashef 2006	150	3.6 (3.1)	150	3.3 (3.8)		88.5 %	0.09 [-0.14, 0.31]
Shoptaw 2008	7	0.5 (1.1)	5	1.8 (3.5)		3.3 %	-0.51 [-1.68, 0.67]
Stine 1995	15	4.2 (6.2)	13	4.3 (7.6)		8.2 %	-0.01 [-0.76, 0.73]
Subtotal (95% CI)	**172**		**168**			**100.0 %**	**0.06 [-0.15, 0.27]**
Heterogeneity: Chi^2 = 0.98, df = 2 (P = 0.61); I^2 =0.0%							
Test for overall effect: Z = 0.54 (P = 0.59)							
Total (95% CI)	**172**		**168**			**100.0 %**	**0.06 [-0.15, 0.27]**
Heterogeneity: Chi^2 = 0.98, df = 2 (P = 0.61); I^2 =0.0%							
Test for overall effect: Z = 0.54 (P = 0.59)							



Analysis 5.4. Comparison 5 Subgroup analysis 4: Comorbid ADHD as inclusion criterion, Outcome 4 Depressive symptoms severity.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 5 Subgroup analysis 4: Comorbid ADHD as inclusion criterion

Outcome: 4 Depressive symptoms severity

Study or subgroup	Psychostimulants N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 With comorbid ADHD							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Without comorbid ADHD							
Poling 2006	32	6 (6.2)	30	6.2 (6)		69.0 %	-0.03 [-0.53, 0.47]
Stine 1995	15	12 (7.7)	13	13 (7.2)		31.0 %	-0.13 [-0.87, 0.61]
Subtotal (95% CI)	**47**		**43**			**100.0 %**	**-0.06 [-0.48, 0.35]**
Heterogeneity: $Chi^2 = 0.05$, df = 1 (P = 0.83); $I^2 = 0.0\%$							
Test for overall effect: Z = 0.30 (P = 0.77)							
Total (95% CI)	**47**		**43**			**100.0 %**	**-0.06 [-0.48, 0.35]**
Heterogeneity: $Chi^2 = 0.05$, df = 1 (P = 0.83); $I^2 = 0.0\%$							
Test for overall effect: Z = 0.30 (P = 0.77)							

Analysis 5.5. Comparison 5 Subgroup analysis 4: Comorbid ADHD as inclusion criterion, Outcome 5 Patients dropped out due to any adverse events.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 5 Subgroup analysis 4: Comorbid ADHD as inclusion criterion

Outcome: 5 Patients dropped out due to any adverse events

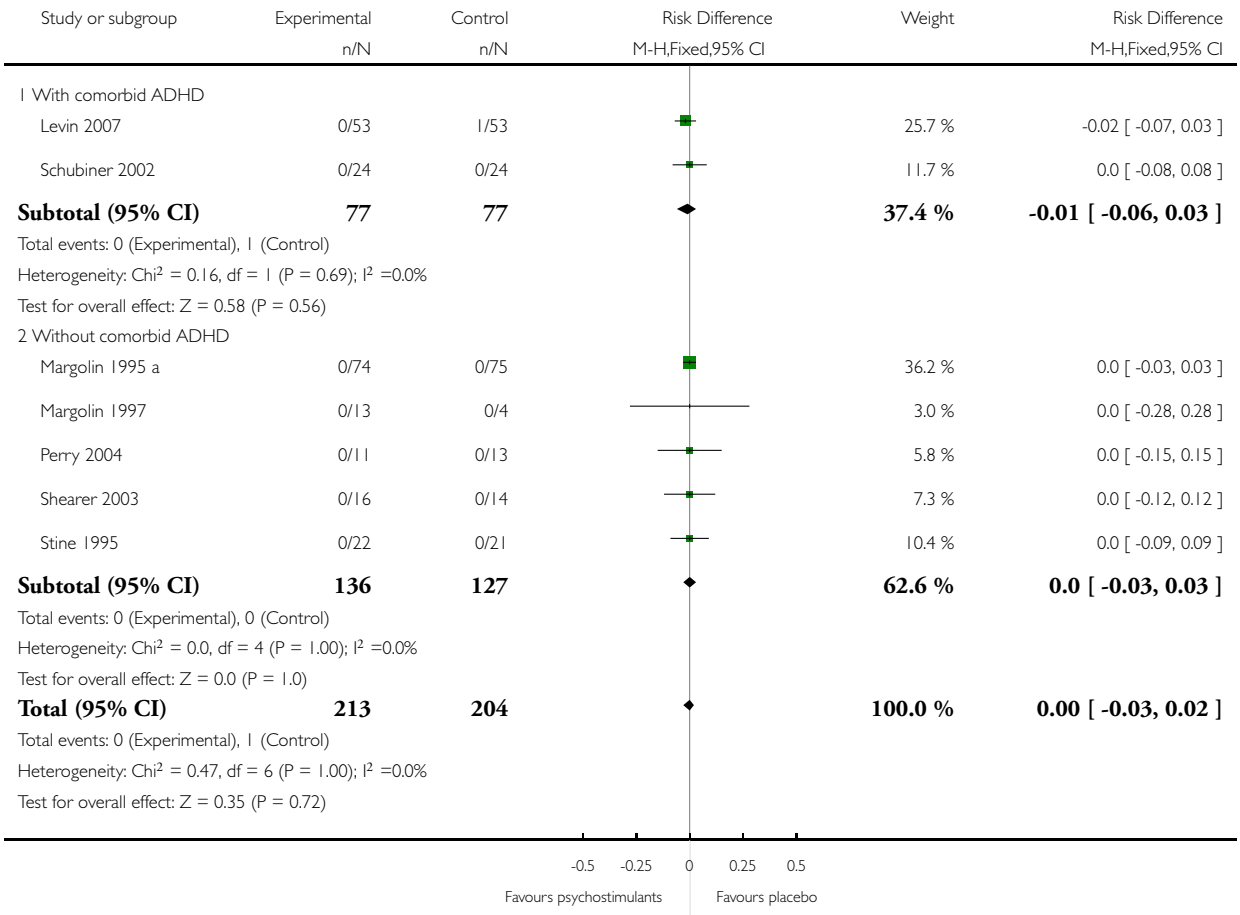
Study or subgroup	Psychostimulants n/N	Placebo n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
1 With comorbid ADHD					
Levin 2007	1/53	1/53		14.7 %	0.0 [-0.05, 0.05]
Schubiner 2002	0/24	1/24		4.8 %	-0.04 [-0.15, 0.07]
Subtotal (95% CI)	**77**	**77**		**19.5 %**	**-0.01 [-0.05, 0.04]**
Total events: 1 (Psychostimulants), 2 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.51$, df = 1 (P = 0.47); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.33 (P = 0.74)					
2 Without comorbid ADHD					
Elkashef 2006	0/150	0/150		34.1 %	0.0 [-0.01, 0.01]
Grabowski 2001	7/93	0/35		10.5 %	0.08 [0.01, 0.14]
Margolin 1995 a	2/74	2/75		14.6 %	0.00 [-0.05, 0.05]
Margolin 1995 b	2/18	1/19		2.0 %	0.06 [-0.12, 0.23]
Margolin 1997	0/13	0/4		0.8 %	0.0 [-0.28, 0.28]
Mooney 2009	1/55	0/27		10.9 %	0.02 [-0.05, 0.08]
Perry 2004	0/11	0/13		2.7 %	0.0 [-0.15, 0.15]
Shearer 2003	5/16	1/14		0.9 %	0.24 [-0.02, 0.51]
Stine 1995	0/22	1/21		4.0 %	-0.05 [-0.17, 0.07]
Subtotal (95% CI)	**452**	**358**		**80.5 %**	**0.02 [-0.02, 0.06]**
Total events: 17 (Psychostimulants), 5 (Placebo)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 17.65$, df = 8 (P = 0.02); $I^2 = 55\%$					
Test for overall effect: Z = 0.93 (P = 0.35)					
Total (95% CI)	**529**	**435**		**100.0 %**	**0.01 [-0.02, 0.03]**
Total events: 18 (Psychostimulants), 7 (Placebo)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 14.48$, df = 10 (P = 0.15); $I^2 = 31\%$					
Test for overall effect: Z = 0.72 (P = 0.47)					

Analysis 5.6. Comparison 5 Subgroup analysis 4: Comorbid ADHD as inclusion criterion, Outcome 6 Patients dropped out due to cardiovascular adverse events.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 5 Subgroup analysis 4: Comorbid ADHD as inclusion criterion

Outcome: 6 Patients dropped out due to cardiovascular adverse events



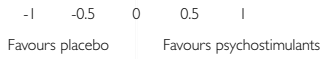
Analysis 5.7. Comparison 5 Subgroup analysis 4: Comorbid ADHD as inclusion criterion, Outcome 7 Heroin use assessed by the mean (SD) of the proportion of heroin-free UA across the study per patient.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 5 Subgroup analysis 4: Comorbid ADHD as inclusion criterion

Outcome: 7 Heroin use assessed by the mean (SD) of the proportion of heroin-free UA across the study per patient

Study or subgroup	Psychostimulants N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 With comorbid ADHD							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Without comorbid ADHD							
Grabowski 2004	43	37.9 (15.2)	19	33 (17)		33.6 %	0.31 [-0.24, 0.85]
Poling 2006	57	52.2 (32.1)	48	42.9 (33.1)		66.4 %	0.28 [-0.10, 0.67]
Subtotal (95% CI)	**100**		**67**			**100.0 %**	**0.29 [-0.02, 0.61]**
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.95); I^2 =0.0%							
Test for overall effect: Z = 1.82 (P = 0.069)							
Total (95% CI)	**100**		**67**			**100.0 %**	**0.29 [-0.02, 0.61]**
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.95); I^2 =0.0%							
Test for overall effect: Z = 1.82 (P = 0.069)							



Analysis 5.8. Comparison 5 Subgroup analysis 4: Comorbid ADHD as inclusion criterion, Outcome 8 Sustained heroin abstinence.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 5 Subgroup analysis 4: Comorbid ADHD as inclusion criterion

Outcome: 8 Sustained heroin abstinence

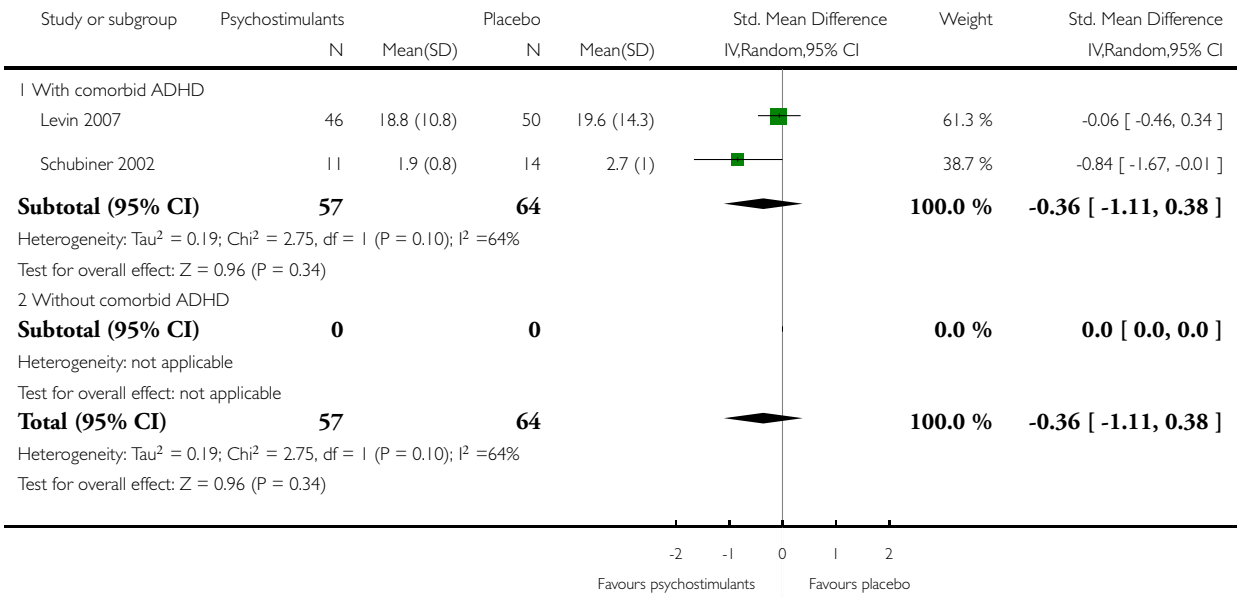
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 With comorbid ADHD					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Experimental), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Withou comorbid ADHD					
Grabowski 2004	40/54	15/40		46.9 %	1.98 [1.28, 3.04]
Poling 2006	34/57	18/48		53.1 %	1.59 [1.04, 2.43]
Subtotal (95% CI)	**111**	**88**		**100.0 %**	**1.77 [1.31, 2.39]**
Total events: 74 (Experimental), 33 (Control)					
Heterogeneity: Chi^2 = 0.50, df = 1 (P = 0.48); I^2 =0.0%					
Test for overall effect: Z = 3.72 (P = 0.00020)					
Total (95% CI)	**111**	**88**		**100.0 %**	**1.77 [1.31, 2.39]**
Total events: 74 (Experimental), 33 (Control)					
Heterogeneity: Chi^2 = 0.50, df = 1 (P = 0.48); I^2 =0.0%					
Test for overall effect: Z = 3.72 (P = 0.00020)					

Analysis 5.9. Comparison 5 Subgroup analysis 4: Comorbid ADHD as inclusion criterion, Outcome 9 ADHD severity.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 5 Subgroup analysis 4: Comorbid ADHD as inclusion criterion

Outcome: 9 ADHD severity



Analysis 6.1. Comparison 6 Subgroup analysis 5: Comorbid opioid dependence as inclusion criterion, Outcome 1 Cocaine use assessed by the mean (SD) of the proportion of cocaine-free UA across the study per patient.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 6 Subgroup analysis 5: Comorbid opioid dependence as inclusion criterion

Outcome: 1 Cocaine use assessed by the mean (SD) of the proportion of cocaine-free UA across the study per patient

Study or subgroup	Psychostimulants N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 With a comorbid opioid dependence							
Grabowski 2004	41	21 (16.8)	19	16.1 (16.9)		11.3 %	0.29 [-0.26, 0.83]
Poling 2006	57	52.2 (32.1)	49	43 (35.8)		22.9 %	0.27 [-0.11, 0.65]
Subtotal (95% CI)	**98**		**68**			**34.1 %**	**0.28 [-0.04, 0.59]**
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.96); I² =0.0%							
Test for overall effect: Z = 1.72 (P = 0.085)							
2 Without a comorbid opioid dependence							
Grabowski 1997	25	30.7 (40)	24	43.8 (41)		10.6 %	-0.32 [-0.88, 0.25]
Levin 2007	53	27 (29)	53	30 (29)		23.2 %	-0.10 [-0.48, 0.28]
Schubiner 2002	24	50 (50)	24	42 (32)		10.5 %	0.19 [-0.38, 0.75]
Shearer 2003	16	38.6 (34.3)	14	27.1 (30)		6.4 %	0.35 [-0.38, 1.07]
Shoptaw 2008	37	13.1 (14.2)	33	10.3 (11.2)		15.2 %	0.22 [-0.26, 0.69]
Subtotal (95% CI)	**155**		**148**			**65.9 %**	**0.03 [-0.20, 0.25]**
Heterogeneity: Chi² = 3.55, df = 4 (P = 0.47); I² =0.0%							
Test for overall effect: Z = 0.22 (P = 0.82)							
Total (95% CI)	**253**		**216**			**100.0 %**	**0.11 [-0.07, 0.29]**
Heterogeneity: Chi² = 5.15, df = 6 (P = 0.52); I² =0.0%							
Test for overall effect: Z = 1.19 (P = 0.24)							
Test for subgroup differences: Chi² = 1.60, df = 1 (P = 0.21), I² =38%							

Analysis 6.2. Comparison 6 Subgroup analysis 5: Comorbid opioid dependence as inclusion criterion, Outcome 2 Number of patients who finished the study.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 6 Subgroup analysis 5: Comorbid opioid dependence as inclusion criterion

Outcome: 2 Number of patients who finished the study

Study or subgroup	Psychostimulants n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 With a comorbid opioid dependence					
Grabowski 2004	24/54	10/40		1.8 %	1.78 [0.96, 3.29]
Margolin 1995 a	63/74	62/75		33.7 %	1.03 [0.89, 1.19]
Margolin 1995 b	15/18	15/19		6.9 %	1.06 [0.77, 1.44]
Margolin 1997	10/13	4/4		3.8 %	0.83 [0.55, 1.27]
Poling 2006	32/57	30/49		6.5 %	0.92 [0.67, 1.26]
Subtotal (95% CI)	**216**	**187**		**52.7 %**	**1.02 [0.88, 1.18]**
Total events: 144 (Psychostimulants), 121 (Placebo)					
Heterogeneity: Tau² = 0.01; Chi² = 4.97, df = 4 (P = 0.29); I² =19%					
Test for overall effect: Z = 0.28 (P = 0.78)					
2 Without a comorbid opioid dependence					
Dackis 2005	19/30	21/32		4.9 %	0.97 [0.67, 1.40]
Elkashef 2006	97/150	110/150		28.6 %	0.88 [0.76, 1.03]
Grabowski 1997	12/25	12/24		2.0 %	0.96 [0.54, 1.70]
Grabowski 2001	23/93	8/35		1.3 %	1.08 [0.53, 2.19]
Levin 2007	23/53	24/53		3.7 %	0.96 [0.63, 1.47]
Mooney 2009	17/55	8/27		1.4 %	1.04 [0.52, 2.11]
Perry 2004	3/11	5/13		0.5 %	0.71 [0.22, 2.32]
Schubiner 2002	11/24	14/24		2.2 %	0.79 [0.45, 1.36]
Shearer 2003	6/16	5/14		0.7 %	1.05 [0.41, 2.70]
Shoptaw 2008	7/37	5/33		0.6 %	1.25 [0.44, 3.56]
Stine 1995	9/22	9/21		1.3 %	0.95 [0.47, 1.93]
Subtotal (95% CI)	**516**	**426**		**47.3 %**	**0.91 [0.81, 1.03]**
Total events: 227 (Psychostimulants), 221 (Placebo)					
Heterogeneity: Tau² = 0.0; Chi² = 1.70, df = 10 (P = 1.00); I² =0.0%					
Test for overall effect: Z = 1.55 (P = 0.12)					
Total (95% CI)	**732**	**613**		**100.0 %**	**0.97 [0.89, 1.05]**
Total events: 371 (Psychostimulants), 342 (Placebo)					
Heterogeneity: Tau² = 0.0; Chi² = 8.08, df = 15 (P = 0.92); I² =0.0%					
Test for overall effect: Z = 0.79 (P = 0.43)					

Analysis 6.3. Comparison 6 Subgroup analysis 5: Comorbid opioid dependence as inclusion criterion, Outcome 3 Cocaine craving.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 6 Subgroup analysis 5: Comorbid opioid dependence as inclusion criterion

Outcome: 3 Cocaine craving

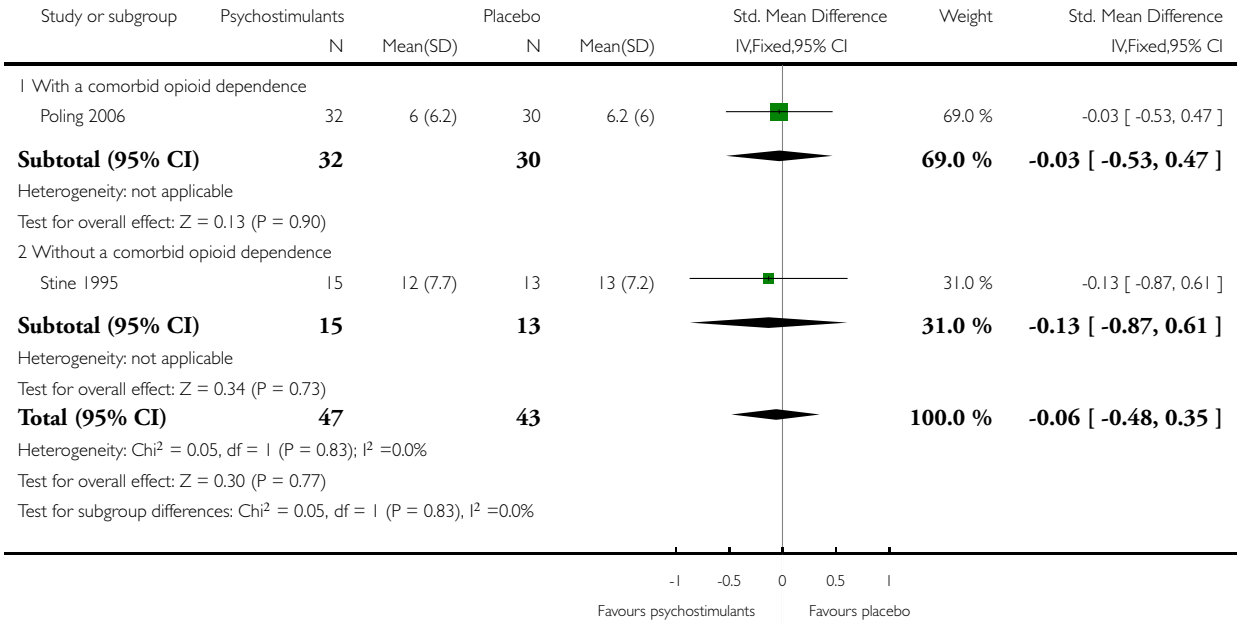
Study or subgroup	Psychostimulants N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 With a comorbid opioid dependence							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Without a comorbid opioid dependence							
Elkashef 2006	150	3.6 (3.1)	150	3.3 (3.8)		88.5 %	0.09 [-0.14, 0.31]
Shoptaw 2008	7	0.5 (1.1)	5	1.8 (3.5)		3.3 %	-0.51 [-1.68, 0.67]
Stine 1995	15	4.2 (6.2)	13	4.3 (7.6)		8.2 %	-0.01 [-0.76, 0.73]
Subtotal (95% CI)	**172**		**168**			**100.0 %**	**0.06 [-0.15, 0.27]**
Heterogeneity: Chi^2 = 0.98, df = 2 (P = 0.61); I^2 =0.0%							
Test for overall effect: Z = 0.54 (P = 0.59)							
Total (95% CI)	**172**		**168**			**100.0 %**	**0.06 [-0.15, 0.27]**
Heterogeneity: Chi^2 = 0.98, df = 2 (P = 0.61); I^2 =0.0%							
Test for overall effect: Z = 0.54 (P = 0.59)							

Analysis 6.4. Comparison 6 Subgroup analysis 5: Comorbid opioid dependence as inclusion criterion, Outcome 4 Depressive symptoms severity.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 6 Subgroup analysis 5: Comorbid opioid dependence as inclusion criterion

Outcome: 4 Depressive symptoms severity



Analysis 6.5. Comparison 6 Subgroup analysis 5: Comorbid opioid dependence as inclusion criterion, Outcome 5 Patients dropped out due to any adverse events.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 6 Subgroup analysis 5: Comorbid opioid dependence as inclusion criterion

Outcome: 5 Patients dropped out due to any adverse events

Study or subgroup	Psychostimulants n/N	Placebo n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
1 With a comorbid opioid dependence					
Margolin 1995 a	2/74	2/75		14.6 %	0.00 [-0.05, 0.05]
Margolin 1995 b	2/18	1/19		2.0 %	0.06 [-0.12, 0.23]
Margolin 1997	0/13	0/4		0.8 %	0.0 [-0.28, 0.28]
Subtotal (95% CI)	**105**	**98**		**17.4 %**	**0.00 [-0.04, 0.05]**
Total events: 4 (Psychostimulants), 3 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.45$, df = 2 (P = 0.80); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.19 (P = 0.85)					
2 Without a comorbid opioid dependence					
Elkashef 2006	0/150	0/150		34.1 %	0.0 [-0.01, 0.01]
Grabowski 2001	7/93	0/35		10.5 %	0.08 [0.01, 0.14]
Levin 2007	1/53	1/53		14.7 %	0.0 [-0.05, 0.05]
Mooney 2009	1/55	0/27		10.9 %	0.02 [-0.05, 0.08]
Perry 2004	0/11	0/13		2.7 %	0.0 [-0.15, 0.15]
Schubiner 2002	0/24	1/24		4.8 %	-0.04 [-0.15, 0.07]
Shearer 2003	5/16	1/14		0.9 %	0.24 [-0.02, 0.51]
Stine 1995	0/22	1/21		4.0 %	-0.05 [-0.17, 0.07]
Subtotal (95% CI)	**424**	**337**		**82.6 %**	**0.01 [-0.02, 0.05]**
Total events: 14 (Psychostimulants), 4 (Placebo)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 14.78$, df = 7 (P = 0.04); $I^2 = 53\%$					
Test for overall effect: Z = 0.63 (P = 0.53)					
Total (95% CI)	**529**	**435**		**100.0 %**	**0.01 [-0.02, 0.03]**
Total events: 18 (Psychostimulants), 7 (Placebo)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 14.48$, df = 10 (P = 0.15); $I^2 = 31\%$					
Test for overall effect: Z = 0.72 (P = 0.47)					

Analysis 6.6. Comparison 6 Subgroup analysis 5: Comorbid opioid dependence as inclusion criterion, Outcome 6 Patients dropped out due to cardiovascular adverse events.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 6 Subgroup analysis 5: Comorbid opioid dependence as inclusion criterion

Outcome: 6 Patients dropped out due to cardiovascular adverse events

Study or subgroup	Experimental n/N	Control n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
1 With a comorbid opioid dependence					
Margolin 1995 a	0/74	0/75		36.2 %	0.0 [-0.03, 0.03]
Margolin 1997	0/13	0/4		3.0 %	0.0 [-0.28, 0.28]
Subtotal (95% CI)	**87**	**79**		**39.1 %**	**0.0 [-0.04, 0.04]**
Total events: 0 (Experimental), 0 (Control)					
Heterogeneity: Chi^2 = 0.0, df = 1 (P = 1.00); I^2 =0.0%					
Test for overall effect: Z = 0.0 (P = 1.0)					
2 Without a comorbid opioid dependence					
Levin 2007	0/53	1/53		25.7 %	-0.02 [-0.07, 0.03]
Perry 2004	0/11	0/13		5.8 %	0.0 [-0.15, 0.15]
Schubiner 2002	0/24	0/24		11.7 %	0.0 [-0.08, 0.08]
Shearer 2003	0/16	0/14		7.3 %	0.0 [-0.12, 0.12]
Stine 1995	0/22	0/21		10.4 %	0.0 [-0.09, 0.09]
Subtotal (95% CI)	**126**	**125**		**60.9 %**	**-0.01 [-0.05, 0.03]**
Total events: 0 (Experimental), 1 (Control)					
Heterogeneity: Chi^2 = 0.28, df = 4 (P = 0.99); I^2 =0.0%					
Test for overall effect: Z = 0.41 (P = 0.68)					
Total (95% CI)	**213**	**204**		**100.0 %**	**0.00 [-0.03, 0.02]**
Total events: 0 (Experimental), 1 (Control)					
Heterogeneity: Chi^2 = 0.47, df = 6 (P = 1.00); I^2 =0.0%					
Test for overall effect: Z = 0.35 (P = 0.72)					

Analysis 6.7. Comparison 6 Subgroup analysis 5: Comorbid opioid dependence as inclusion criterion, Outcome 7 Heroin use assessed by the mean (SD) of the proportion of heroin-free UA across the study per patient.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 6 Subgroup analysis 5: Comorbid opioid dependence as inclusion criterion

Outcome: 7 Heroin use assessed by the mean (SD) of the proportion of heroin-free UA across the study per patient

Study or subgroup	Psychostimulants N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 With a comorbid opioid dependence							
Grabowski 2004	43	37.9 (15.2)	19	33 (17)		33.6 %	0.31 [-0.24, 0.85]
Poling 2006	57	52.2 (32.1)	48	42.9 (33.1)		66.4 %	0.28 [-0.10, 0.67]
Subtotal (95% CI)	**100**		**67**			**100.0 %**	**0.29 [-0.02, 0.61]**
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.95); I^2 =0.0%							
Test for overall effect: Z = 1.82 (P = 0.069)							
2 Without a comorbid opioid dependence							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
Total (95% CI)	**100**		**67**			**100.0 %**	**0.29 [-0.02, 0.61]**
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.95); I^2 =0.0%							
Test for overall effect: Z = 1.82 (P = 0.069)							

Analysis 6.8. Comparison 6 Subgroup analysis 5: Comorbid opioid dependence as inclusion criterion, Outcome 8 Sustained heroin abstinence.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 6 Subgroup analysis 5: Comorbid opioid dependence as inclusion criterion

Outcome: 8 Sustained heroin abstinence

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 With a comorbid opioid dependence					
Grabowski 2004	40/54	15/40		46.9 %	1.98 [1.28, 3.04]
Poling 2006	34/57	18/48		53.1 %	1.59 [1.04, 2.43]
Subtotal (95% CI)	**111**	**88**		**100.0 %**	**1.77 [1.31, 2.39]**
Total events: 74 (Experimental), 33 (Control)					
Heterogeneity: Chi^2 = 0.50, df = 1 (P = 0.48); I^2 =0.0%					
Test for overall effect: Z = 3.72 (P = 0.00020)					
2 Without a comorbid opioid dependence					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Experimental), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**111**	**88**		**100.0 %**	**1.77 [1.31, 2.39]**
Total events: 74 (Experimental), 33 (Control)					
Heterogeneity: Chi^2 = 0.50, df = 1 (P = 0.48); I^2 =0.0%					
Test for overall effect: Z = 3.72 (P = 0.00020)					

Analysis 6.9. Comparison 6 Subgroup analysis 5: Comorbid opioid dependence as inclusion criterion, Outcome 9 ADHD severity.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 6 Subgroup analysis 5: Comorbid opioid dependence as inclusion criterion

Outcome: 9 ADHD severity

Study or subgroup	Psychostimulants N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 With a comorbid opioid dependence							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Without a comorbid opioid dependence							
Levin 2007	46	18.8 (10.8)	50	19.6 (14.3)		61.3 %	-0.06 [-0.46, 0.34]
Schubiner 2002	11	1.9 (0.8)	14	2.7 (1)		38.7 %	-0.84 [-1.67, -0.01]
Subtotal (95% CI)	**57**		**64**			**100.0 %**	**-0.36 [-1.11, 0.38]**
Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 2.75$, df = 1 (P = 0.10); $I^2 = 64\%$							
Test for overall effect: Z = 0.96 (P = 0.34)							
Total (95% CI)	**57**		**64**			**100.0 %**	**-0.36 [-1.11, 0.38]**
Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 2.75$, df = 1 (P = 0.10); $I^2 = 64\%$							
Test for overall effect: Z = 0.96 (P = 0.34)							

Analysis 7.1. Comparison 7 Subgroup analysis 6: Clinical trial reporting quality: Sequence generation, Outcome 1 Cocaine use assessed by the mean (SD) of the proportion of cocaine-free UA across the study per patient.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 7 Subgroup analysis 6: Clinical trial reporting quality: Sequence generation

Outcome: 1 Cocaine use assessed by the mean (SD) of the proportion of cocaine-free UA across the study per patient

Study or subgroup	Psychostimulants N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 Low risk of bias							
Poling 2006	57	52.2 (32.1)	49	43 (35.8)		22.9 %	0.27 [-0.11, 0.65]
Shearer 2003	16	38.6 (34.3)	14	27.1 (30)		6.4 %	0.35 [-0.38, 1.07]
Subtotal (95% CI)	**73**		**63**			**29.3 %**	**0.29 [-0.05, 0.63]**
Heterogeneity: Chi^2 = 0.03, df = 1 (P = 0.86); I^2 =0.0%							
Test for overall effect: Z = 1.66 (P = 0.098)							
2 Intermediate or high risk of bias							
Grabowski 1997	25	30.7 (40)	24	43.8 (41)		10.6 %	-0.32 [-0.88, 0.25]
Grabowski 2004	41	21 (16.8)	19	16.1 (16.9)		11.3 %	0.29 [-0.26, 0.83]
Levin 2007	53	27 (29)	53	30 (29)		23.2 %	-0.10 [-0.48, 0.28]
Schubiner 2002	24	50 (50)	24	42 (32)		10.5 %	0.19 [-0.38, 0.75]
Shoptaw 2008	37	13.1 (14.2)	33	10.3 (11.2)		15.2 %	0.22 [-0.26, 0.69]
Subtotal (95% CI)	**180**		**153**			**70.7 %**	**0.04 [-0.18, 0.26]**
Heterogeneity: Chi^2 = 3.67, df = 4 (P = 0.45); I^2 =0.0%							
Test for overall effect: Z = 0.35 (P = 0.73)							
Total (95% CI)	**253**		**216**			**100.0 %**	**0.11 [-0.07, 0.29]**
Heterogeneity: Chi^2 = 5.15, df = 6 (P = 0.52); I^2 =0.0%							
Test for overall effect: Z = 1.19 (P = 0.24)							
Test for subgroup differences: Chi^2 = 1.45, df = 1 (P = 0.23), I^2 =31%							

Analysis 7.2. Comparison 7 Subgroup analysis 6: Clinical trial reporting quality: Sequence generation, Outcome 2 Number of patients who finished the study.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 7 Subgroup analysis 6: Clinical trial reporting quality: Sequence generation

Outcome: 2 Number of patients who finished the study

Study or subgroup	Psychostimulants n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low risk of bias					
Dackis 2005	19/30	21/32		5.7 %	0.97 [0.67, 1.40]
Elkashef 2006	97/150	110/150		31.1 %	0.88 [0.76, 1.03]
Poling 2006	32/57	30/49		9.1 %	0.92 [0.67, 1.26]
Shearer 2003	6/16	5/14		1.5 %	1.05 [0.41, 2.70]
Subtotal (95% CI)	**253**	**245**		**47.4 %**	**0.90 [0.79, 1.03]**
Total events: 154 (Psychostimulants), 166 (Placebo)					
Heterogeneity: Chi² = 0.33, df = 3 (P = 0.96); I² =0.0%					
Test for overall effect: Z = 1.53 (P = 0.13)					
2 Intermediate or high risk of bias					
Grabowski 1997	12/25	12/24		3.5 %	0.96 [0.54, 1.70]
Grabowski 2001	23/93	8/35		3.3 %	1.08 [0.53, 2.19]
Grabowski 2004	24/54	10/40		3.2 %	1.78 [0.96, 3.29]
Levin 2007	23/53	24/53		6.8 %	0.96 [0.63, 1.47]
Margolin 1995 a	63/74	62/75		17.4 %	1.03 [0.89, 1.19]
Margolin 1995 b	15/18	15/19		4.1 %	1.06 [0.77, 1.44]
Margolin 1997	10/13	4/4		1.9 %	0.83 [0.55, 1.27]
Mooney 2009	17/55	8/27		3.0 %	1.04 [0.52, 2.11]
Perry 2004	3/11	5/13		1.3 %	0.71 [0.22, 2.32]
Schubiner 2002	11/24	14/24		4.0 %	0.79 [0.45, 1.36]
Shoptaw 2008	7/37	5/33		1.5 %	1.25 [0.44, 3.56]
Stine 1995	9/22	9/21		2.6 %	0.95 [0.47, 1.93]
Subtotal (95% CI)	**479**	**368**		**52.6 %**	**1.04 [0.91, 1.18]**
Total events: 217 (Psychostimulants), 176 (Placebo)					
Heterogeneity: Chi² = 5.79, df = 11 (P = 0.89); I² =0.0%					
Test for overall effect: Z = 0.55 (P = 0.58)					
Total (95% CI)	**732**	**613**		**100.0 %**	**0.97 [0.89, 1.07]**
Total events: 371 (Psychostimulants), 342 (Placebo)					
Heterogeneity: Chi² = 8.08, df = 15 (P = 0.92); I² =0.0%					
Test for overall effect: Z = 0.55 (P = 0.58)					

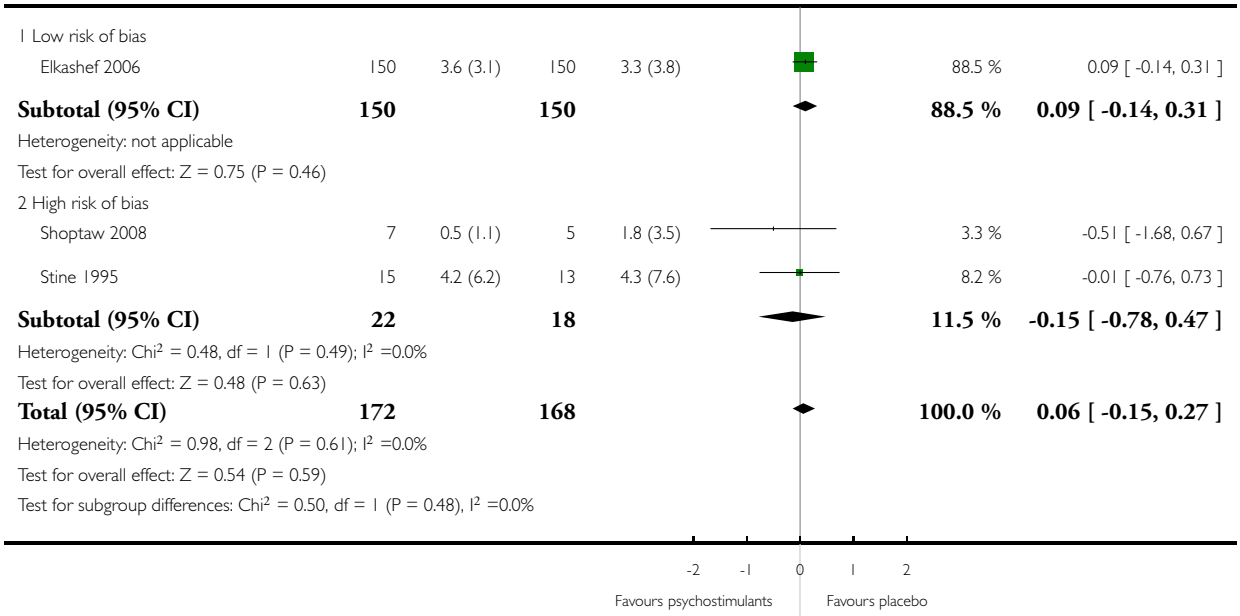
Analysis 7.3. Comparison 7 Subgroup analysis 6: Clinical trial reporting quality: Sequence generation, Outcome 3 Cocaine craving.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 7 Subgroup analysis 6: Clinical trial reporting quality: Sequence generation

Outcome: 3 Cocaine craving

Study or subgroup	Favours psychostimulants N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 Low risk of bias							
Elkashef 2006	150	3.6 (3.1)	150	3.3 (3.8)		88.5 %	0.09 [-0.14, 0.31]
Subtotal (95% CI)	**150**		**150**			**88.5 %**	**0.09 [-0.14, 0.31]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.75 (P = 0.46)							
2 High risk of bias							
Shoptaw 2008	7	0.5 (1.1)	5	1.8 (3.5)		3.3 %	-0.51 [-1.68, 0.67]
Stine 1995	15	4.2 (6.2)	13	4.3 (7.6)		8.2 %	-0.01 [-0.76, 0.73]
Subtotal (95% CI)	**22**		**18**			**11.5 %**	**-0.15 [-0.78, 0.47]**
Heterogeneity: Chi^2 = 0.48, df = 1 (P = 0.49); I^2 =0.0%							
Test for overall effect: Z = 0.48 (P = 0.63)							
Total (95% CI)	**172**		**168**			**100.0 %**	**0.06 [-0.15, 0.27]**
Heterogeneity: Chi^2 = 0.98, df = 2 (P = 0.61); I^2 =0.0%							
Test for overall effect: Z = 0.54 (P = 0.59)							
Test for subgroup differences: Chi^2 = 0.50, df = 1 (P = 0.48), I^2 =0.0%							

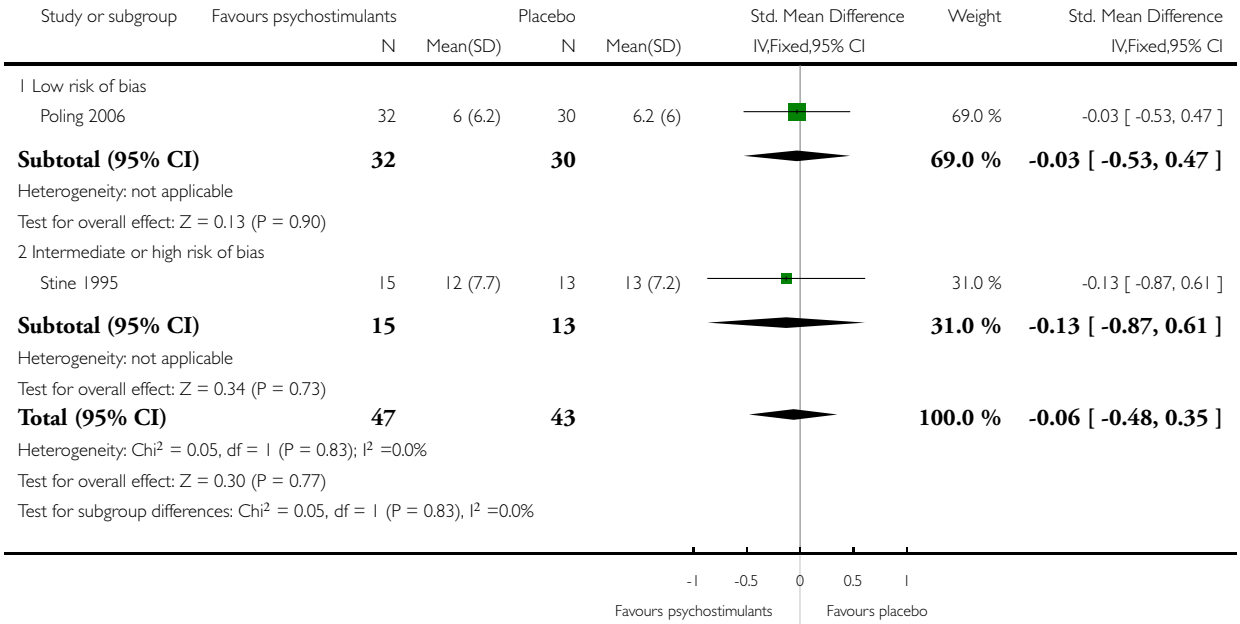


Analysis 7.4. Comparison 7 Subgroup analysis 6: Clinical trial reporting quality: Sequence generation, Outcome 4 Depressive symptoms severity.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 7 Subgroup analysis 6: Clinical trial reporting quality: Sequence generation

Outcome: 4 Depressive symptoms severity

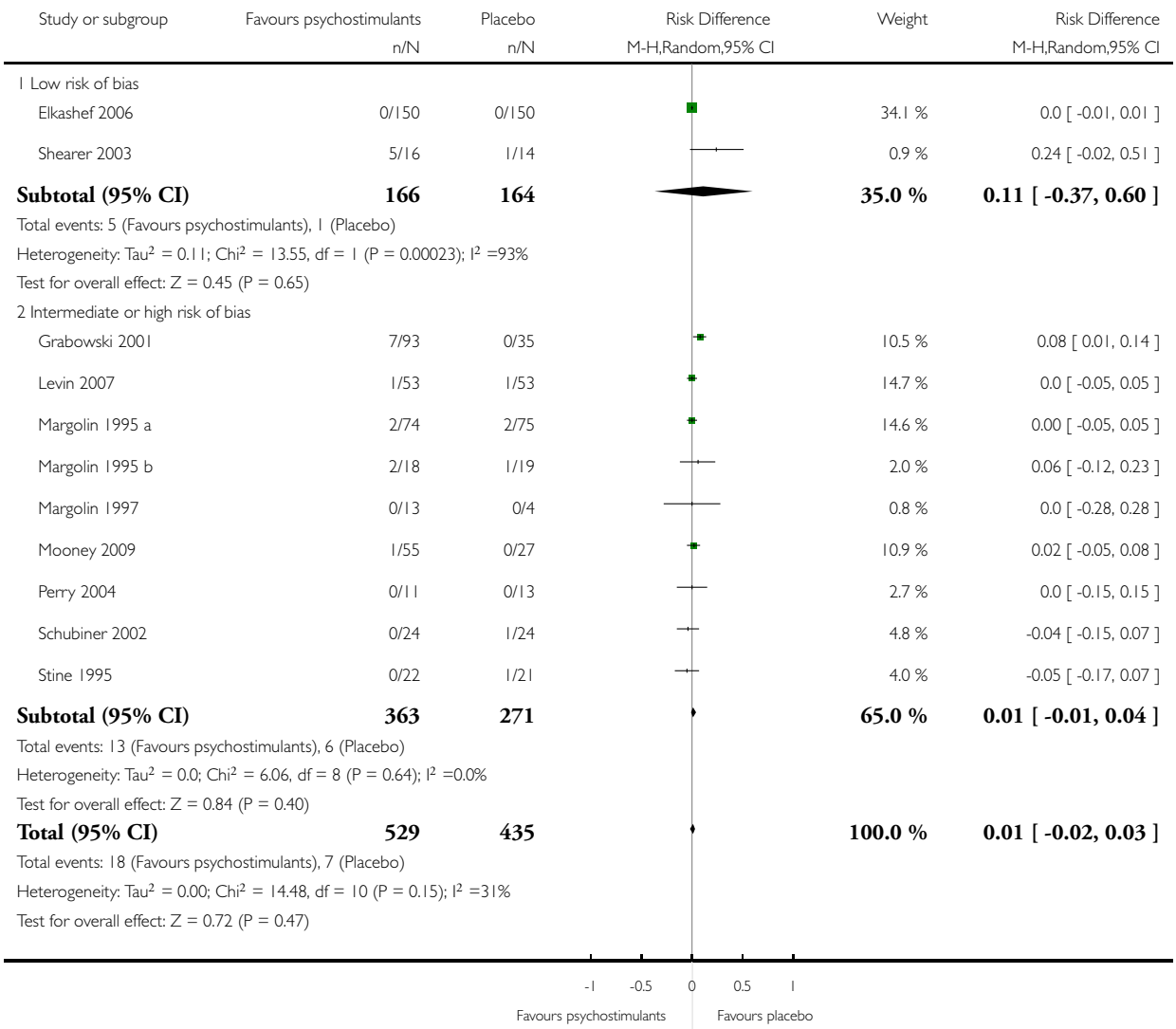


Analysis 7.5. Comparison 7 Subgroup analysis 6: Clinical trial reporting quality: Sequence generation, Outcome 5 Patients dropped out due to any adverse events.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 7 Subgroup analysis 6: Clinical trial reporting quality: Sequence generation

Outcome: 5 Patients dropped out due to any adverse events

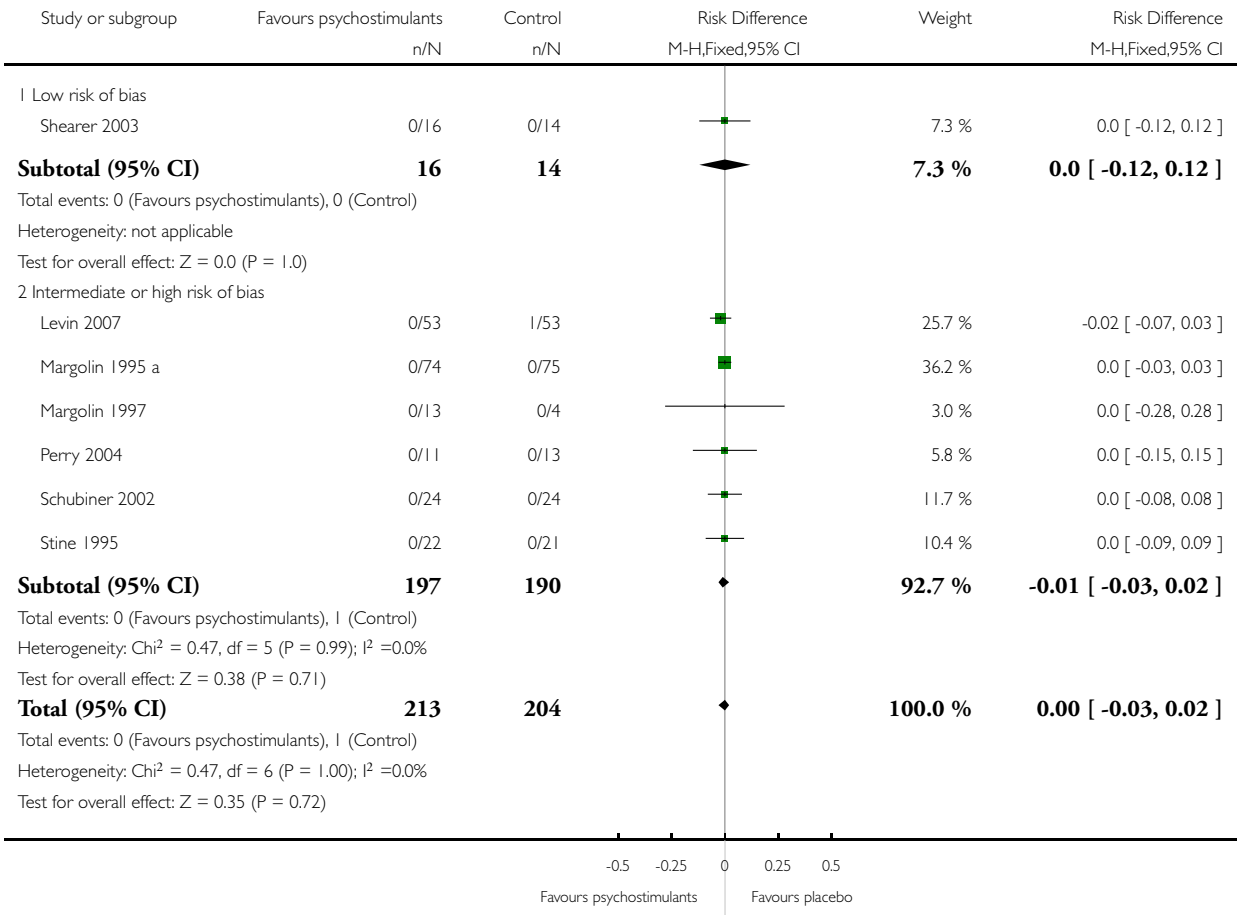


Analysis 7.6. Comparison 7 Subgroup analysis 6: Clinical trial reporting quality: Sequence generation, Outcome 6 Patients dropped out due to cardiovascular adverse events.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 7 Subgroup analysis 6: Clinical trial reporting quality: Sequence generation

Outcome: 6 Patients dropped out due to cardiovascular adverse events



Analysis 7.7. Comparison 7 Subgroup analysis 6: Clinical trial reporting quality: Sequence generation, Outcome 7 Heroin use assessed by the mean (SD) of the proportion of heroin-free UA across the study per patient.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 7 Subgroup analysis 6: Clinical trial reporting quality: Sequence generation

Outcome: 7 Heroin use assessed by the mean (SD) of the proportion of heroin-free UA across the study per patient

Study or subgroup	Favours placebo N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 Low risk of bias							
Poling 2006	57	52.2 (32.1)	48	42.9 (33.1)		66.4 %	0.28 [-0.10, 0.67]
Subtotal (95% CI)	**57**		**48**			**66.4 %**	**0.28 [-0.10, 0.67]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.44 (P = 0.15)							
2 Intermediate or high risk of bias							
Grabowski 2004	43	37.9 (15.2)	19	33 (17)		33.6 %	0.31 [-0.24, 0.85]
Subtotal (95% CI)	**43**		**19**			**33.6 %**	**0.31 [-0.24, 0.85]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.11 (P = 0.27)							
Total (95% CI)	**100**		**67**			**100.0 %**	**0.29 [-0.02, 0.61]**
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.95); I^2 =0.0%							
Test for overall effect: Z = 1.82 (P = 0.069)							
Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 0.95), I^2 =0.0%							

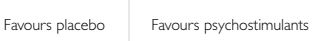
Analysis 7.8. Comparison 7 Subgroup analysis 6: Clinical trial reporting quality: Sequence generation, Outcome 8 Sustained heroin abstinence.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 7 Subgroup analysis 6: Clinical trial reporting quality: Sequence generation

Outcome: 8 Sustained heroin abstinence

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low risk of bias					
Poling 2006	34/57	18/48		53.1 %	1.59 [1.04, 2.43]
Subtotal (95% CI)	**57**	**48**		**53.1 %**	**1.59 [1.04, 2.43]**
Total events: 34 (Experimental), 18 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.15 (P = 0.032)					
2 Intermediate or high risk of bias					
Grabowski 2004	40/54	15/40		46.9 %	1.98 [1.28, 3.04]
Subtotal (95% CI)	**54**	**40**		**46.9 %**	**1.98 [1.28, 3.04]**
Total events: 40 (Experimental), 15 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.10 (P = 0.0019)					
Total (95% CI)	**111**	**88**		**100.0 %**	**1.77 [1.31, 2.39]**
Total events: 74 (Experimental), 33 (Control)					
Heterogeneity: Chi^2 = 0.50, df = 1 (P = 0.48); I^2 =0.0%					
Test for overall effect: Z = 3.72 (P = 0.00020)					

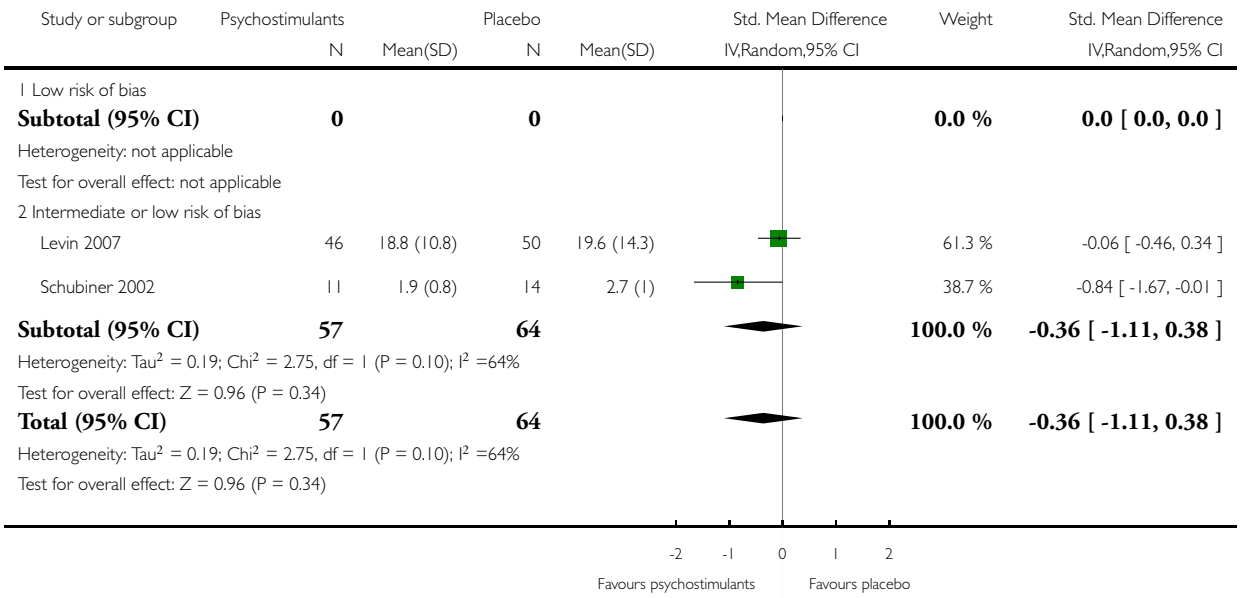


Analysis 7.9. Comparison 7 Subgroup analysis 6: Clinical trial reporting quality: Sequence generation, Outcome 9 ADHD severity.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 7 Subgroup analysis 6: Clinical trial reporting quality: Sequence generation

Outcome: 9 ADHD severity



Analysis 8.1. Comparison 8 Subgroup analysis 7: Clinical trial reporting quality: Blinding, Outcome 1 Cocaine use assessed by the mean (SD) of the proportion of cocaine-free UA across the study per patient.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 8 Subgroup analysis 7: Clinical trial reporting quality: Blinding

Outcome: 1 Cocaine use assessed by the mean (SD) of the proportion of cocaine-free UA across the study per patient

Study or subgroup	Psychostimulants N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 Low risk of bias							
Grabowski 1997	25	30.7 (40)	24	43.8 (41)		10.6 %	-0.32 [-0.88, 0.25]
Grabowski 2004	41	21 (16.8)	19	16.1 (16.9)		11.3 %	0.29 [-0.26, 0.83]
Levin 2007	53	27 (29)	53	30 (29)		23.2 %	-0.10 [-0.48, 0.28]
Poling 2006	57	52.2 (32.1)	49	43 (35.8)		22.9 %	0.27 [-0.11, 0.65]
Schubiner 2002	24	50 (50)	24	42 (32)		10.5 %	0.19 [-0.38, 0.75]
Shearer 2003	16	38.6 (34.3)	14	27.1 (30)		6.4 %	0.35 [-0.38, 1.07]
Shoptaw 2008	37	13.1 (14.2)	33	10.3 (11.2)		15.2 %	0.22 [-0.26, 0.69]
Subtotal (95% CI)	**253**		**216**			**100.0 %**	**0.11 [-0.07, 0.29]**
Heterogeneity: Chi² = 5.15, df = 6 (P = 0.52); I² =0.0%							
Test for overall effect: Z = 1.19 (P = 0.24)							
2 Intermediate or high risk of bias							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
Total (95% CI)	**253**		**216**			**100.0 %**	**0.11 [-0.07, 0.29]**
Heterogeneity: Chi² = 5.15, df = 6 (P = 0.52); I² =0.0%							
Test for overall effect: Z = 1.19 (P = 0.24)							

Analysis 8.2. Comparison 8 Subgroup analysis 7: Clinical trial reporting quality: Blinding, Outcome 2 Number of patients who finished the study (retention).

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 8 Subgroup analysis 7: Clinical trial reporting quality: Blinding

Outcome: 2 Number of patients who finished the study (retention)

Study or subgroup	Psychostimulants n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low risk of bias					
Grabowski 1997	12/25	12/24		3.5 %	0.96 [0.54, 1.70]
Grabowski 2001	23/93	8/35		3.3 %	1.08 [0.53, 2.19]
Grabowski 2004	24/54	10/40		3.2 %	1.78 [0.96, 3.29]
Mooney 2009	17/55	8/27		3.0 %	1.04 [0.52, 2.11]
Poling 2006	32/57	30/49		9.1 %	0.92 [0.67, 1.26]
Subtotal (95% CI)	**284**	**175**		**22.1 %**	**1.09 [0.86, 1.38]**
Total events: 108 (Psychostimulants), 68 (Placebo)					
Heterogeneity: Chi^2 = 3.78, df = 4 (P = 0.44); I^2 =0.0%					
Test for overall effect: Z = 0.74 (P = 0.46)					
2 Intermediate or high risk of bias					
Dackis 2005	19/30	21/32		5.7 %	0.97 [0.67, 1.40]
Elkashef 2006	97/150	110/150		31.1 %	0.88 [0.76, 1.03]
Levin 2007	23/53	24/53		6.8 %	0.96 [0.63, 1.47]
Margolin 1995 a	63/74	62/75		17.4 %	1.03 [0.89, 1.19]
Margolin 1995 b	15/18	15/19		4.1 %	1.06 [0.77, 1.44]
Margolin 1997	10/13	4/4		1.9 %	0.83 [0.55, 1.27]
Perry 2004	3/11	5/13		1.3 %	0.71 [0.22, 2.32]
Schubiner 2002	11/24	14/24		4.0 %	0.79 [0.45, 1.36]
Shearer 2003	6/16	5/14		1.5 %	1.05 [0.41, 2.70]
Shoptaw 2008	7/37	5/33		1.5 %	1.25 [0.44, 3.56]
Stine 1995	9/22	9/21		2.6 %	0.95 [0.47, 1.93]
Subtotal (95% CI)	**448**	**438**		**77.9 %**	**0.94 [0.85, 1.04]**
Total events: 263 (Psychostimulants), 274 (Placebo)					
Heterogeneity: Chi^2 = 4.11, df = 10 (P = 0.94); I^2 =0.0%					
Test for overall effect: Z = 1.23 (P = 0.22)					
Total (95% CI)	**732**	**613**		**100.0 %**	**0.97 [0.89, 1.07]**
Total events: 371 (Psychostimulants), 342 (Placebo)					
Heterogeneity: Chi^2 = 8.08, df = 15 (P = 0.92); I^2 =0.0%					
Test for overall effect: Z = 0.55 (P = 0.58)					

Analysis 8.3. Comparison 8 Subgroup analysis 7: Clinical trial reporting quality: Blinding, Outcome 3 Cocaine craving.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 8 Subgroup analysis 7: Clinical trial reporting quality: Blinding

Outcome: 3 Cocaine craving

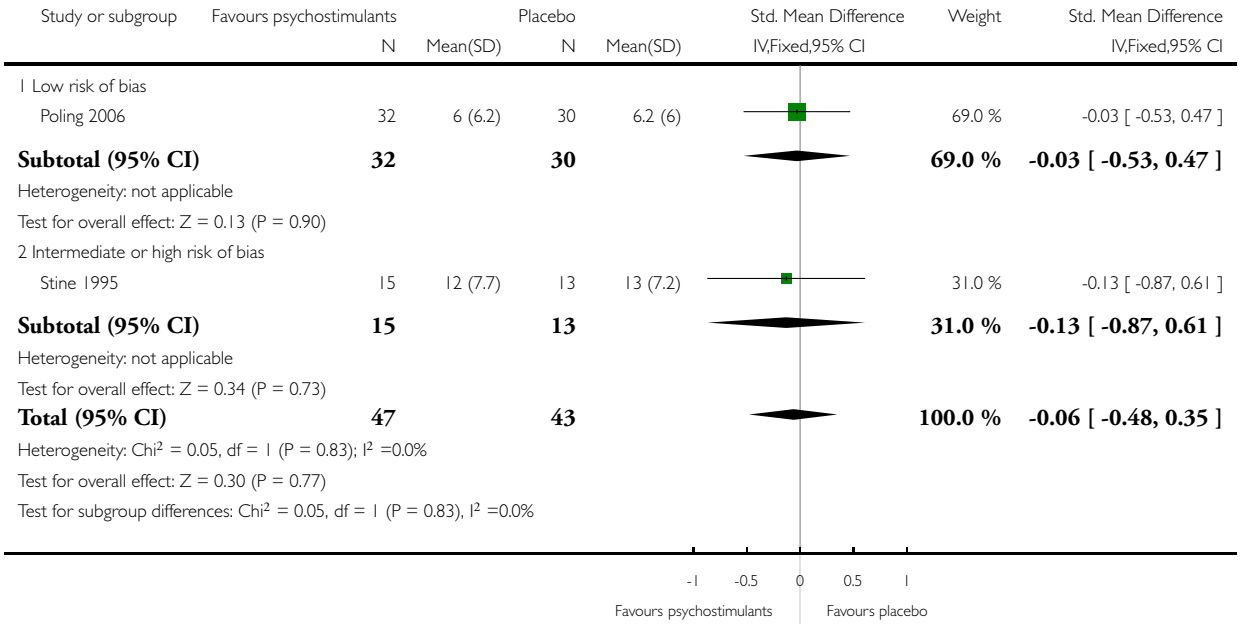
Study or subgroup	Favours psychostimulants N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 Low risk of bias							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 High risk of bias							
Elkashef 2006	150	3.6 (3.1)	150	3.3 (3.8)		88.5 %	0.09 [-0.14, 0.31]
Shoptaw 2008	7	0.5 (1.1)	5	1.8 (3.5)		3.3 %	-0.51 [-1.68, 0.67]
Stine 1995	15	4.2 (6.2)	13	4.3 (7.6)		8.2 %	-0.01 [-0.76, 0.73]
Subtotal (95% CI)	**172**		**168**			**100.0 %**	**0.06 [-0.15, 0.27]**
Heterogeneity: Chi^2 = 0.98, df = 2 (P = 0.61); I^2 =0.0%							
Test for overall effect: Z = 0.54 (P = 0.59)							
Total (95% CI)	**172**		**168**			**100.0 %**	**0.06 [-0.15, 0.27]**
Heterogeneity: Chi^2 = 0.98, df = 2 (P = 0.61); I^2 =0.0%							
Test for overall effect: Z = 0.54 (P = 0.59)							

Analysis 8.4. Comparison 8 Subgroup analysis 7: Clinical trial reporting quality: Blinding, Outcome 4 Depressive symptoms severity.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 8 Subgroup analysis 7: Clinical trial reporting quality: Blinding

Outcome: 4 Depressive symptoms severity

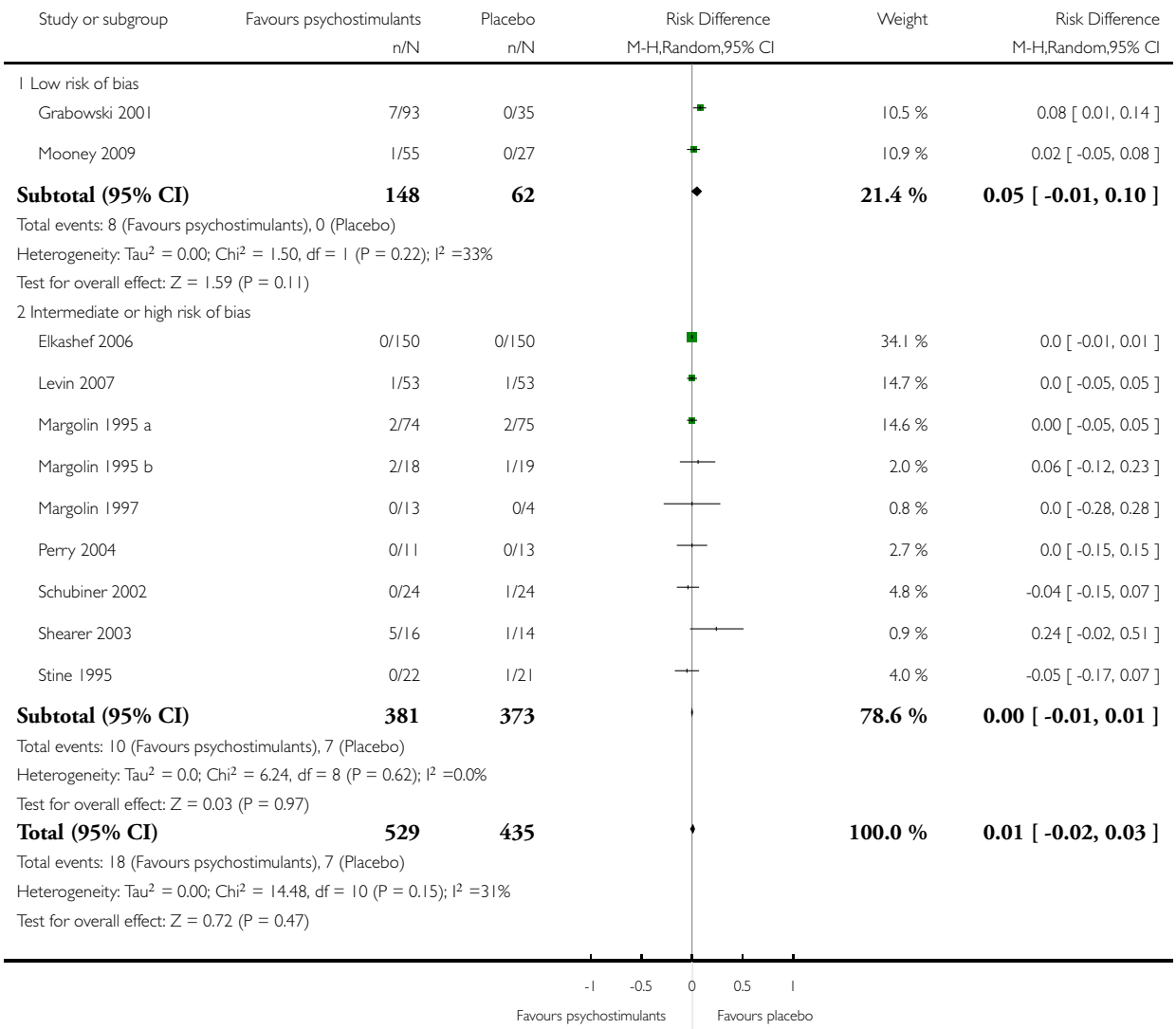


Analysis 8.5. Comparison 8 Subgroup analysis 7: Clinical trial reporting quality: Blinding, Outcome 5 Patients dropped out due to any adverse events.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 8 Subgroup analysis 7: Clinical trial reporting quality: Blinding

Outcome: 5 Patients dropped out due to any adverse events



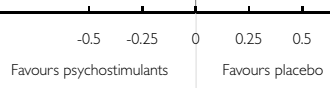
Analysis 8.6. Comparison 8 Subgroup analysis 7: Clinical trial reporting quality: Blinding, Outcome 6 Patients dropped out due to cardiovascular adverse events.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 8 Subgroup analysis 7: Clinical trial reporting quality: Blinding

Outcome: 6 Patients dropped out due to cardiovascular adverse events

Study or subgroup	Favours psychostimulants n/N	Control n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
1 Low risk of bias					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Favours psychostimulants), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Intermediate or high risk of bias					
Levin 2007	0/53	1/53		25.7 %	-0.02 [-0.07, 0.03]
Margolin 1995 a	0/74	0/75		36.2 %	0.0 [-0.03, 0.03]
Margolin 1997	0/13	0/4		3.0 %	0.0 [-0.28, 0.28]
Perry 2004	0/11	0/13		5.8 %	0.0 [-0.15, 0.15]
Schubiner 2002	0/24	0/24		11.7 %	0.0 [-0.08, 0.08]
Shearer 2003	0/16	0/14		7.3 %	0.0 [-0.12, 0.12]
Stine 1995	0/22	0/21		10.4 %	0.0 [-0.09, 0.09]
Subtotal (95% CI)	**213**	**204**		**100.0 %**	**0.00 [-0.03, 0.02]**
Total events: 0 (Favours psychostimulants), 1 (Control)					
Heterogeneity: $Chi^2 = 0.47$, df = 6 (P = 1.00); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.35 (P = 0.72)					
Total (95% CI)	**213**	**204**		**100.0 %**	**0.00 [-0.03, 0.02]**
Total events: 0 (Favours psychostimulants), 1 (Control)					
Heterogeneity: $Chi^2 = 0.47$, df = 6 (P = 1.00); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.35 (P = 0.72)					

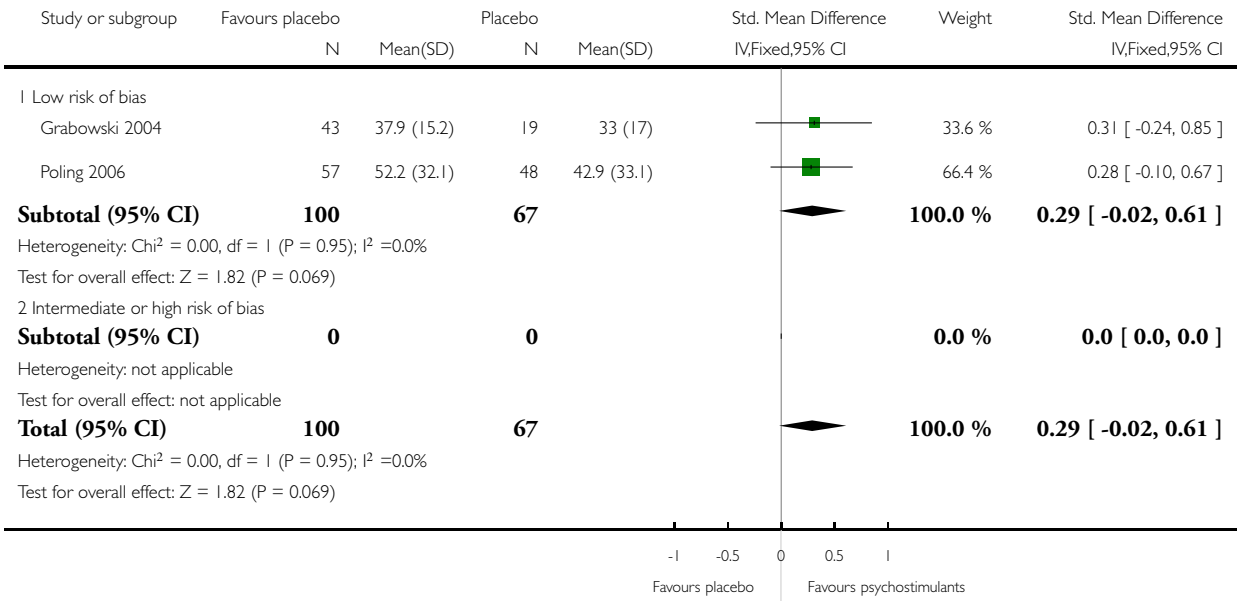


Analysis 8.7. Comparison 8 Subgroup analysis 7: Clinical trial reporting quality: Blinding, Outcome 7 Heroin use assessed by the mean (SD) of the proportion of heroin-free UA across the study per patient.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 8 Subgroup analysis 7: Clinical trial reporting quality: Blinding

Outcome: 7 Heroin use assessed by the mean (SD) of the proportion of heroin-free UA across the study per patient



Analysis 8.8. Comparison 8 Subgroup analysis 7: Clinical trial reporting quality: Blinding, Outcome 8 Sustained heroin abstinence.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 8 Subgroup analysis 7: Clinical trial reporting quality: Blinding

Outcome: 8 Sustained heroin abstinence

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low risk of bias					
Grabowski 2004	40/54	15/40		46.9 %	1.98 [1.28, 3.04]
Poling 2006	34/57	18/48		53.1 %	1.59 [1.04, 2.43]
Subtotal (95% CI)	**111**	**88**		**100.0 %**	**1.77 [1.31, 2.39]**
Total events: 74 (Experimental), 33 (Control)					
Heterogeneity: Chi^2 = 0.50, df = 1 (P = 0.48); I^2 =0.0%					
Test for overall effect: Z = 3.72 (P = 0.00020)					
2 Intermediate or high risk of bias					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Experimental), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**111**	**88**		**100.0 %**	**1.77 [1.31, 2.39]**
Total events: 74 (Experimental), 33 (Control)					
Heterogeneity: Chi^2 = 0.50, df = 1 (P = 0.48); I^2 =0.0%					
Test for overall effect: Z = 3.72 (P = 0.00020)					

Analysis 8.9. Comparison 8 Subgroup analysis 7: Clinical trial reporting quality: Blinding, Outcome 9 ADHD severity.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 8 Subgroup analysis 7: Clinical trial reporting quality: Blinding

Outcome: 9 ADHD severity

Study or subgroup	Psychostimulants N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Low risk of bias							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Intermediate or low risk of bias							
Levin 2007	46	18.8 (10.8)	50	19.6 (14.3)		61.3 %	-0.06 [-0.46, 0.34]
Schubiner 2002	11	1.9 (0.8)	14	2.7 (1)		38.7 %	-0.84 [-1.67, -0.01]
Subtotal (95% CI)	**57**		**64**			**100.0 %**	**-0.36 [-1.11, 0.38]**
Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 2.75$, df = 1 (P = 0.10); $I^2 = 64\%$							
Test for overall effect: Z = 0.96 (P = 0.34)							
Total (95% CI)	**57**		**64**			**100.0 %**	**-0.36 [-1.11, 0.38]**
Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 2.75$, df = 1 (P = 0.10); $I^2 = 64\%$							
Test for overall effect: Z = 0.96 (P = 0.34)							

Analysis 9.1. Comparison 9 Subgroup analysis 8: Clinical trial reporting quality: Allocation concealment, Outcome 1 Cocaine use assessed by the mean (SD) of the proportion of cocaine-free UA across the study per patient.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 9 Subgroup analysis 8: Clinical trial reporting quality: Allocation concealment

Outcome: 1 Cocaine use assessed by the mean (SD) of the proportion of cocaine-free UA across the study per patient

Study or subgroup	Psychostimulants N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 Low risk of bias							
Poling 2006	57	52.2 (32.1)	49	43 (35.8)		22.9 %	0.27 [-0.11, 0.65]
Shearer 2003	16	38.6 (34.3)	14	27.1 (30)		6.4 %	0.35 [-0.38, 1.07]
Subtotal (95% CI)	**73**		**63**			**29.3 %**	**0.29 [-0.05, 0.63]**
Heterogeneity: Chi^2 = 0.03, df = 1 (P = 0.86); I^2 =0.0%							
Test for overall effect: Z = 1.66 (P = 0.098)							
2 Intermediate or high risk of bias							
Grabowski 1997	25	30.7 (40)	24	43.8 (41)		10.6 %	-0.32 [-0.88, 0.25]
Grabowski 2004	41	21 (16.8)	19	16.1 (16.9)		11.3 %	0.29 [-0.26, 0.83]
Levin 2007	53	27 (29)	53	30 (29)		23.2 %	-0.10 [-0.48, 0.28]
Schubiner 2002	24	50 (50)	24	42 (32)		10.5 %	0.19 [-0.38, 0.75]
Shoptaw 2008	37	13.1 (14.2)	33	10.3 (11.2)		15.2 %	0.22 [-0.26, 0.69]
Subtotal (95% CI)	**180**		**153**			**70.7 %**	**0.04 [-0.18, 0.26]**
Heterogeneity: Chi^2 = 3.67, df = 4 (P = 0.45); I^2 =0.0%							
Test for overall effect: Z = 0.35 (P = 0.73)							
Total (95% CI)	**253**		**216**			**100.0 %**	**0.11 [-0.07, 0.29]**
Heterogeneity: Chi^2 = 5.15, df = 6 (P = 0.52); I^2 =0.0%							
Test for overall effect: Z = 1.19 (P = 0.24)							
Test for subgroup differences: Chi^2 = 1.45, df = 1 (P = 0.23), I^2 =31%							

Analysis 9.2. Comparison 9 Subgroup analysis 8: Clinical trial reporting quality: Allocation concealment, Outcome 2 Number of patients who finished the study.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 9 Subgroup analysis 8: Clinical trial reporting quality: Allocation concealment

Outcome: 2 Number of patients who finished the study

Study or subgroup	Psychostimulants n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low risk of bias					
Dackis 2005	19/30	21/32		5.7 %	0.97 [0.67, 1.40]
Margolin 1995 b	15/18	15/19		4.1 %	1.06 [0.77, 1.44]
Margolin 1997	10/13	4/4		1.9 %	0.83 [0.55, 1.27]
Poling 2006	32/57	30/49		9.1 %	0.92 [0.67, 1.26]
Shearer 2003	6/16	5/14		1.5 %	1.05 [0.41, 2.70]
Subtotal (95% CI)	**134**	**118**		**22.4 %**	**0.96 [0.79, 1.15]**
Total events: 82 (Psychostimulants), 75 (Placebo)					
Heterogeneity: Chi² = 0.91, df = 4 (P = 0.92); I² =0.0%					
Test for overall effect: Z = 0.47 (P = 0.64)					
2 Intermediate or high risk of bias					
Elkashef 2006	97/150	110/150		31.1 %	0.88 [0.76, 1.03]
Grabowski 1997	12/25	12/24		3.5 %	0.96 [0.54, 1.70]
Grabowski 2001	23/93	8/35		3.3 %	1.08 [0.53, 2.19]
Grabowski 2004	24/54	10/40		3.2 %	1.78 [0.96, 3.29]
Levin 2007	23/53	24/53		6.8 %	0.96 [0.63, 1.47]
Margolin 1995 a	63/74	62/75		17.4 %	1.03 [0.89, 1.19]
Mooney 2009	17/55	8/27		3.0 %	1.04 [0.52, 2.11]
Perry 2004	3/11	5/13		1.3 %	0.71 [0.22, 2.32]
Schubiner 2002	11/24	14/24		4.0 %	0.79 [0.45, 1.36]
Shoptaw 2008	7/37	5/33		1.5 %	1.25 [0.44, 3.56]
Stine 1995	9/22	9/21		2.6 %	0.95 [0.47, 1.93]
Subtotal (95% CI)	**598**	**495**		**77.6 %**	**0.98 [0.88, 1.09]**
Total events: 289 (Psychostimulants), 267 (Placebo)					
Heterogeneity: Chi² = 7.16, df = 10 (P = 0.71); I² =0.0%					
Test for overall effect: Z = 0.39 (P = 0.70)					
Total (95% CI)	**732**	**613**		**100.0 %**	**0.97 [0.89, 1.07]**
Total events: 371 (Psychostimulants), 342 (Placebo)					
Heterogeneity: Chi² = 8.08, df = 15 (P = 0.92); I² =0.0%					
Test for overall effect: Z = 0.55 (P = 0.58)					

Analysis 9.3. Comparison 9 Subgroup analysis 8: Clinical trial reporting quality: Allocation concealment, Outcome 3 Cocaine craving.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 9 Subgroup analysis 8: Clinical trial reporting quality: Allocation concealment

Outcome: 3 Cocaine craving

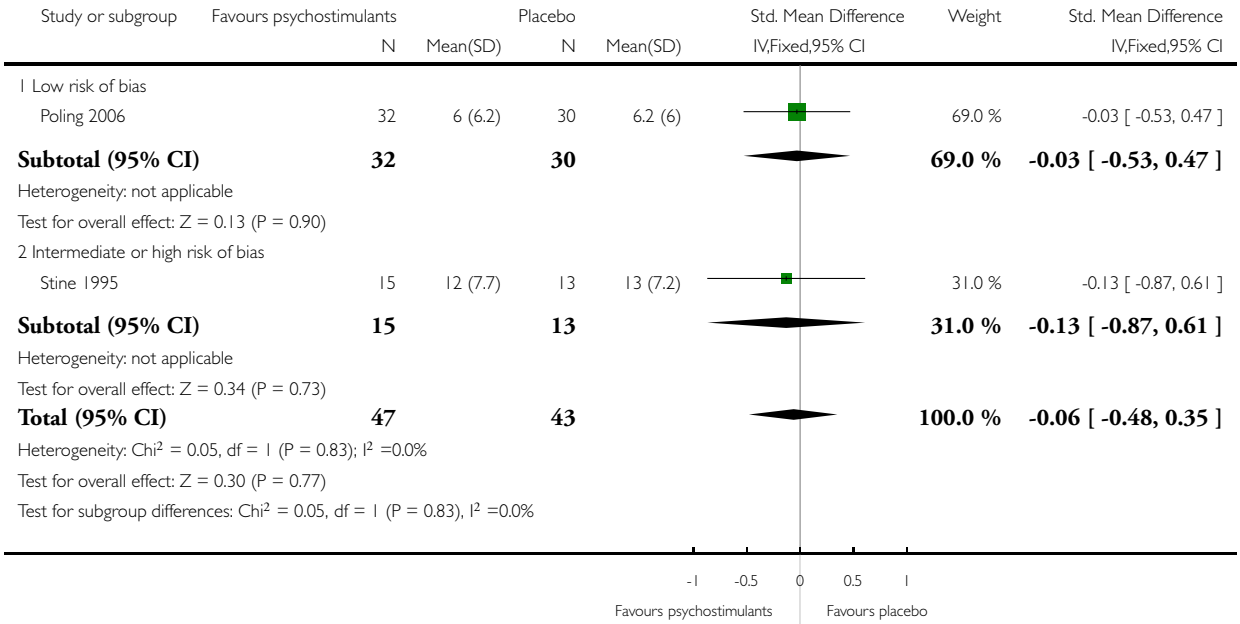
Study or subgroup	Favours psychostimulants N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 Low risk of bias							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Intermediate or high risk of bias							
Elkashef 2006	150	3.6 (3.1)	150	3.3 (3.8)		88.5 %	0.09 [-0.14, 0.31]
Shoptaw 2008	7	0.5 (1.1)	5	1.8 (3.5)		3.3 %	-0.51 [-1.68, 0.67]
Stine 1995	15	4.2 (6.2)	13	4.3 (7.6)		8.2 %	-0.01 [-0.76, 0.73]
Subtotal (95% CI)	**172**		**168**			**100.0 %**	**0.06 [-0.15, 0.27]**
Heterogeneity: Chi^2 = 0.98, df = 2 (P = 0.61); I^2 =0.0%							
Test for overall effect: Z = 0.54 (P = 0.59)							
Total (95% CI)	**172**		**168**			**100.0 %**	**0.06 [-0.15, 0.27]**
Heterogeneity: Chi^2 = 0.98, df = 2 (P = 0.61); I^2 =0.0%							
Test for overall effect: Z = 0.54 (P = 0.59)							

Analysis 9.4. Comparison 9 Subgroup analysis 8: Clinical trial reporting quality: Allocation concealment, Outcome 4 Depressive symptoms severity.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 9 Subgroup analysis 8: Clinical trial reporting quality: Allocation concealment

Outcome: 4 Depressive symptoms severity



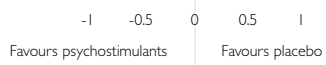
Analysis 9.5. Comparison 9 Subgroup analysis 8: Clinical trial reporting quality: Allocation concealment, Outcome 5 Patients dropped out due to any adverse events.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 9 Subgroup analysis 8: Clinical trial reporting quality: Allocation concealment

Outcome: 5 Patients dropped out due to any adverse events

Study or subgroup	Favours psychostimulants n/N	Placebo n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
1 Low risk of bias					
Margolin 1995 b	2/18	1/19		2.0 %	0.06 [-0.12, 0.23]
Margolin 1997	0/13	0/4		0.8 %	0.0 [-0.28, 0.28]
Shearer 2003	5/16	1/14		0.9 %	0.24 [-0.02, 0.51]
Subtotal (95% CI)	**47**	**37**		**3.7 %**	**0.09 [-0.04, 0.22]**
Total events: 7 (Favours psychostimulants), 2 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.96$, df = 2 (P = 0.38); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.36 (P = 0.17)					
2 Intermediate or high risk of bias					
Elkashef 2006	0/150	0/150		34.1 %	0.0 [-0.01, 0.01]
Grabowski 2001	7/93	0/35		10.5 %	0.08 [0.01, 0.14]
Levin 2007	1/53	1/53		14.7 %	0.0 [-0.05, 0.05]
Margolin 1995 a	2/74	2/75		14.6 %	0.00 [-0.05, 0.05]
Mooney 2009	1/55	0/27		10.9 %	0.02 [-0.05, 0.08]
Perry 2004	0/11	0/13		2.7 %	0.0 [-0.15, 0.15]
Schubiner 2002	0/24	1/24		4.8 %	-0.04 [-0.15, 0.07]
Stine 1995	0/22	1/21		4.0 %	-0.05 [-0.17, 0.07]
Subtotal (95% CI)	**482**	**398**		**96.3 %**	**0.00 [-0.01, 0.01]**
Total events: 11 (Favours psychostimulants), 5 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 6.67$, df = 7 (P = 0.46); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.33 (P = 0.74)					
Total (95% CI)	**529**	**435**		**100.0 %**	**0.01 [-0.02, 0.03]**
Total events: 18 (Favours psychostimulants), 7 (Placebo)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 14.48$, df = 10 (P = 0.15); $I^2 = 31\%$					
Test for overall effect: Z = 0.72 (P = 0.47)					

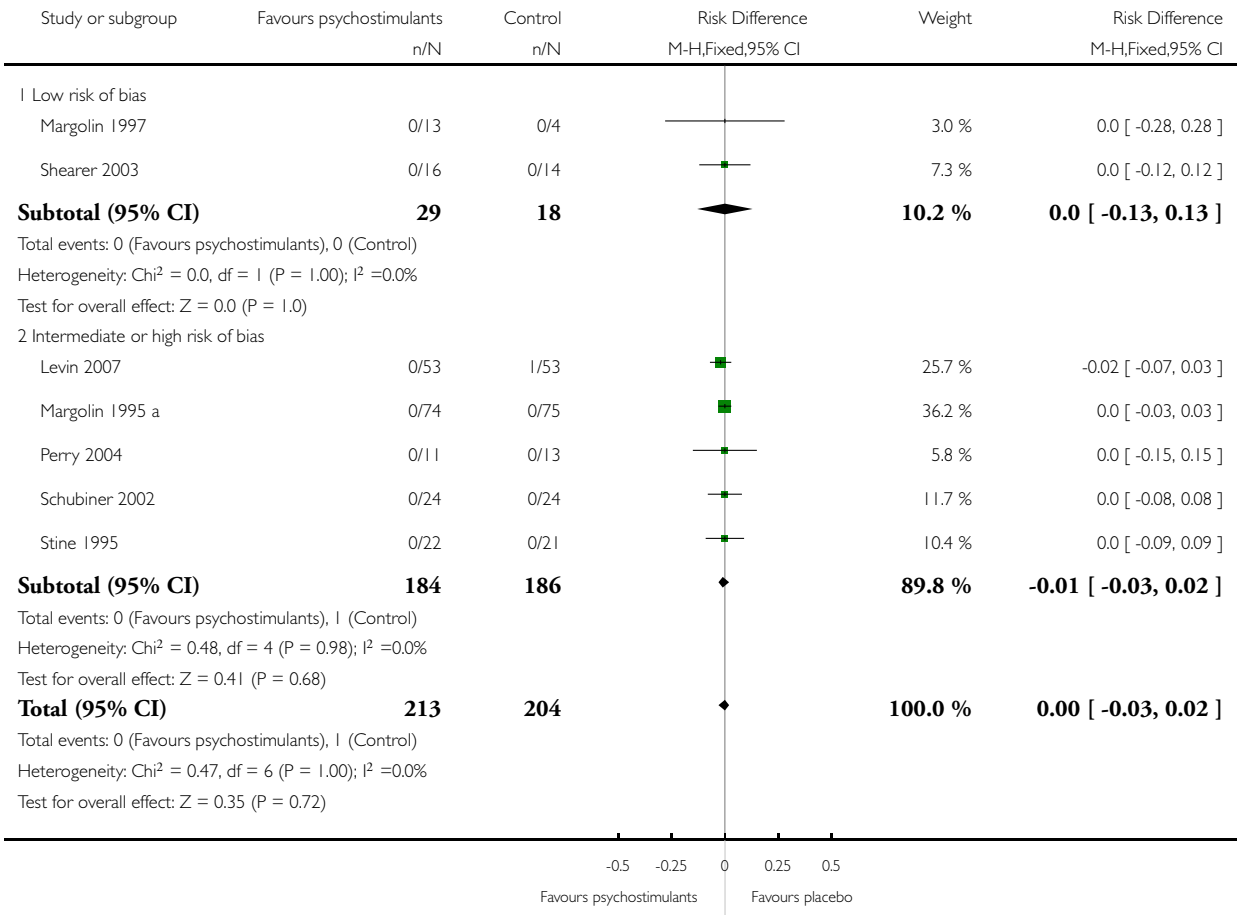


Analysis 9.6. Comparison 9 Subgroup analysis 8: Clinical trial reporting quality: Allocation concealment, Outcome 6 Patients dropped out due to cardiovascular adverse events.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 9 Subgroup analysis 8: Clinical trial reporting quality: Allocation concealment

Outcome: 6 Patients dropped out due to cardiovascular adverse events



Analysis 9.7. Comparison 9 Subgroup analysis 8: Clinical trial reporting quality: Allocation concealment, Outcome 7 Heroin use assessed by the mean (SD) of the proportion of heroin-free UA across the study per patient.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 9 Subgroup analysis 8: Clinical trial reporting quality: Allocation concealment

Outcome: 7 Heroin use assessed by the mean (SD) of the proportion of heroin-free UA across the study per patient

Study or subgroup	Favours placebo N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 Low risk of bias							
Poling 2006	57	52.2 (32.1)	48	42.9 (33.1)		66.4 %	0.28 [-0.10, 0.67]
Subtotal (95% CI)	**57**		**48**			**66.4 %**	**0.28 [-0.10, 0.67]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.44 (P = 0.15)							
2 Intermediate or high risk of bias							
Grabowski 2004	43	37.9 (15.2)	19	33 (17)		33.6 %	0.31 [-0.24, 0.85]
Subtotal (95% CI)	**43**		**19**			**33.6 %**	**0.31 [-0.24, 0.85]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.11 (P = 0.27)							
Total (95% CI)	**100**		**67**			**100.0 %**	**0.29 [-0.02, 0.61]**
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.95); I^2 =0.0%							
Test for overall effect: Z = 1.82 (P = 0.069)							
Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 0.95), I^2 =0.0%							

Analysis 9.8. Comparison 9 Subgroup analysis 8: Clinical trial reporting quality: Allocation concealment, Outcome 8 Sustained heroin abstinence.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 9 Subgroup analysis 8: Clinical trial reporting quality: Allocation concealment

Outcome: 8 Sustained heroin abstinence

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low risk of bias					
Poling 2006	34/57	18/48		53.1 %	1.59 [1.04, 2.43]
Subtotal (95% CI)	**57**	**48**		**53.1 %**	**1.59 [1.04, 2.43]**
Total events: 34 (Experimental), 18 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.15 (P = 0.032)					
2 Intermediate or high risk of bias					
Grabowski 2004	40/54	15/40		46.9 %	1.98 [1.28, 3.04]
Subtotal (95% CI)	**54**	**40**		**46.9 %**	**1.98 [1.28, 3.04]**
Total events: 40 (Experimental), 15 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.10 (P = 0.0019)					
Total (95% CI)	**111**	**88**		**100.0 %**	**1.77 [1.31, 2.39]**
Total events: 74 (Experimental), 33 (Control)					
Heterogeneity: Chi^2 = 0.50, df = 1 (P = 0.48); I^2 =0.0%					
Test for overall effect: Z = 3.72 (P = 0.00020)					

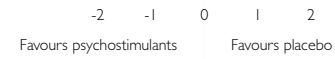
Analysis 9.9. Comparison 9 Subgroup analysis 8: Clinical trial reporting quality: Allocation concealment, Outcome 9 ADHD severity.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 9 Subgroup analysis 8: Clinical trial reporting quality: Allocation concealment

Outcome: 9 ADHD severity

Study or subgroup	Psychostimulants N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Low risk of bias							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Intermediate or low risk of bias							
Levin 2007	46	18.8 (10.8)	50	19.6 (14.3)		61.3 %	-0.06 [-0.46, 0.34]
Schubiner 2002	11	1.9 (0.8)	14	2.7 (1)		38.7 %	-0.84 [-1.67, -0.01]
Subtotal (95% CI)	**57**		**64**			**100.0 %**	**-0.36 [-1.11, 0.38]**
Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 2.75$, df = 1 (P = 0.10); $I^2 = 64\%$							
Test for overall effect: Z = 0.96 (P = 0.34)							
Total (95% CI)	**57**		**64**			**100.0 %**	**-0.36 [-1.11, 0.38]**
Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 2.75$, df = 1 (P = 0.10); $I^2 = 64\%$							
Test for overall effect: Z = 0.96 (P = 0.34)							



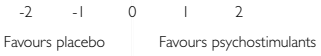
Analysis 10.1. Comparison 10 Subgroup analysis 9: Clinical trial reporting quality: Incomplete outcome data, Outcome 1 Cocaine use assessed by the mean (SD) of the proportion of cocaine-free UA across the study per patient.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 10 Subgroup analysis 9: Clinical trial reporting quality: Incomplete outcome data

Outcome: 1 Cocaine use assessed by the mean (SD) of the proportion of cocaine-free UA across the study per patient

Study or subgroup	Psychostimulants N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 Low risk of bias							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Intermediate or high risk of bias							
Grabowski 1997	25	30.7 (40)	24	43.8 (41)		10.6 %	-0.32 [-0.88, 0.25]
Grabowski 2004	41	21 (16.8)	19	16.1 (16.9)		11.3 %	0.29 [-0.26, 0.83]
Levin 2007	53	27 (29)	53	30 (29)		23.2 %	-0.10 [-0.48, 0.28]
Poling 2006	57	52.2 (32.1)	49	43 (35.8)		22.9 %	0.27 [-0.11, 0.65]
Schubiner 2002	24	50 (50)	24	42 (32)		10.5 %	0.19 [-0.38, 0.75]
Shearer 2003	16	38.6 (34.3)	14	27.1 (30)		6.4 %	0.35 [-0.38, 1.07]
Shoptaw 2008	37	13.1 (14.2)	33	10.3 (11.2)		15.2 %	0.22 [-0.26, 0.69]
Subtotal (95% CI)	**253**		**216**			**100.0 %**	**0.11 [-0.07, 0.29]**
Heterogeneity: Chi^2 = 5.15, df = 6 (P = 0.52); I^2 =0.0%							
Test for overall effect: Z = 1.19 (P = 0.24)							
Total (95% CI)	**253**		**216**			**100.0 %**	**0.11 [-0.07, 0.29]**
Heterogeneity: Chi^2 = 5.15, df = 6 (P = 0.52); I^2 =0.0%							
Test for overall effect: Z = 1.19 (P = 0.24)							



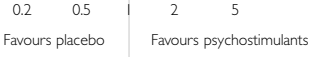
Analysis 10.2. Comparison 10 Subgroup analysis 9: Clinical trial reporting quality: Incomplete outcome data, Outcome 2 Number of patients who finished the study.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 10 Subgroup analysis 9: Clinical trial reporting quality: Incomplete outcome data

Outcome: 2 Number of patients who finished the study

Study or subgroup	Psychostimulants n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low risk of bias					
Dackis 2005	19/30	21/32		5.7 %	0.97 [0.67, 1.40]
Elkashef 2006	97/150	110/150		31.1 %	0.88 [0.76, 1.03]
Grabowski 1997	12/25	12/24		3.5 %	0.96 [0.54, 1.70]
Grabowski 2001	23/93	8/35		3.3 %	1.08 [0.53, 2.19]
Grabowski 2004	24/54	10/40		3.2 %	1.78 [0.96, 3.29]
Levin 2007	23/53	24/53		6.8 %	0.96 [0.63, 1.47]
Margolin 1995 a	63/74	62/75		17.4 %	1.03 [0.89, 1.19]
Margolin 1995 b	15/18	15/19		4.1 %	1.06 [0.77, 1.44]
Margolin 1997	10/13	4/4		1.9 %	0.83 [0.55, 1.27]
Mooney 2009	17/55	8/27		3.0 %	1.04 [0.52, 2.11]
Perry 2004	3/11	5/13		1.3 %	0.71 [0.22, 2.32]
Poling 2006	32/57	30/49		9.1 %	0.92 [0.67, 1.26]
Schubiner 2002	11/24	14/24		4.0 %	0.79 [0.45, 1.36]
Shearer 2003	6/16	5/14		1.5 %	1.05 [0.41, 2.70]
Shoptaw 2008	7/37	5/33		1.5 %	1.25 [0.44, 3.56]
Stine 1995	9/22	9/21		2.6 %	0.95 [0.47, 1.93]
Subtotal (95% CI)	**732**	**613**		**100.0 %**	**0.97 [0.89, 1.07]**
Total events: 371 (Psychostimulants), 342 (Placebo)					
Heterogeneity: Chi^2 = 8.08, df = 15 (P = 0.92); I^2 =0.0%					
Test for overall effect: Z = 0.55 (P = 0.58)					
2 Intermediate or high risk of bias					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Psychostimulants), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**732**	**613**		**100.0 %**	**0.97 [0.89, 1.07]**
Total events: 371 (Psychostimulants), 342 (Placebo)					
Heterogeneity: Chi^2 = 8.08, df = 15 (P = 0.92); I^2 =0.0%					
Test for overall effect: Z = 0.55 (P = 0.58)					



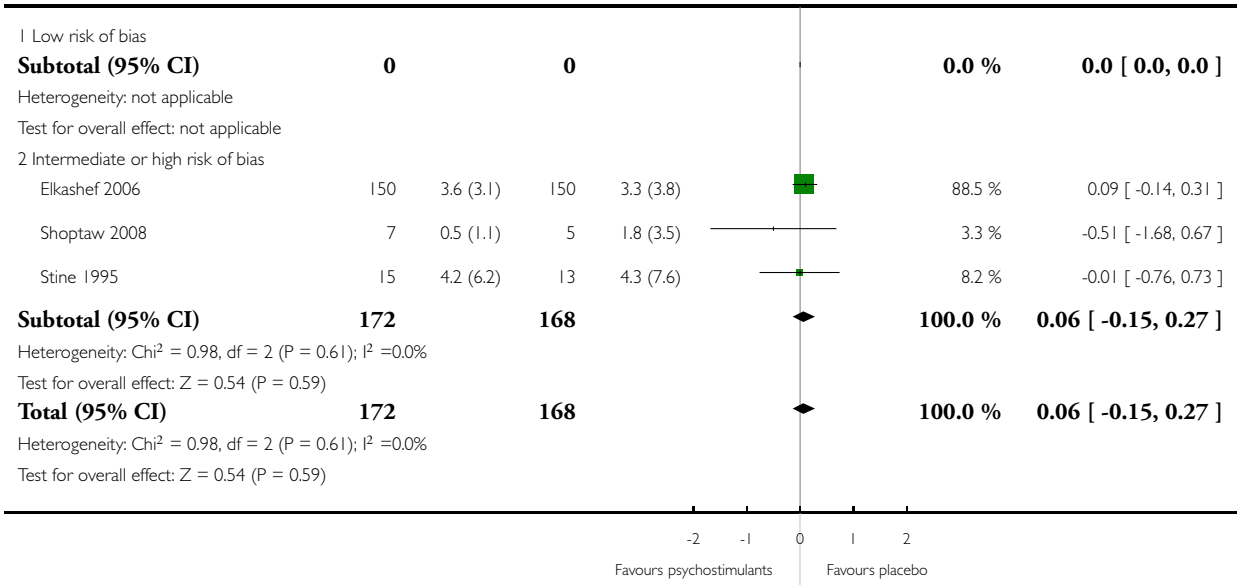
Analysis 10.3. Comparison 10 Subgroup analysis 9: Clinical trial reporting quality: Incomplete outcome data, Outcome 3 Cocaine craving.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 10 Subgroup analysis 9: Clinical trial reporting quality: Incomplete outcome data

Outcome: 3 Cocaine craving

Study or subgroup	Favours psychostimulants N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 Low risk of bias							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Intermediate or high risk of bias							
Elkashef 2006	150	3.6 (3.1)	150	3.3 (3.8)		88.5 %	0.09 [-0.14, 0.31]
Shoptaw 2008	7	0.5 (1.1)	5	1.8 (3.5)		3.3 %	-0.51 [-1.68, 0.67]
Stine 1995	15	4.2 (6.2)	13	4.3 (7.6)		8.2 %	-0.01 [-0.76, 0.73]
Subtotal (95% CI)	**172**		**168**			**100.0 %**	**0.06 [-0.15, 0.27]**
Heterogeneity: Chi^2 = 0.98, df = 2 (P = 0.61); I^2 =0.0%							
Test for overall effect: Z = 0.54 (P = 0.59)							
Total (95% CI)	**172**		**168**			**100.0 %**	**0.06 [-0.15, 0.27]**
Heterogeneity: Chi^2 = 0.98, df = 2 (P = 0.61); I^2 =0.0%							
Test for overall effect: Z = 0.54 (P = 0.59)							

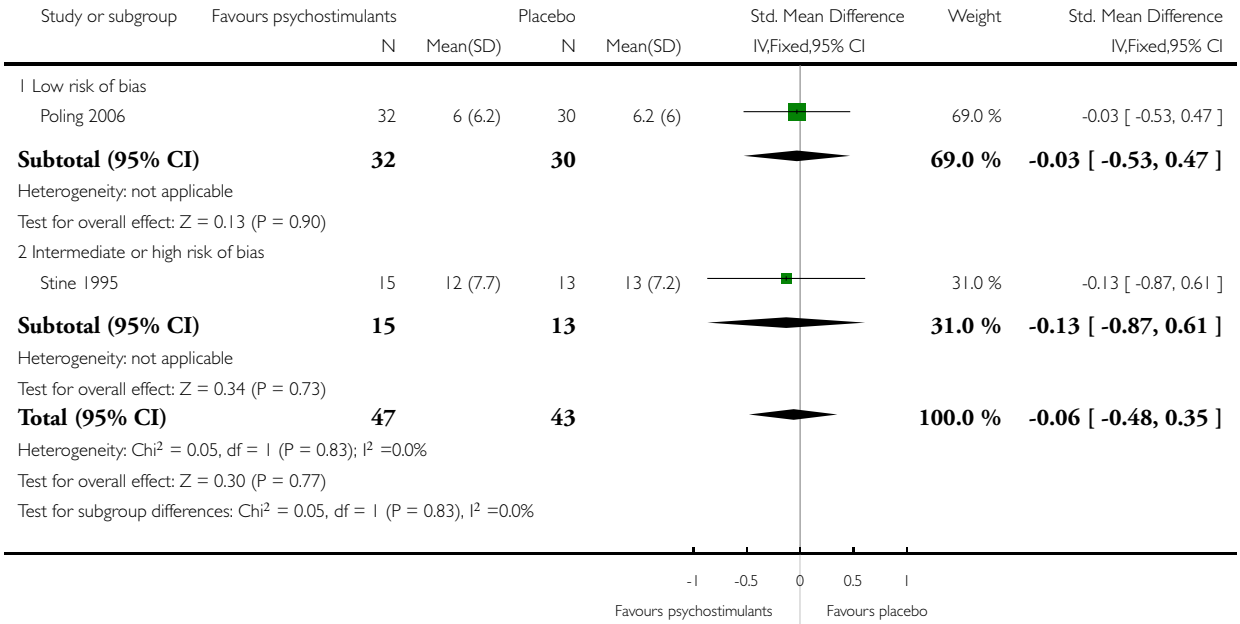


Analysis 10.4. Comparison 10 Subgroup analysis 9: Clinical trial reporting quality: Incomplete outcome data, Outcome 4 Depressive symptoms severity.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 10 Subgroup analysis 9: Clinical trial reporting quality: Incomplete outcome data

Outcome: 4 Depressive symptoms severity



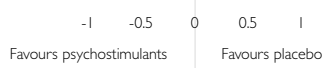
Analysis 10.5. Comparison 10 Subgroup analysis 9: Clinical trial reporting quality: Incomplete outcome data, Outcome 5 Patients dropped out due to any adverse events.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 10 Subgroup analysis 9: Clinical trial reporting quality: Incomplete outcome data

Outcome: 5 Patients dropped out due to any adverse events

Study or subgroup	Favours psychostimulants n/N	Placebo n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
1 Low risk of bias					
Margolin 1995 b	2/18	1/19		2.0 %	0.06 [-0.12, 0.23]
Margolin 1997	0/13	0/4		0.8 %	0.0 [-0.28, 0.28]
Shearer 2003	5/16	1/14		0.9 %	0.24 [-0.02, 0.51]
Subtotal (95% CI)	**47**	**37**		**3.7 %**	**0.09 [-0.04, 0.22]**
Total events: 7 (Favours psychostimulants), 2 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.96$, df = 2 (P = 0.38); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.36 (P = 0.17)					
2 Intermediate or high risk of bias					
Elkashef 2006	0/150	0/150		34.1 %	0.0 [-0.01, 0.01]
Grabowski 2001	7/93	0/35		10.5 %	0.08 [0.01, 0.14]
Levin 2007	1/53	1/53		14.7 %	0.0 [-0.05, 0.05]
Margolin 1995 a	2/74	2/75		14.6 %	0.00 [-0.05, 0.05]
Mooney 2009	1/55	0/27		10.9 %	0.02 [-0.05, 0.08]
Perry 2004	0/11	0/13		2.7 %	0.0 [-0.15, 0.15]
Schubiner 2002	0/24	1/24		4.8 %	-0.04 [-0.15, 0.07]
Stine 1995	0/22	1/21		4.0 %	-0.05 [-0.17, 0.07]
Subtotal (95% CI)	**482**	**398**		**96.3 %**	**0.00 [-0.01, 0.01]**
Total events: 11 (Favours psychostimulants), 5 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 6.67$, df = 7 (P = 0.46); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.33 (P = 0.74)					
Total (95% CI)	**529**	**435**		**100.0 %**	**0.01 [-0.02, 0.03]**
Total events: 18 (Favours psychostimulants), 7 (Placebo)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 14.48$, df = 10 (P = 0.15); $I^2 = 31\%$					
Test for overall effect: Z = 0.72 (P = 0.47)					

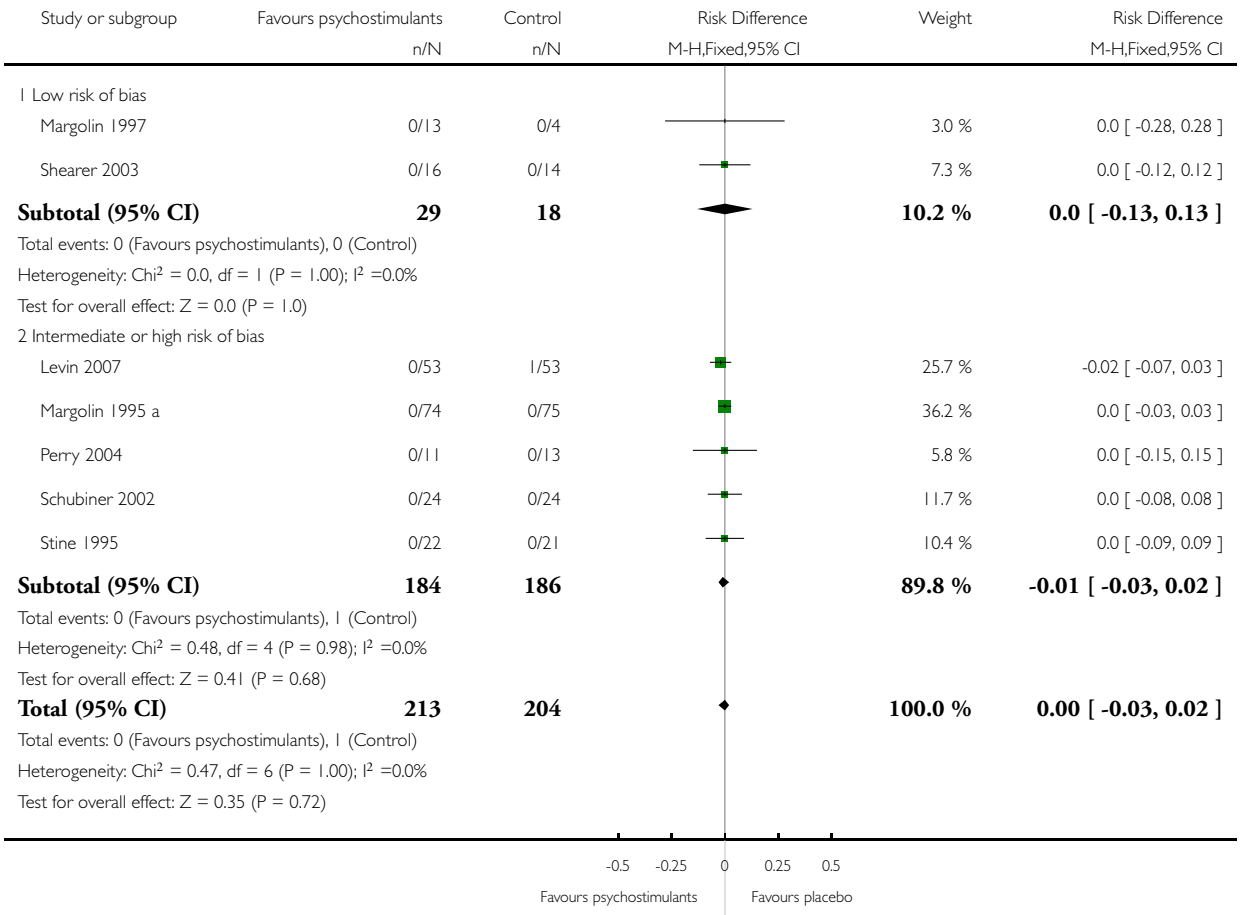


Analysis 10.6. Comparison 10 Subgroup analysis 9: Clinical trial reporting quality: Incomplete outcome data, Outcome 6 Patients dropped out due to cardiovascular adverse events.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 10 Subgroup analysis 9: Clinical trial reporting quality: Incomplete outcome data

Outcome: 6 Patients dropped out due to cardiovascular adverse events



Analysis 10.7. Comparison 10 Subgroup analysis 9: Clinical trial reporting quality: Incomplete outcome data, Outcome 7 Heroin use assessed by the mean (SD) of the proportion of heroin-free UA across the study per patient.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 10 Subgroup analysis 9: Clinical trial reporting quality: Incomplete outcome data

Outcome: 7 Heroin use assessed by the mean (SD) of the proportion of heroin-free UA across the study per patient

Study or subgroup	Favours placebo N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 Low risk of bias							
Poling 2006	57	52.2 (32.1)	48	42.9 (33.1)		66.4 %	0.28 [-0.10, 0.67]
Subtotal (95% CI)	**57**		**48**			**66.4 %**	**0.28 [-0.10, 0.67]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.44 (P = 0.15)							
2 Intermediate or high risk of bias							
Grabowski 2004	43	37.9 (15.2)	19	33 (17)		33.6 %	0.31 [-0.24, 0.85]
Subtotal (95% CI)	**43**		**19**			**33.6 %**	**0.31 [-0.24, 0.85]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.11 (P = 0.27)							
Total (95% CI)	**100**		**67**			**100.0 %**	**0.29 [-0.02, 0.61]**
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.95); I^2 =0.0%							
Test for overall effect: Z = 1.82 (P = 0.069)							
Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 0.95), I^2 =0.0%							

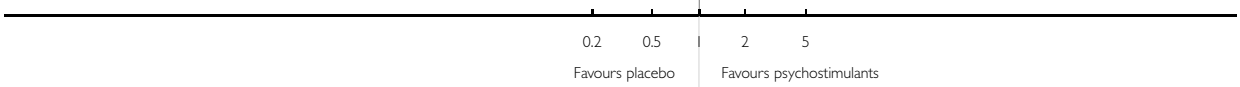
Analysis 10.8. Comparison 10 Subgroup analysis 9: Clinical trial reporting quality: Incomplete outcome data, Outcome 8 Sustained heroin abstinence.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 10 Subgroup analysis 9: Clinical trial reporting quality: Incomplete outcome data

Outcome: 8 Sustained heroin abstinence

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low risk of bias					
Poling 2006	34/57	18/48		53.1 %	1.59 [1.04, 2.43]
Subtotal (95% CI)	**57**	**48**		**53.1 %**	**1.59 [1.04, 2.43]**
Total events: 34 (Experimental), 18 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.15 (P = 0.032)					
2 Intermediate or high risk of bias					
Grabowski 2004	40/54	15/40		46.9 %	1.98 [1.28, 3.04]
Subtotal (95% CI)	**54**	**40**		**46.9 %**	**1.98 [1.28, 3.04]**
Total events: 40 (Experimental), 15 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.10 (P = 0.0019)					
Total (95% CI)	**111**	**88**		**100.0 %**	**1.77 [1.31, 2.39]**
Total events: 74 (Experimental), 33 (Control)					
Heterogeneity: Chi^2 = 0.50, df = 1 (P = 0.48); I^2 =0.0%					
Test for overall effect: Z = 3.72 (P = 0.00020)					

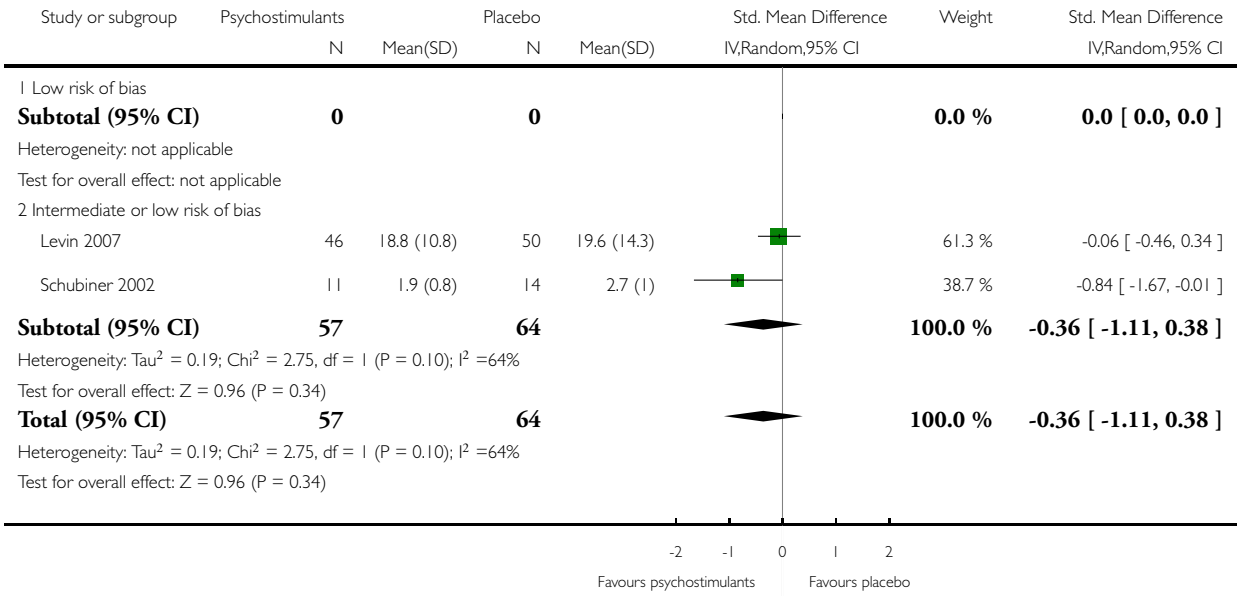


Analysis 10.9. Comparison 10 Subgroup analysis 9: Clinical trial reporting quality: Incomplete outcome data, Outcome 9 ADHD severity.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 10 Subgroup analysis 9: Clinical trial reporting quality: Incomplete outcome data

Outcome: 9 ADHD severity



Analysis 11.1. Comparison 11 Subgroup analysis 10: Clinical trial reporting quality: Other bias, Outcome 1 Cocaine use assessed by the mean (SD) of the proportion of cocaine-free UA across the study per patient.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 11 Subgroup analysis 10: Clinical trial reporting quality: Other bias

Outcome: 1 Cocaine use assessed by the mean (SD) of the proportion of cocaine-free UA across the study per patient

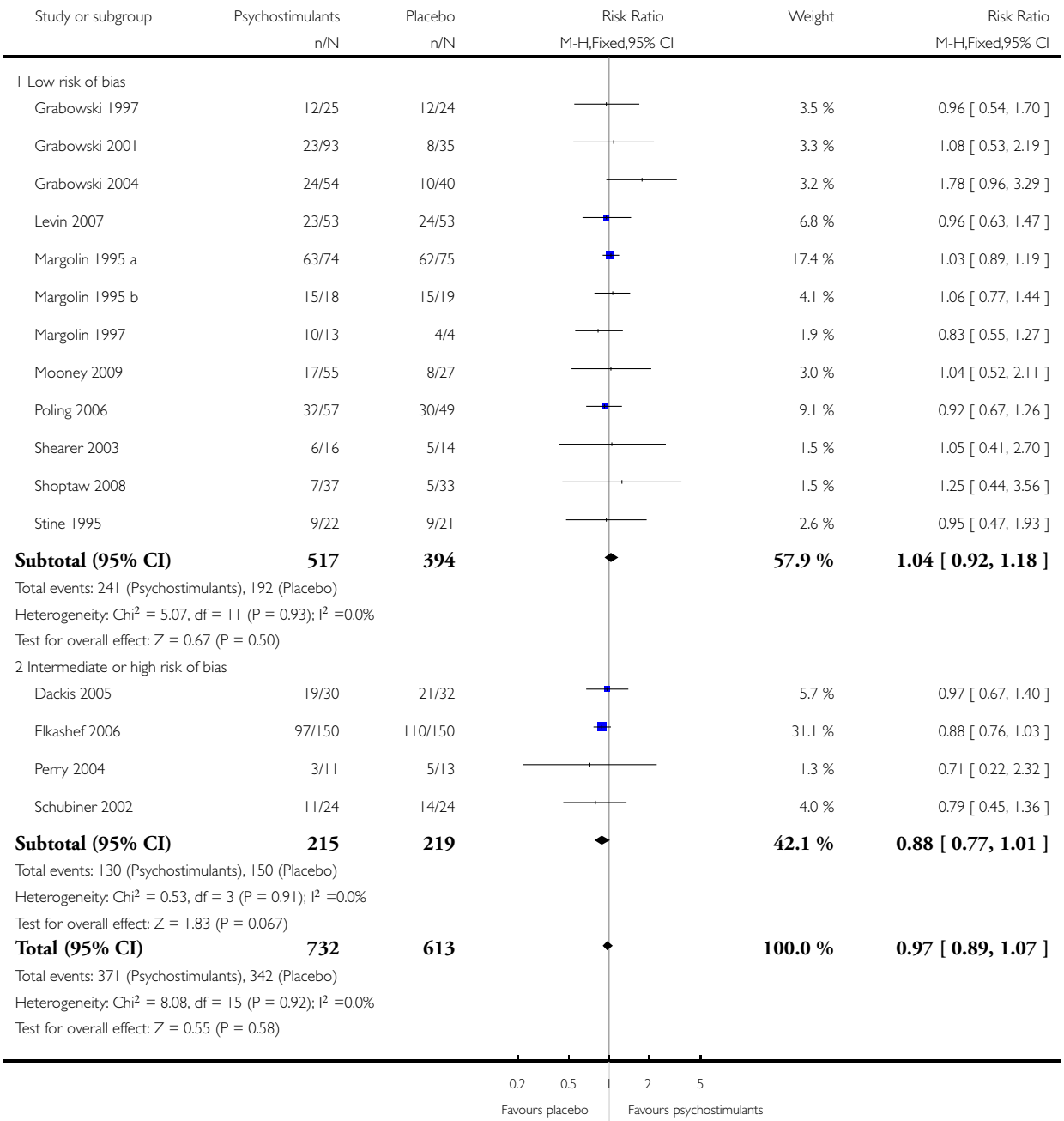
Study or subgroup	Psychostimulants N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Low risk of bias							
Grabowski 1997	25	30.7 (40)	24	43.8 (41)		10.6 %	-0.32 [-0.88, 0.25]
Grabowski 2004	41	21 (16.8)	19	16.1 (16.9)		11.3 %	0.29 [-0.26, 0.83]
Levin 2007	53	27 (29)	53	30 (29)		23.2 %	-0.10 [-0.48, 0.28]
Poling 2006	57	52.2 (32.1)	49	43 (35.8)		22.9 %	0.27 [-0.11, 0.65]
Shearer 2003	16	38.6 (34.3)	14	27.1 (30)		6.4 %	0.35 [-0.38, 1.07]
Shoptaw 2008	37	13.1 (14.2)	33	10.3 (11.2)		15.2 %	0.22 [-0.26, 0.69]
Subtotal (95% CI)	**229**		**192**			**89.5 %**	**0.10 [-0.09, 0.30]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.08$, df = 5 (P = 0.41); $I^2 = 2\%$							
Test for overall effect: Z = 1.02 (P = 0.31)							
2 Intermediate or high risk of bias							
Schubiner 2002	24	50 (50)	24	42 (32)		10.5 %	0.19 [-0.38, 0.75]
Subtotal (95% CI)	**24**		**24**			**10.5 %**	**0.19 [-0.38, 0.75]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.65 (P = 0.52)							
Total (95% CI)	**253**		**216**			**100.0 %**	**0.11 [-0.07, 0.29]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 5.15$, df = 6 (P = 0.52); $I^2 = 0.0\%$							
Test for overall effect: Z = 1.19 (P = 0.24)							

Analysis 11.2. Comparison 11 Subgroup analysis 10: Clinical trial reporting quality: Other bias, Outcome 2 Number of patients who finished the study.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 11 Subgroup analysis 10: Clinical trial reporting quality: Other bias

Outcome: 2 Number of patients who finished the study



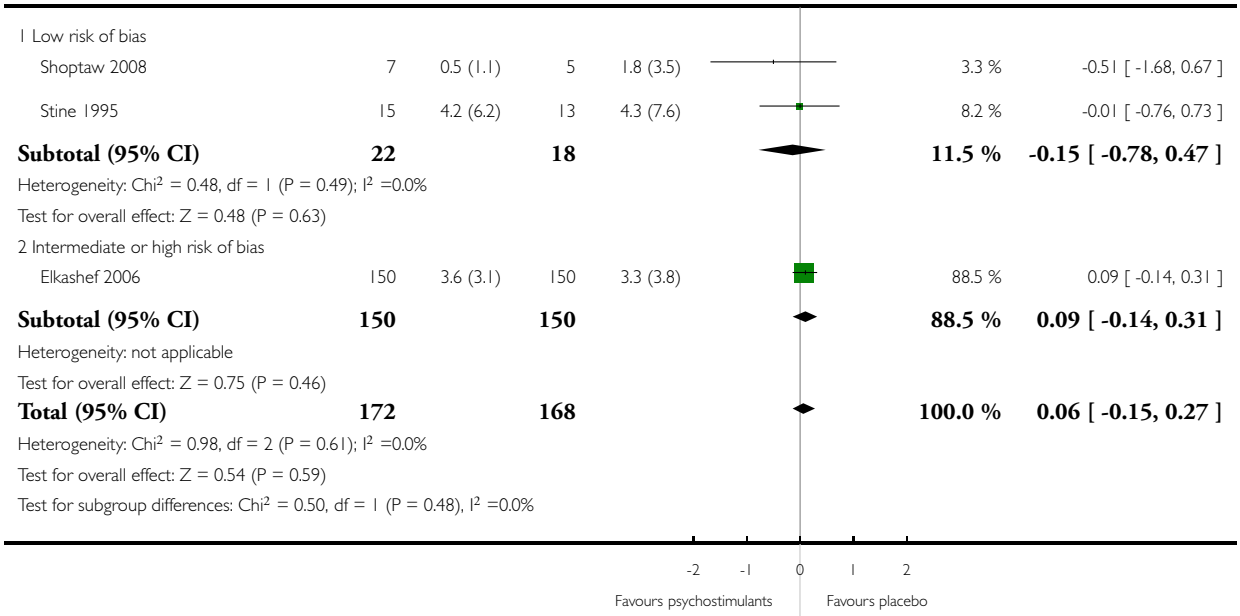
Analysis 11.3. Comparison 11 Subgroup analysis 10: Clinical trial reporting quality: Other bias, Outcome 3 Cocaine craving.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 11 Subgroup analysis 10: Clinical trial reporting quality: Other bias

Outcome: 3 Cocaine craving

Study or subgroup	Favours psychostimulants N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 Low risk of bias							
Shoptaw 2008	7	0.5 (1.1)	5	1.8 (3.5)		3.3 %	-0.51 [-1.68, 0.67]
Stine 1995	15	4.2 (6.2)	13	4.3 (7.6)		8.2 %	-0.01 [-0.76, 0.73]
Subtotal (95% CI)	**22**		**18**			**11.5 %**	**-0.15 [-0.78, 0.47]**
Heterogeneity: Chi^2 = 0.48, df = 1 (P = 0.49); I^2 =0.0%							
Test for overall effect: Z = 0.48 (P = 0.63)							
2 Intermediate or high risk of bias							
Elkashef 2006	150	3.6 (3.1)	150	3.3 (3.8)		88.5 %	0.09 [-0.14, 0.31]
Subtotal (95% CI)	**150**		**150**			**88.5 %**	**0.09 [-0.14, 0.31]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.75 (P = 0.46)							
Total (95% CI)	**172**		**168**			**100.0 %**	**0.06 [-0.15, 0.27]**
Heterogeneity: Chi^2 = 0.98, df = 2 (P = 0.61); I^2 =0.0%							
Test for overall effect: Z = 0.54 (P = 0.59)							
Test for subgroup differences: Chi^2 = 0.50, df = 1 (P = 0.48), I^2 =0.0%							



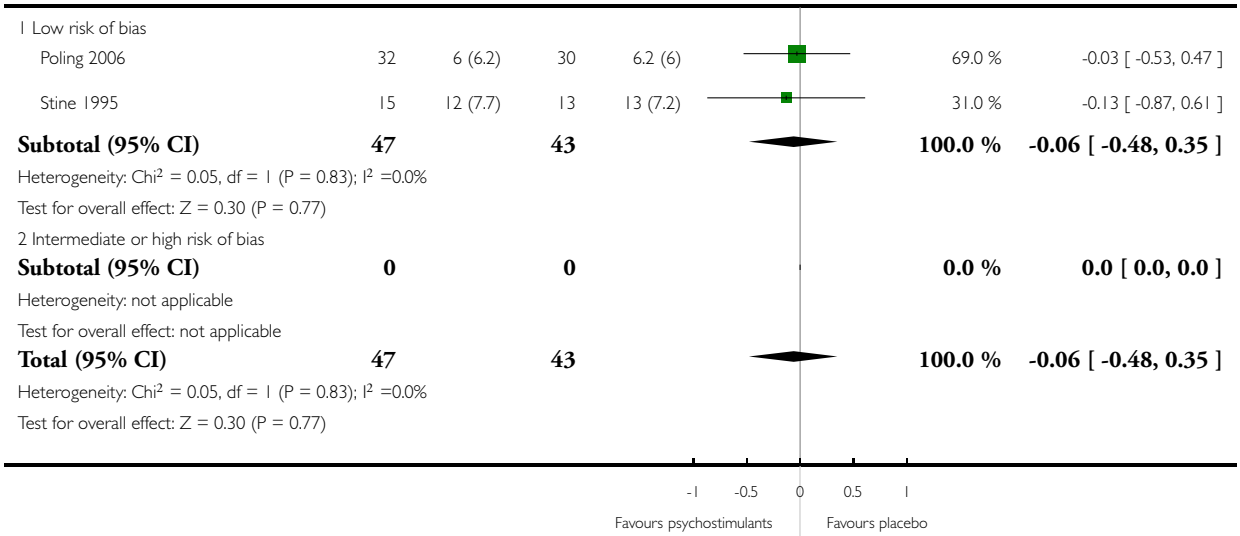
Analysis 11.4. Comparison 11 Subgroup analysis 10: Clinical trial reporting quality: Other bias, Outcome 4 Depressive symptoms severity.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 11 Subgroup analysis 10: Clinical trial reporting quality: Other bias

Outcome: 4 Depressive symptoms severity

Study or subgroup	Favours psychostimulants N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 Low risk of bias							
Poling 2006	32	6 (6.2)	30	6.2 (6)		69.0 %	-0.03 [-0.53, 0.47]
Stine 1995	15	12 (7.7)	13	13 (7.2)		31.0 %	-0.13 [-0.87, 0.61]
Subtotal (95% CI)	**47**		**43**			**100.0 %**	**-0.06 [-0.48, 0.35]**
Heterogeneity: Chi^2 = 0.05, df = 1 (P = 0.83); I^2 =0.0%							
Test for overall effect: Z = 0.30 (P = 0.77)							
2 Intermediate or high risk of bias							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
Total (95% CI)	**47**		**43**			**100.0 %**	**-0.06 [-0.48, 0.35]**
Heterogeneity: Chi^2 = 0.05, df = 1 (P = 0.83); I^2 =0.0%							
Test for overall effect: Z = 0.30 (P = 0.77)							



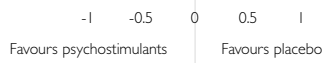
Analysis 11.5. Comparison 11 Subgroup analysis 10: Clinical trial reporting quality: Other bias, Outcome 5 Patients dropped out due to any adverse events.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 11 Subgroup analysis 10: Clinical trial reporting quality: Other bias

Outcome: 5 Patients dropped out due to any adverse events

Study or subgroup	Favours psychostimulants n/N	Placebo n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
1 Low risk of bias					
Grabowski 2001	7/93	0/35		10.5 %	0.08 [0.01, 0.14]
Levin 2007	1/53	1/53		14.7 %	0.0 [-0.05, 0.05]
Margolin 1995 a	2/74	2/75		14.6 %	0.00 [-0.05, 0.05]
Margolin 1995 b	2/18	1/19		2.0 %	0.06 [-0.12, 0.23]
Margolin 1997	0/13	0/4		0.8 %	0.0 [-0.28, 0.28]
Mooney 2009	1/55	0/27		10.9 %	0.02 [-0.05, 0.08]
Shearer 2003	5/16	1/14		0.9 %	0.24 [-0.02, 0.51]
Stine 1995	0/22	1/21		4.0 %	-0.05 [-0.17, 0.07]
Subtotal (95% CI)	**344**	**248**		**58.4 %**	**0.02 [-0.01, 0.05]**
Total events: 18 (Favours psychostimulants), 6 (Placebo)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 8.57$, df = 7 (P = 0.29); $I^2 = 18\%$					
Test for overall effect: Z = 1.16 (P = 0.25)					
2 Intermediate or high risk of bias					
Elkashef 2006	0/150	0/150		34.1 %	0.0 [-0.01, 0.01]
Perry 2004	0/11	0/13		2.7 %	0.0 [-0.15, 0.15]
Schubiner 2002	0/24	1/24		4.8 %	-0.04 [-0.15, 0.07]
Subtotal (95% CI)	**185**	**187**		**41.6 %**	**0.00 [-0.01, 0.01]**
Total events: 0 (Favours psychostimulants), 1 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.10$, df = 2 (P = 0.58); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.09 (P = 0.93)					
Total (95% CI)	**529**	**435**		**100.0 %**	**0.01 [-0.02, 0.03]**
Total events: 18 (Favours psychostimulants), 7 (Placebo)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 14.48$, df = 10 (P = 0.15); $I^2 = 31\%$					
Test for overall effect: Z = 0.72 (P = 0.47)					



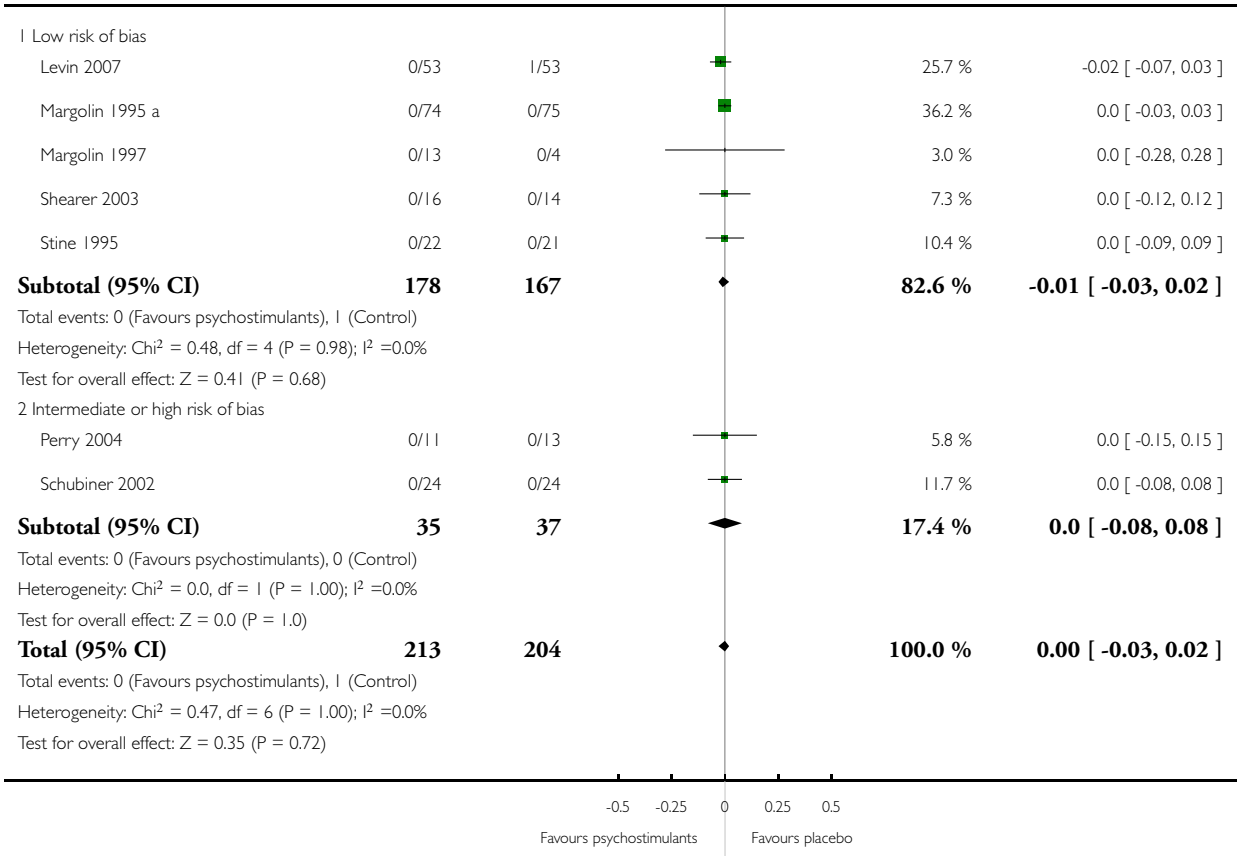
Analysis 11.6. Comparison 11 Subgroup analysis 10: Clinical trial reporting quality: Other bias, Outcome 6 Patients dropped out due to cardiovascular adverse events.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 11 Subgroup analysis 10: Clinical trial reporting quality: Other bias

Outcome: 6 Patients dropped out due to cardiovascular adverse events

Study or subgroup	Favours psychostimulants n/N	Control n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
1 Low risk of bias					
Levin 2007	0/53	1/53		25.7 %	-0.02 [-0.07, 0.03]
Margolin 1995 a	0/74	0/75		36.2 %	0.0 [-0.03, 0.03]
Margolin 1997	0/13	0/4		3.0 %	0.0 [-0.28, 0.28]
Shearer 2003	0/16	0/14		7.3 %	0.0 [-0.12, 0.12]
Stine 1995	0/22	0/21		10.4 %	0.0 [-0.09, 0.09]
Subtotal (95% CI)	**178**	**167**		**82.6 %**	**-0.01 [-0.03, 0.02]**
Total events: 0 (Favours psychostimulants), 1 (Control)					
Heterogeneity: Chi^2 = 0.48, df = 4 (P = 0.98); I^2 =0.0%					
Test for overall effect: Z = 0.41 (P = 0.68)					
2 Intermediate or high risk of bias					
Perry 2004	0/11	0/13		5.8 %	0.0 [-0.15, 0.15]
Schubiner 2002	0/24	0/24		11.7 %	0.0 [-0.08, 0.08]
Subtotal (95% CI)	**35**	**37**		**17.4 %**	**0.0 [-0.08, 0.08]**
Total events: 0 (Favours psychostimulants), 0 (Control)					
Heterogeneity: Chi^2 = 0.0, df = 1 (P = 1.00); I^2 =0.0%					
Test for overall effect: Z = 0.0 (P = 1.0)					
Total (95% CI)	**213**	**204**		**100.0 %**	**0.00 [-0.03, 0.02]**
Total events: 0 (Favours psychostimulants), 1 (Control)					
Heterogeneity: Chi^2 = 0.47, df = 6 (P = 1.00); I^2 =0.0%					
Test for overall effect: Z = 0.35 (P = 0.72)					



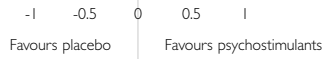
Analysis 11.7. Comparison 11 Subgroup analysis 10: Clinical trial reporting quality: Other bias, Outcome 7 Heroin use assessed by the mean (SD) of the proportion of heroin-free UA across the study per patient.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 11 Subgroup analysis 10: Clinical trial reporting quality: Other bias

Outcome: 7 Heroin use assessed by the mean (SD) of the proportion of heroin-free UA across the study per patient

Study or subgroup	Favours placebo N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 Low risk of bias							
Grabowski 2004	43	37.9 (15.2)	19	33 (17)		33.6 %	0.31 [-0.24, 0.85]
Poling 2006	57	52.2 (32.1)	48	42.9 (33.1)		66.4 %	0.28 [-0.10, 0.67]
Subtotal (95% CI)	**100**		**67**			**100.0 %**	**0.29 [-0.02, 0.61]**
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.95); I^2 =0.0%							
Test for overall effect: Z = 1.82 (P = 0.069)							
2 Intermediate or high risk of bias							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
Total (95% CI)	**100**		**67**			**100.0 %**	**0.29 [-0.02, 0.61]**
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.95); I^2 =0.0%							
Test for overall effect: Z = 1.82 (P = 0.069)							



Analysis 11.8. Comparison 11 Subgroup analysis 10: Clinical trial reporting quality: Other bias, Outcome 8 Sustained heroin abstinence.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 11 Subgroup analysis 10: Clinical trial reporting quality: Other bias

Outcome: 8 Sustained heroin abstinence

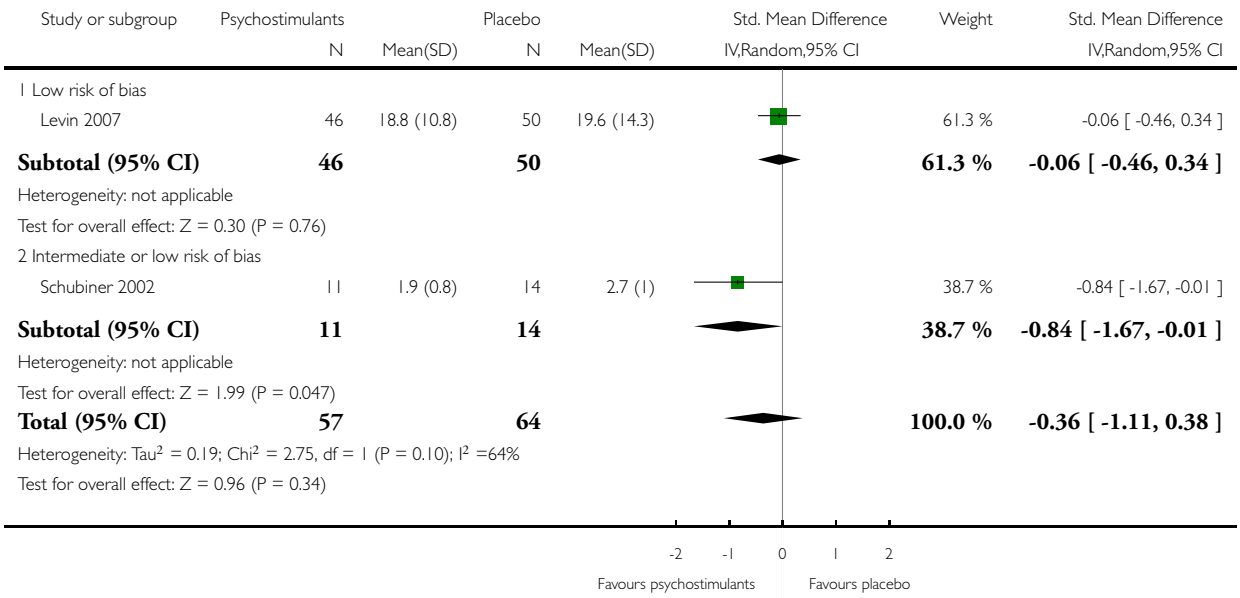
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low risk of bias					
Grabowski 2004	40/54	15/40		46.9 %	1.98 [1.28, 3.04]
Poling 2006	34/57	18/48		53.1 %	1.59 [1.04, 2.43]
Subtotal (95% CI)	**111**	**88**		**100.0 %**	**1.77 [1.31, 2.39]**
Total events: 74 (Experimental), 33 (Control)					
Heterogeneity: Chi^2 = 0.50, df = 1 (P = 0.48); I^2 =0.0%					
Test for overall effect: Z = 3.72 (P = 0.00020)					
2 Intermediate or high risk of bias					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Experimental), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**111**	**88**		**100.0 %**	**1.77 [1.31, 2.39]**
Total events: 74 (Experimental), 33 (Control)					
Heterogeneity: Chi^2 = 0.50, df = 1 (P = 0.48); I^2 =0.0%					
Test for overall effect: Z = 3.72 (P = 0.00020)					

Analysis 11.9. Comparison 11 Subgroup analysis 10: Clinical trial reporting quality: Other bias, Outcome 9 ADHD severity.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 11 Subgroup analysis 10: Clinical trial reporting quality: Other bias

Outcome: 9 ADHD severity

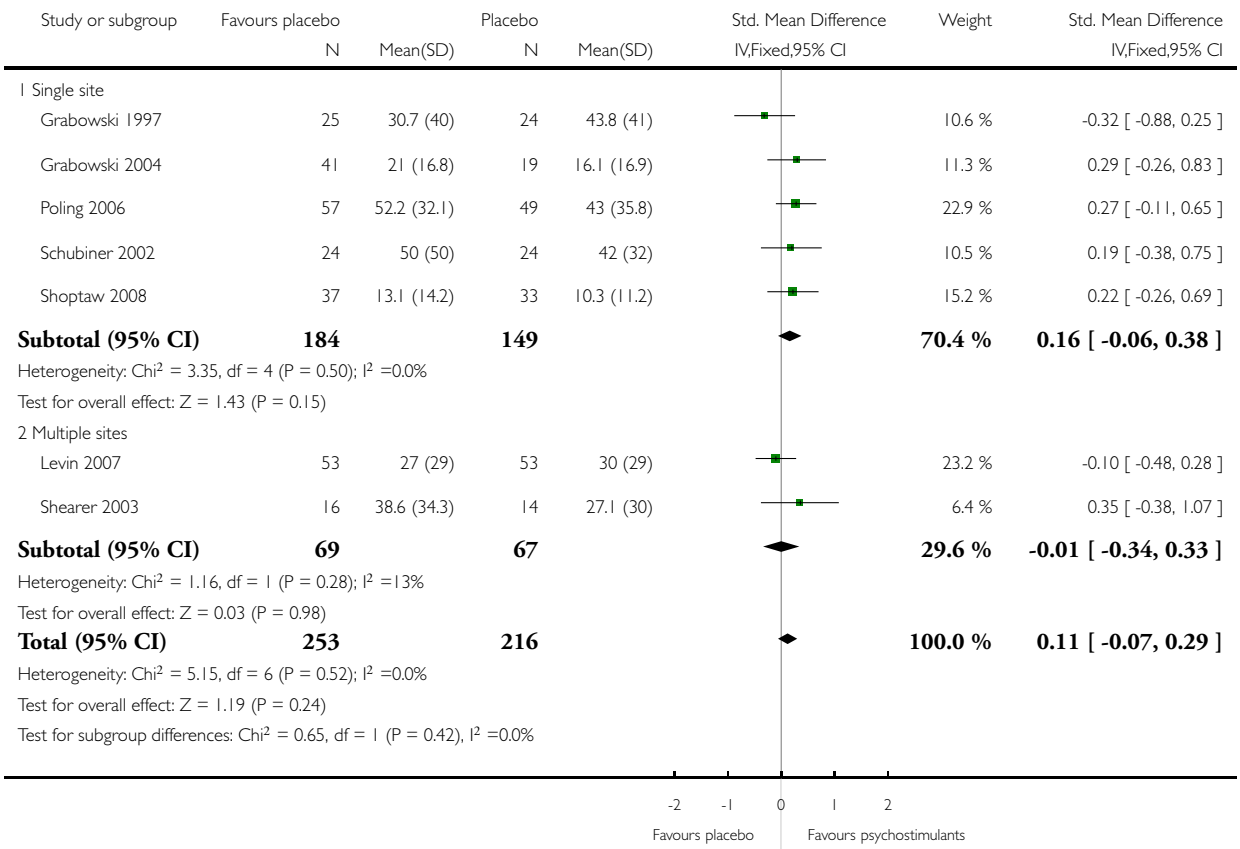


Analysis 12.1. Comparison 12 Subgroup analysis 11: Single vs. Multiple sites, Outcome 1 Cocaine use assessed by the mean (SD) of the proportion of cocaine-free UA across the study per patient.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 12 Subgroup analysis 11: Single vs. Multiple sites

Outcome: 1 Cocaine use assessed by the mean (SD) of the proportion of cocaine-free UA across the study per patient



Analysis 12.2. Comparison 12 Subgroup analysis 11: Single vs. Multiple sites, Outcome 2 Number of patients who finished the study (retention).

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 12 Subgroup analysis 11: Single vs. Multiple sites

Outcome: 2 Number of patients who finished the study (retention)

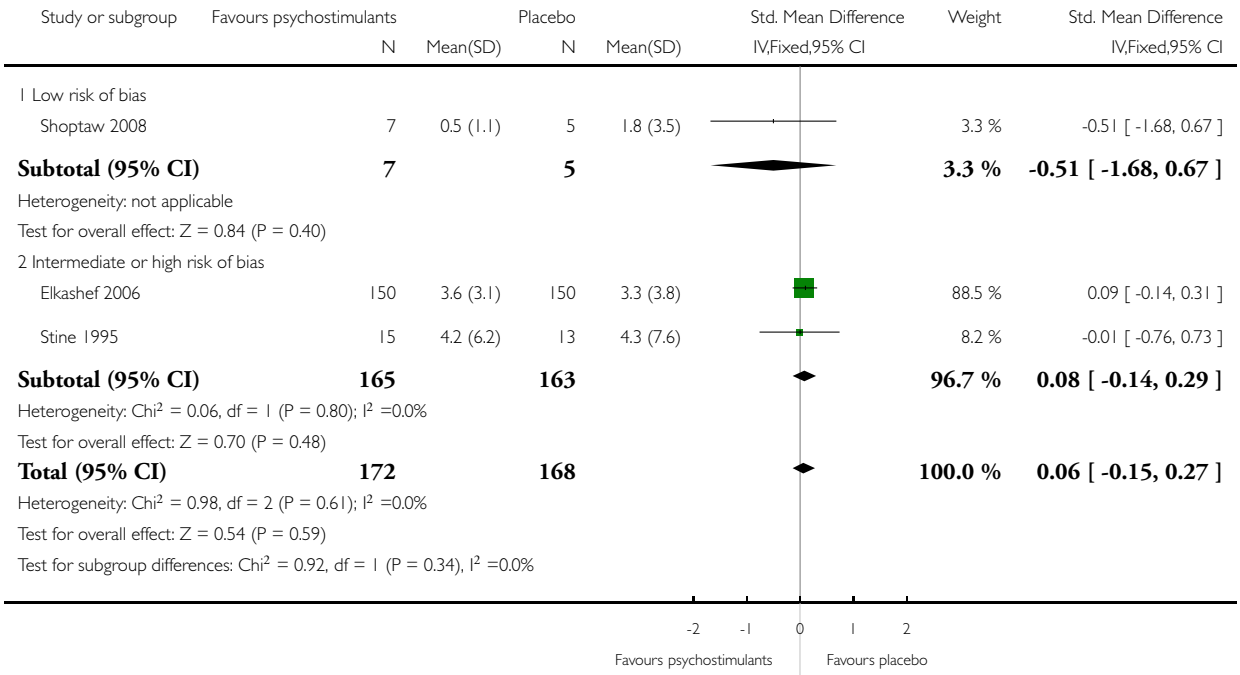
Study or subgroup	Psychostimulants n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Single site					
Dackis 2005	19/30	21/32		5.7 %	0.97 [0.67, 1.40]
Grabowski 1997	12/25	12/24		3.5 %	0.96 [0.54, 1.70]
Grabowski 2001	23/93	8/35		3.3 %	1.08 [0.53, 2.19]
Grabowski 2004	24/54	10/40		3.2 %	1.78 [0.96, 3.29]
Margolin 1995 b	15/18	15/19		4.1 %	1.06 [0.77, 1.44]
Margolin 1997	10/13	4/4		1.9 %	0.83 [0.55, 1.27]
Mooney 2009	17/55	8/27		3.0 %	1.04 [0.52, 2.11]
Perry 2004	3/11	5/13		1.3 %	0.71 [0.22, 2.32]
Poling 2006	32/57	30/49		9.1 %	0.92 [0.67, 1.26]
Schubiner 2002	11/24	14/24		4.0 %	0.79 [0.45, 1.36]
Shoptaw 2008	7/37	5/33		1.5 %	1.25 [0.44, 3.56]
Subtotal (95% CI)	**417**	**300**		**40.6 %**	**1.02 [0.87, 1.20]**
Total events: 173 (Psychostimulants), 132 (Placebo)					
Heterogeneity: Chi^2 = 6.06, df = 10 (P = 0.81); I^2 =0.0%					
Test for overall effect: Z = 0.26 (P = 0.79)					
2 Multiple sites					
Elkashef 2006	97/150	110/150		31.1 %	0.88 [0.76, 1.03]
Levin 2007	23/53	24/53		6.8 %	0.96 [0.63, 1.47]
Margolin 1995 a	63/74	62/75		17.4 %	1.03 [0.89, 1.19]
Shearer 2003	6/16	5/14		1.5 %	1.05 [0.41, 2.70]
Stine 1995	9/22	9/21		2.6 %	0.95 [0.47, 1.93]
Subtotal (95% CI)	**315**	**313**		**59.4 %**	**0.94 [0.84, 1.05]**
Total events: 198 (Psychostimulants), 210 (Placebo)					
Heterogeneity: Chi^2 = 2.33, df = 4 (P = 0.68); I^2 =0.0%					
Test for overall effect: Z = 1.09 (P = 0.28)					
Total (95% CI)	**732**	**613**		**100.0 %**	**0.97 [0.89, 1.07]**
Total events: 371 (Psychostimulants), 342 (Placebo)					
Heterogeneity: Chi^2 = 8.08, df = 15 (P = 0.92); I^2 =0.0%					
Test for overall effect: Z = 0.55 (P = 0.58)					

Analysis 12.3. Comparison 12 Subgroup analysis 11: Single vs. Multiple sites, Outcome 3 Cocaine craving.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 12 Subgroup analysis 11: Single vs. Multiple sites

Outcome: 3 Cocaine craving

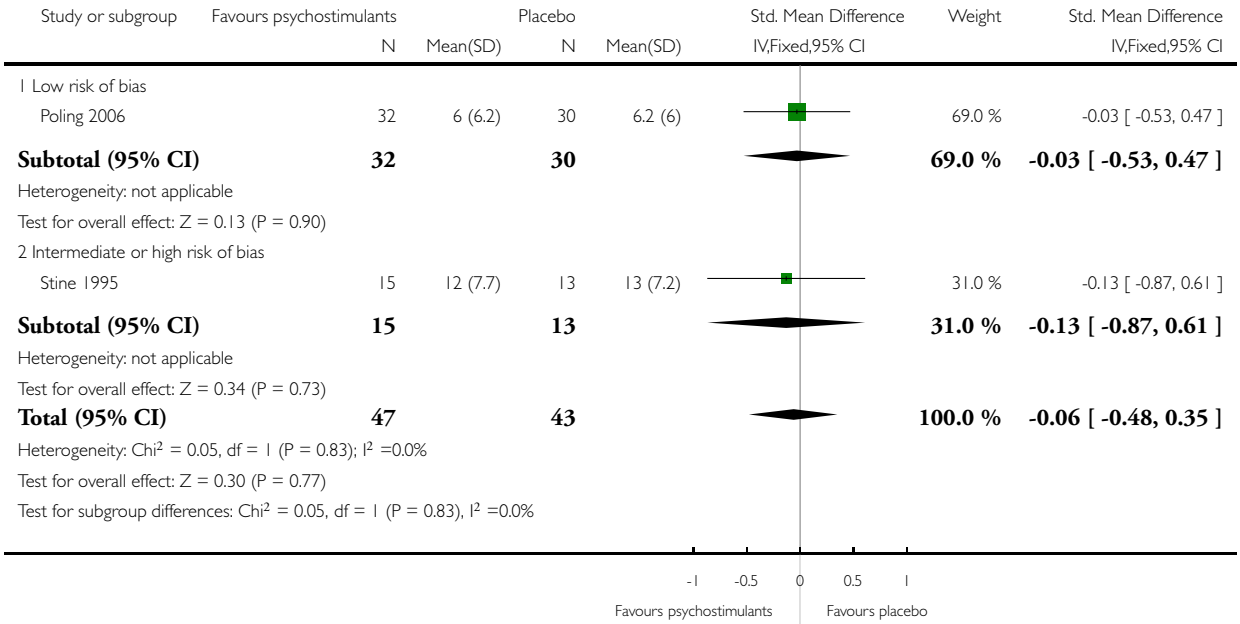


Analysis 12.4. Comparison 12 Subgroup analysis 11: Single vs. Multiple sites, Outcome 4 Depressive symptoms severity.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 12 Subgroup analysis 11: Single vs. Multiple sites

Outcome: 4 Depressive symptoms severity



Analysis 12.5. Comparison 12 Subgroup analysis 11: Single vs. Multiple sites, Outcome 5 Patients dropped out due to any adverse events.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 12 Subgroup analysis 11: Single vs. Multiple sites

Outcome: 5 Patients dropped out due to any adverse events

Study or subgroup	Favours psychostimulants n/N	Placebo n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
1 Low risk of bias					
Grabowski 2001	7/93	0/35		10.5 %	0.08 [0.01, 0.14]
Margolin 1995 b	2/18	1/19		2.0 %	0.06 [-0.12, 0.23]
Margolin 1997	0/13	0/4		0.8 %	0.0 [-0.28, 0.28]
Mooney 2009	1/55	0/27		10.9 %	0.02 [-0.05, 0.08]
Perry 2004	0/11	0/13		2.7 %	0.0 [-0.15, 0.15]
Schubiner 2002	0/24	1/24		4.8 %	-0.04 [-0.15, 0.07]
Subtotal (95% CI)	**214**	**122**		**31.7 %**	**0.03 [-0.01, 0.07]**
Total events: 10 (Favours psychostimulants), 2 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.88$, df = 5 (P = 0.57); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.51 (P = 0.13)					
2 Intermediate or high risk of bias					
Elkashef 2006	0/150	0/150		34.1 %	0.0 [-0.01, 0.01]
Levin 2007	1/53	1/53		14.7 %	0.0 [-0.05, 0.05]
Margolin 1995 a	2/74	2/75		14.6 %	0.00 [-0.05, 0.05]
Shearer 2003	5/16	1/14		0.9 %	0.24 [-0.02, 0.51]
Stine 1995	0/22	1/21		4.0 %	-0.05 [-0.17, 0.07]
Subtotal (95% CI)	**315**	**313**		**68.3 %**	**0.00 [-0.03, 0.03]**
Total events: 8 (Favours psychostimulants), 5 (Placebo)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.56$, df = 4 (P = 0.23); $I^2 = 28\%$					
Test for overall effect: Z = 0.02 (P = 0.98)					
Total (95% CI)	**529**	**435**		**100.0 %**	**0.01 [-0.02, 0.03]**
Total events: 18 (Favours psychostimulants), 7 (Placebo)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 14.48$, df = 10 (P = 0.15); $I^2 = 31\%$					
Test for overall effect: Z = 0.72 (P = 0.47)					

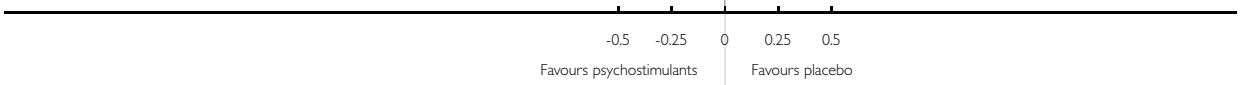
Analysis 12.6. Comparison 12 Subgroup analysis 11: Single vs. Multiple sites, Outcome 6 Patients dropped out due to cardiovascular adverse events.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 12 Subgroup analysis 11: Single vs. Multiple sites

Outcome: 6 Patients dropped out due to cardiovascular adverse events

Study or subgroup	Favours psychostimulants n/N	Control n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
1 Low risk of bias					
Margolin 1997	0/13	0/4		3.0 %	0.0 [-0.28, 0.28]
Perry 2004	0/11	0/13		5.8 %	0.0 [-0.15, 0.15]
Schubiner 2002	0/24	0/24		11.7 %	0.0 [-0.08, 0.08]
Subtotal (95% CI)	**48**	**41**		**20.4 %**	**0.0 [-0.08, 0.08]**
Total events: 0 (Favours psychostimulants), 0 (Control)					
Heterogeneity: Chi^2 = 0.0, df = 2 (P = 1.00); I^2 =0.0%					
Test for overall effect: Z = 0.0 (P = 1.0)					
2 Intermediate or high risk of bias					
Levin 2007	0/53	1/53		25.7 %	-0.02 [-0.07, 0.03]
Margolin 1995 a	0/74	0/75		36.2 %	0.0 [-0.03, 0.03]
Shearer 2003	0/16	0/14		7.3 %	0.0 [-0.12, 0.12]
Stine 1995	0/22	0/21		10.4 %	0.0 [-0.09, 0.09]
Subtotal (95% CI)	**165**	**163**		**79.6 %**	**-0.01 [-0.03, 0.02]**
Total events: 0 (Favours psychostimulants), 1 (Control)					
Heterogeneity: Chi^2 = 0.49, df = 3 (P = 0.92); I^2 =0.0%					
Test for overall effect: Z = 0.45 (P = 0.65)					
Total (95% CI)	**213**	**204**		**100.0 %**	**0.00 [-0.03, 0.02]**
Total events: 0 (Favours psychostimulants), 1 (Control)					
Heterogeneity: Chi^2 = 0.47, df = 6 (P = 1.00); I^2 =0.0%					
Test for overall effect: Z = 0.35 (P = 0.72)					



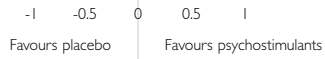
Analysis 12.7. Comparison 12 Subgroup analysis 11: Single vs. Multiple sites, Outcome 7 Heroin use assessed by the mean (SD) of the proportion of heroin-free UA across the study per patient.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 12 Subgroup analysis 11: Single vs. Multiple sites

Outcome: 7 Heroin use assessed by the mean (SD) of the proportion of heroin-free UA across the study per patient

Study or subgroup	Favours placebo N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 Low risk of bias							
Grabowski 2004	43	37.9 (15.2)	19	33 (17)		33.6 %	0.31 [-0.24, 0.85]
Poling 2006	57	52.2 (32.1)	48	42.9 (33.1)		66.4 %	0.28 [-0.10, 0.67]
Subtotal (95% CI)	**100**		**67**			**100.0 %**	**0.29 [-0.02, 0.61]**
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.95); I^2 =0.0%							
Test for overall effect: Z = 1.82 (P = 0.069)							
2 Intermediate or high risk of bias							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
Total (95% CI)	**100**		**67**			**100.0 %**	**0.29 [-0.02, 0.61]**
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.95); I^2 =0.0%							
Test for overall effect: Z = 1.82 (P = 0.069)							



Analysis 12.8. Comparison 12 Subgroup analysis 11: Single vs. Multiple sites, Outcome 8 Sustained heroin abstinence.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 12 Subgroup analysis 11: Single vs. Multiple sites

Outcome: 8 Sustained heroin abstinence

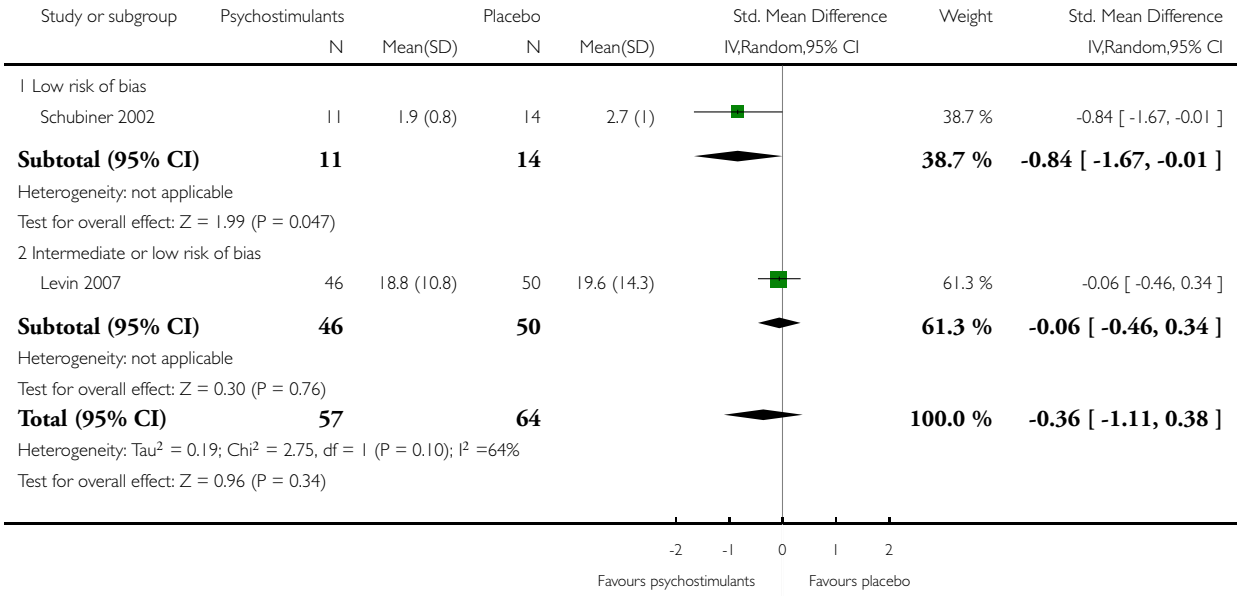
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low risk of bias					
Grabowski 2004	40/54	15/40		46.9 %	1.98 [1.28, 3.04]
Poling 2006	34/57	18/48		53.1 %	1.59 [1.04, 2.43]
Subtotal (95% CI)	**111**	**88**		**100.0 %**	**1.77 [1.31, 2.39]**
Total events: 74 (Experimental), 33 (Control)					
Heterogeneity: Chi^2 = 0.50, df = 1 (P = 0.48); I^2 =0.0%					
Test for overall effect: Z = 3.72 (P = 0.00020)					
2 Intermediate or high risk of bias					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Experimental), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**111**	**88**		**100.0 %**	**1.77 [1.31, 2.39]**
Total events: 74 (Experimental), 33 (Control)					
Heterogeneity: Chi^2 = 0.50, df = 1 (P = 0.48); I^2 =0.0%					
Test for overall effect: Z = 3.72 (P = 0.00020)					

Analysis 12.9. Comparison 12 Subgroup analysis 11: Single vs. Multiple sites, Outcome 9 ADHD severity.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 12 Subgroup analysis 11: Single vs. Multiple sites

Outcome: 9 ADHD severity



Analysis 13.1. Comparison 13 Psychostimulants vs. Placebo: Sensitivity analyses of the safety measures, Outcome 1 Patients dropped out due to any adverse events.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 13 Psychostimulants vs. Placebo: Sensitivity analyses of the safety measures

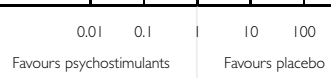
Outcome: 1 Patients dropped out due to any adverse events

Study or subgroup	Favours psychostimulants n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Grabowski 2001	7/93	0/35		7.7 %	5.74 [0.34, 98.01]
Levin 2007	1/53	1/53		10.6 %	1.00 [0.06, 15.57]
Margolin 1995 a	2/74	2/75		21.0 %	1.01 [0.15, 7.01]
Margolin 1995 b	2/18	1/19		10.3 %	2.11 [0.21, 21.32]
Mooney 2009	1/55	0/27		7.1 %	1.50 [0.06, 35.65]
Schubiner 2002	0/24	1/24		15.9 %	0.33 [0.01, 7.80]
Shearer 2003	5/16	1/14		11.3 %	4.38 [0.58, 33.10]
Stine 1995	0/22	1/21		16.2 %	0.32 [0.01, 7.42]
Total (95% CI)	**355**	**268**		**100.0 %**	**1.68 [0.74, 3.79]**

Total events: 18 (Favours psychostimulants), 7 (Placebo)

Heterogeneity: Chi^2 = 4.11, df = 7 (P = 0.77); I^2 =0.0%

Test for overall effect: Z = 1.25 (P = 0.21)



Analysis 13.2. Comparison 13 Psychostimulants vs. Placebo: Sensitivity analyses of the safety measures, Outcome 2 Patients dropped out due to cardiovascular adverse events.

Review: Efficacy of Psychostimulant Drugs for Cocaine Dependence

Comparison: 13 Psychostimulants vs. Placebo: Sensitivity analyses of the safety measures

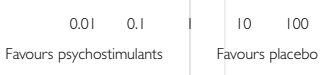
Outcome: 2 Patients dropped out due to cardiovascular adverse events

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Levin 2007	0/53	1/53		100.0 %	0.33 [0.01, 8.00]
Total (95% CI)	**53**	**53**		**100.0 %**	**0.33 [0.01, 8.00]**

Total events: 0 (Experimental), 1 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.68 (P = 0.50)



APPENDICES

Appendix 1. CENTRAL (*The Cochrane Library* 2008, issue 4) (09 Jan 2009)

Search terms	N° records
1. Cocaine-Related Disorders:mesh	366
2. (cocaine OR crack) AND (abuse* OR dependen* OR misuse OR addict*)	1351
3. #1 OR #2	1361
4. Amphetamines:mesh	897
5. (amphetamine OR amfetamine OR acefylline piperazine OR adrafinil OR amfebutamone OR amfepramone OR aminorex OR aminophylline OR bamifylline OR benzphetamine OR bufylline OR bupropion OR caffeine OR cathine OR cathinone OR choline theophyllinate OR clobenzorex OR dexamphetamine OR dexanfetamine OR dexmethylphenidate OR diethylpropion OR diprophylline OR doxofylline OR dyphylline OR ephedrine OR etamiphylline OR ethylamphetamine OR fencamfamine OR fenetylline OR fenozolone OR lisdexanfetamine OR mazindol OR mefenorex OR mesocarb OR methamphetamine OR methylenedioxymethamphetamine OR methylphenidate OR modafinil OR nicotine OR norpseudoephedrine OR pemoline OR phentermine OR pipradrol OR prolintane OR propentofylline OR proxyphylline OR selegiline OR sydnocarb OR theobromine OR theophylline):TI;AB	9647
6. #4 or #5	9915
7. #3 AND #6	135

Appendix 2. MEDLINE search strategy (via OVID) (08 Jan 2009)

Search terms	N° records
1. Cocaine-related disorders[MeSH]	8348
2. (cocaine OR crack) AND (abuse* OR dependen* OR misuse OR addict* OR disorder*).ti,ab	6635
3. 1 or 2	10460
4. Amphetamine[mesh]	
5. (amphetamine* OR amfetamine OR acefylline piperazine OR adrafinil OR amfebutamone OR amfepramone OR aminorex OR aminophylline OR bamifylline OR benzphetamine OR bufylline OR bupropion OR caffeine OR cathine OR cathinoneOR choline theophyllinate OR clobenzorex OR dexamphetamine OR dexanfetamine OR dexmethylphenidate OR diethylpropion OR diprophylline OR doxofylline OR dyphylline OR ephedrine OR etamiphylline OR ethylamphetamine OR fencamfamine OR fenetylline OR fenozolone OR lisdexanfetamine OR mazindol OR mefenorex OR mesocarb* OR methamphetamine OR methylenedioxymethamphetamine* OR methylphenidate OR modafinil OR nicotine OR norpseudoephedrine OR pemoline OR phentermine OR pipradrol OR prolintane OR propentofylline OR proxyphylline OR selegiline OR sydnocarb OR theobromine OR theophylline).ti,ab	22455
6. 4 OR 5	
7. 3 AND 6	
8. randomized controlled trial.pt.	
9. controlled clinical trial.pt.	
10. randomized.ab.	
11. placebo.ab.	
12. drug therapy.fs.	
13. randomly.ab.	
14. trial.ab.	
15. groups.ab.	

(*Continued*)

16. 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15	
17. exp animals/ not humans.sh.	
18. 16 NOT 17	
19. 7 AND 18	

Appendix 3. EMBASE search strategy (Ovid) (08 Jan 2009)

Search terms	N° records
1. exp Cocaine Dependence	4678
2. ((cocaine or crack) ADJ (abuse* or dependen* or misuse or addict* or disorder*)).ti,ab.	10188
3. 1 or 2	12251
4. (amphetamine or amfetamine or acefylline piperazine or adrafinil or amfebutamone or amfepramone or aminorex or aminophylline or bamifylline or benzphetamine or bufylline or bupropion or caffeine or cathine or cathinone or choline theophyllinate or clobenzorex or dexamphetamine or dexanfetamine or dexmethylphenidate or diethylpropion or diprophylline or doxofylline or dyphylline or ephedrine or etamiphylline or ethylamphetamine or fencamfamine or fenetylline or fenozolone or lisdexanfetamine or mazindol or mefenorex or mesocarb or methamphetamine or methylenedioxymethamphetamine or methylphenidate or modafinil or nicotine or norpseudoephedrine or pemoline or phentermine or pipradrol or prolintane or propentofylline or proxyphylline or selegiline or sydnocarb or theobromine or theophylline).ti,ab.	73116
5. 4 OR 5	1975
6. Clinical Trials/exp	525591
7. Randomized controlled trials/	164239
8. Random Allocation/	26411
9. Single-Blind Method/	7885
10. Double-Blind Method/	70933
11. Cross-Over Studies/	20840
12. Placebos/	121581
13 Randomi?ed controlled trial$.tw.	31652
14 RCT.tw.	2593
15 Random allocation.tw.	632
16 Randomly allocated.tw.	10058

(*Continued*)

16. Double blind$.tw.	83790
17 Allocated randomly.tw.	1342
18 (allocated adj2 random).tw.	558
19 Single blind$.tw.	7363
20 Double blind$.tw.	83790
21 ((treble or triple) adj blind$).tw.	139
22 Placebo$.tw.	108512
23 Prospective Studies	79108
24 11 or 21 or 7 or 17 or 22 or 18 or 23 or 16 or 13 or 6 or 9 or 12 or 14 or 15 or 20 or 8 or 10 or 19	691258
25. Case study/	5859
26. Case report.tw.	117324
27. Abstract report/ or letter/	487063
28 27 or 25 or 26	608015
29 24 not 28	667160
30. animal/ not human/	14481
31. 24 NOT 28	667064
32. 31 AND 5	202

Appendix 4. PsycINFO (Ovid) (09 Jan 2009)

Search terms	N° records
1. exp Cocaine	8348
2 ((cocaine or crack) and (abuse* or dependen* or misuse or addict*)).ti,ab.	6635
3. 1 or 2	10460
4. (amphetamine or amfetamine or acefylline piperazine or adrafinil or amfebutamone or amfepramone or aminorex or aminophylline or bamifylline or benzphetamine or bufylline or bupropion or caffeine or cathine or cathinone or choline theophyllinate or clobenzorex or dexamphetamine or dexanfetamine or dexmethylphenidate or diethylpropion or diprophylline or doxofylline or dyphylline or ephedrine or etamiphylline or ethylamphetamine or fencamfamine or fenetylline or fenozolone or lisdexanfetamine or mazindol or mefenorex or mesocarb or methamphetamine or methylenedioxymethamphetamine or methylphenidate or modafinil or nicotine or norpseudoephedrine or pemoline or phentermine or pipradrol or prolintane or propentofylline or proxyphylline or selegiline or sydnocarb or theobromine or theophylline).ti,ab.	22455
5. 4 OR 5	1549
6 randomi*.mp.	22297
7 ((singl$ or doubl$ or trebl$ or tripl$) adj10 (blind$ or mask$)).mp.	13567
8 (clin$ adj10 trial$).mp.	12550
9 placebo$.mp. or placebo/ or crossover.mp. or treatment-effectiveness-evaluation/ or mental-health-program-evaluation/	34178
10 (random$ adj10 (assign$ or allocate$)).mp.	19844
11 8 or 6 or 7 or 10 or 9	74234
12 11 and 5	116

HISTORY

Protocol first published: Issue 4, 2008

Review first published: Issue 2, 2010

18 December 2009	Amended	minor amendments
25 July 2008	Amended	protocol first published in issue 4, 2008
24 July 2008	New citation required and major changes	Change the status: from registered title to protocol

CONTRIBUTIONS OF AUTHORS

All authors have contributed to the protocol design.

XC wrote the protocol background.

XC wrote the remaining sections of the protocol.

XC and CP performed the selection of the studies.

XC, CP carried out the data extraction.

XC, XV did the statistical analysis.

All authors have participated in the discussion and the witting of the final report.

DECLARATIONS OF INTEREST

Xavier Castells has received speaker support from Jansen-Cilag.

Miguel Casas and Carlos Roncero have served as advisor/consultant to and have received research support and speaker support from Jansen-Cilag.

SOURCES OF SUPPORT

Internal sources

- The authors received no funding for this project, Not specified.

External sources

- The authors received no funding for this project, Not specified.

ANNEX IV: Escala de Jadad

L'estudi és aleatoritzat?

0	No	0
1	Sí	+1

L'estudi és doble cec?

0	No	0
1	Sí	+1

S'han descrit els abandonaments i les retirades?

0	No	0
1	Sí	+1

És apropiat el mètode d'aleatorització?

0	No	-1
1	Sí	+1
2	NE	0

És apropiat el mètode d'emmascarament?

0	No	-1
1	Sí	+1
2	NE	0

Total:

ANNEX 5: Avaluació qualitat segons l'escala de la Cochrane

Generació de la seqüència d'aleatorització (*Sequence generation*):

El mètode emprat per a generar la seqüència d'aleatorització ha estat descrita amb prou detall com per a valorar i garantir que ha produït grups comparables?

0 No
1 Sí
2 Poc clar

Ocultació de l'assignació (*Allocation concealment*)

El mètode emprat per a ocultar la seqüència d'aleatorització ha estat descrit amb prou detall com per a garantir que no s'ha pogut preveure l'ordre d'assignació de les intervencions investigades?

0 No
1 Sí
2 Poc clar

Encegament (*Blinding*)

El mètode emprat per a encegar els participants i els investigadors ha estat descrit amb prou detall com per assegurar que no s'ha descobert la intervenció d'estudi administrada?

0 No
1 Sí
2 Poc clar

Dades incompletes (*Incomplete outcome data*)

El mètode emprat per a gestionar les dades perdudes és adequat?

0 No
1 Sí
2 Poc clar

Publicació selectiva de resultats (Selective outcome reporting)

Està l'estudi lliure de biaix causat per la publicació selectiva de resultats?

0 No
1 Sí
2 Poc clar

Altres biaixos (*Free of other bias*)

Està l'estudi lliure d'altres problemes que puguin esbiaixar els seus resultats?

0 No
1 Sí
2 Poc clar