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Review

Effectiveness of secondary prevention and treatment interventions for crack-cocaine abuse: A comprehensive narrative overview of English-language studies

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ABSTRACT

There are an estimated several million crack-cocaine users globally; use is highest in the Americas. Most crack users are socio-economically marginalized (e.g., homeless), and feature elevated risks for morbidity (e.g., blood-borne viruses), mortality and crime/violence involvement, resulting in extensive burdens. No comprehensive reviews of evidence-based prevention and/or treatment interventions specifically for crack use exist. We conducted a comprehensive narrative overview of English-language studies on the efficacy of secondary prevention and treatment interventions for crack (cocaine) abuse/dependence. Literature searches (1990–2014) using pertinent keywords were conducted in main scientific databases. Titles/abstracts were reviewed for relevance, and full studies were included in the review if involving a primary prevention/treatment intervention study comprising a substantive crack user sample. Intervention outcomes considered included drug use, health risks/status (e.g., HIV or sexual risks) and select social outcome indicators. Targeted (e.g., behavioral/community-based) prevention measures show mixed and short-term effects on crack use/HIV risk outcomes. Material (e.g., safer crack use kit distribution) interventions also document modest efficacy in risk reduction; empirical assessments of environmental (e.g., drug consumption facilities) for crack smokers are not available. Diverse psychosocial treatment (including contingency management) interventions for crack abuse/dependence show some positive but also limited/short-term efficacy, yet likely constitute best currently available treatment options. Ancillary treatments show little effects but are understudied. Despite ample studies, pharmacotherapeutic/immunotherapy treatment agents have not produced convincing evidence; select agents may hold potential combined with personalized approaches and/or psycho-social strategies. No comprehensively effective 'gold-standard' prevention/treatment interventions for crack abuse exist; concerted research towards improved interventions is urgently needed.

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Background

Based on recent studies, 0.3–0.5% (or 14–21 million people) of the global population aged 15–64, are estimated to be cocaine users (Degenhardt & Hall, 2012; United Nations Office on Drugs and Crime (UNODC), 2014). The prevalence of cocaine use is estimated to be highest – (1.4%) with some national surveys indicating even higher 'past year' prevalence rates – in the region of the Americas where it is recorded as the second most common type of illicit drug use following cannabis (Carlini, Galduróz, Noto, & Nappo, 2006; Health Canada, 2014; Substance Abuse and Mental Health Services Administration (SAMHSA), 2013). An extensive – although not precisely estimated – proportion of cocaine use occurs in the form of crack-cocaine use (i.e., the smoked/inhaled use of freebase cocaine), a substance widely and cheaply available in the Americas and increasingly in Europe (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2007; United Nations Office on Drugs and Crime (UNODC), 2012). While – for example, due to the predominant marginalization (Fischer & Coghlan, 2007) – most crack users are not captured by general population surveys, studies from various national jurisdictions have documented sizeable crack use problems in numerous European countries (Haasen, Prinzleve, Gossop, Fischer, & Casas, 2005; Hay et al., 2010; Hope, Hickman, & Tilling, 2005; Ilse, Prinzleve, Zurhold, & Haasan, 2006; Oliveira, Ponce, & Nappo, 2010; Pérez, Cruyff, Benschop, & Korf, 2013; Prinzleve et al., 2004; Stoever, 2002); Canada and the US (Buchanan et al., 2006; Falck, Wang, & Carlson, 2007; Fischer et al., 2006; Santibanez et al., 2005; Werb et al., 2010); Argentina, Brazil, El Salvador (Bastos & Bertoni, 2013; Santos Cruz et al., 2013a; Dickson-Gomez, Bodnar, Guevara, Rodriguez, & Gaborit, 2007; Dualibi, Ribeiro, & Laranjeira, 2008; Epele, 2011). Among many street drug user populations in North and South America, crack-cocaine is reported to be the most commonly used non-injection drug (Dualibi et al., 2008; Fischer & Coghlan, 2007; Strathdee & Stockman, 2010).

Crack/cocaine use or dependence commonly result in acute or intensive expressions of euphoria, impulsivity, psychotic effects and cognitive impairment; withdrawal, craving and drug-seeking; as well as cardiac, neurological and gastrointestinal problems (Coffey, Dansky, Carrigan, & Brady, 2000; Dackis & O'Brien, 2001; Glauser & Queen, 2007; Kloner, Hale, Alker, & Rezkalla, 1992). In addition, several other severe physical and mental health problems are common in crack users, rendering these a high-risk population for individual and public health. For example, numerous studies have identified crack use as an independent risk factor – whether through direct drug use-related, or indirect risk (e.g., sex-related) risk behaviors – of several chronic infectious diseases (CIDs), including HCV, HIV, Tuberculosis, and rates for these CIDs are commonly higher among crack users compared to other illicit drug users (Booth, Kwiatkowski, & Chitwood, 2000; DeBeck et al., 2009; Edlin et al., 1994; Fischer et al., 2006; Howard, Klein, Schoenbaum, & Gourevitch, 2002; Khan et al., 2013; Nyamathi et al., 2002; Tortu, Neaigus, McMahon, & Hagen, 2001). Crack users indicate disproportionately elevated rates of psychiatric problems, including depression, anxiety and personality disorders, and suicide attempts (Conway, Compton, Stinson, & Grant, 2006; Ford et al., 2009; Kessler, Chiu, Demier, & Walters, 2005; Torchalla, Strehlau, Li, & Krausz, 2011). Evidence from North & South American jurisdictions indicates strongly elevated mortality rates among crack users (Dias, Ribeiro, Dunn, Sesso, & Laranjeira, 2008; O'Driscoll et al., 2001); a systematic review found that crack/cocaine users experience 4–8 times elevated mortality rates compared to the general population (Degenhardt et al., 2011). In addition, crack use and crack distribution/markets are associated with a high occurrence of crime, including elevated rates of property crime, as well as inter-personal crime and/or systemic violence (Baumer, Lauritsen, Rosenfeld, & Wright, 1998; Bennett, Holloway, & Farrington, 2008; Best, Sidwell, Gossop, Harris, & Strang, 2001; Boles & Miotto, 2003; Fischer, Monga, & Manzoni, 2005; Grogger & Willis, 2000).

Related to their pervasive socio-economic marginalization, many crack users are disconnected from social, health or treatment services (e.g., Santos Cruz et al., 2013b; European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2007; Fischer & Coghlan, 2007; Wood, McKinnon, Strang, & Kendall, 2012). However – despite crack's high prevalence in key risk populations, and different from well-established, evidence-based interventions for other forms of street drug use (e.g., needle exchange programs for injection drug use or opioid maintenance treatment [OMT] for opioid dependence) – targeted prevention and treatment measures specifically for crack use are rare, limited availability and underdeveloped (Santos Cruz et al., 2013a; European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2007; Mattick, Breen, Kimber, & Davoli, 2009; Strathdee & Vlahov, 2001; Strathdee & Navarro, 2010); moreover, comprehensive reviews on the state of interventions for crack use are lacking.

The objective of this study was to provide a comprehensive narrative overview of the published English-language evidence on secondary prevention and treatment interventions- with a primary focus on effectiveness in outcomes -for crack-cocaine misuse and related problems.

Methods

The present overview reports on the results of a series of literature searches, involving the principal search terms "crack cocaine"; "use" or "smoking" or "abuse" or "dependence"; and "prevention" or "intervention" or "treatment" or "harm reduction", were conducted on journal-published English-language literature from 1990 up to March 2014, searching major medical and health-related databases – i.e., Embase, PubMed®, PsycINFO® – for relevant English-language journal publications. In addition to journal articles, government reports, organizational publications, and other 'grey literature' available online were electronically searched and included in the review as appropriate. The beginning of the search period (1990) was set somewhat arbitrarily, both covering the largest part of the time period of research since the prominent arrival and spread of crack-cocaine use in many countries, while keeping study results to a relatively recent period; the limitation to English-study results was due to natural language restrictions of research resources involved. While 'treatment' was defined in the conventional sense, 'secondary prevention' was operationalized as any intervention that targeted existing crack use populations with the aim to at least reduce key drug use, health-related or socially harmful behaviors or improve relevant user status indicators.

All citations/titles and respective abstracts were reviewed by research staff for inclusion based on criteria developed by the research team. Full text articles were obtained providing the article title and abstract met the following eligibility criteria: (1) featured a study sample including at least a substantive (i.e., one third of total study population) partial population of crack/cocaine users, or included separate reporting of study outcome data for the crack user sub-sample, based on information available; (2) any primary study reporting on the efficacy or outcomes of a secondary prevention measure targeting crack-cocaine use or related risks/harms, or the treatment of crack/cocaine abuse or dependence; and (3) systematic reviews or meta-analyses of these above topical areas. Outcomes of interest considered included primary drug use, health (e.g., blood-borne virus transmission or sexual) risks or status, or select social (e.g., employment or crime) indicators, yet with a focus on readily modifiable – as opposed to systemic or environmental – indicators. Study outcome data (e.g., relevant statistics),

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including effect sizes where possible, were reported as available in the study, with a focus on significant changes related to or differences in effects between interventions. Given the fundamentally identical neurophysiological basis and mechanisms of crack-cocaine and cocaine dependence, and the fact that most relevant studies have been conducted principally in cocaine-dependent populations, the scope of literature reviewed for pharmaco-therapeutic treatment was broadened to include cocaine-dependent study populations.

Eligible abstracts were compiled and initially organized into one of two broad categories: (1) secondary prevention for crack-cocaine use and related risks/harms and (2) treatment of crack-cocaine dependence, and subsequently were further sub-categorized. One reviewer extracted key information from the full study texts, including: study design/methods, intervention setting, study population, intervention type, outcome measures, and results. A second reviewer independently checked all data; in case of disagreement of data extracted, the information was harmonized, if necessary, by re-consideration of the evidence and/or by consultation.

Results

Secondary prevention interventions

Literature identified on secondary prevention interventions was heterogeneous, and further sub-categorized into behavioral/psycho-social and environmental/material interventions.

Behavioral/psycho-social interventions

An experimental, peer-delivered intervention ('EachOneTeachOne'; EOTO), randomly compared to a standard National Institute on Drug Abuse (NIDA) HIV intervention, resulted in short-term reductions in select drug use and sexual risk behaviors in a sample of out-of-treatment crack users ($n = 725$); specifically, more people in the women-centred experimental intervention (EI) compared to the control group (83% vs. 76%; $p = 0.015$) stopped or reduced their 'risky' crack use (defined by frequency of use), and both groups (76% and 73%, no significant difference) reduced their number of sexual partners but no changes were observed for condom use (Cottler et al., 1998).

An experimental HIV intervention, compared to a standard intervention, was more effective at 6-months follow-up in reducing select sexual risk behaviors (Odds Ratio (OR) = 2.15, $p < 0.00001$), crack use (OR = 2.85, $p < 0.00001$) and drug injection risk (OR = 0.44, $p = 0.03$), and achieving drug abstinence (OR = 3.27, $p < 0.00001$), among two samples of urban ($n = 541$) and rural ($n = 268$) women crack users; no inter-group differences in intervention efficacy were found (McCoy, McCoy, Lai, Weatherby, & Messiah, 1999).

A multi-session enhanced cognitive–behavioral (C–B) intervention resulted in higher condom use ($p < 0.001$), drug treatment attendance ($p < 0.01$), fewer crack use days ($p < 0.001$) and fewer sex partners ($p < 0.001$) in a sample of $n = 1362$ out-of-treatment crack users and IDUs. For crack user participants ($n = 264$) specifically, there were significant favourable pre-/post-intervention effects for crack smoking ($p < 0.001$), sexual activity ($p < 0.05$), 'barrier protection use' for sex ($p < 0.001$) that were significantly superior to the control intervention (NIDA HIV standard); reductions were also observed for sex with multiple partners ($p < 0.001$), sex exchanges ($p < 0.05$), and sex with an IDU ($p < 0.001$), yet these effects did not differ between interventions (Hershberger, Wood, & Fisher, 2003).

An enhanced motivation intervention, an enhanced negotiation intervention, and a standard NIDA intervention, resulted in reduced prevalence of crack use ($p < 0.001$) and reduced sexual risk behaviors at six months follow-up among $n = 265$ HIV-negative Afro-American women crack users. There were no major differences by interventions; however, responses differed by sub-groups (Sterk, Theall, & Elifson, 2003; Sterk, Theall, & Elifson, 2003).

A randomized study compared an experimental women-centred intervention (EI) to improve HIV risks and related self-sufficiency to: (1) an enhanced NIDA standard intervention and (2) a delayed intervention control group, in a sample of $n = 620$ out-of-treatment African-American women crack users, all groups indicated significant reductions in the number of crack use days and sexual risk behaviors at 3-month follow-up; however, at 6-months, only the NIDA standard group still indicated significant reductions in crack use (regression coefficient = −2.36, $p = 0.023$) and only the EI group showed a significant reduction in unprotected sex (regression coefficient = 0.62, $p = 0.034$) (Wechsberg, Lam, Zule, & Bobashev, 2004). A long-term follow-up ($M = 4.4$ years; $n = 455$) on the above three-arm intervention study did not find changes in outcomes between short- (i.e., 3–6 months) and long-term follow-up across interventions, as the majority of participants (62.8%) remained stable in their risk patterns, i.e. short-term intervention effects were not sustained in the long-term (Wechsberg et al., 2010).

Participants ($n = 149$) in a retrospectively assessed HIV prevention program scored significantly higher on condom use intentions ($p = 0.005$), positive outcome expectancies ($p = 0.007$), and affective ($p = 0.002$) and situational self-efficacy ($p = 0.03$); and had higher male ($p = 0.002$) or female ($p = 0.042$) condom use with their last sex partner, compared to non-participants ($n = 365$), in sample of $n = 514$ African-American crack users (Ross, Timpson, Williams, & Bowen, 2007).

An enhanced peer-delivered HIV education intervention, compared to a standard intervention, resulted in more common reductions in crack use (70% vs. 61%, $p = 0.004$) at 3-month follow-up in a sample of $n = 923$ out-of-treatment crack users. Based on logistic regression analysis, reductions in crack use were independently associated with older yearly increments in age (OR = 1.024; 95% CI = 1.004, 1.045) enhanced intervention assignment (OR = 1.508; 95% CI = 1.141, 1993) and improvements in 'readiness to change' status (OR = 1.737, 95% CI = 1.025, 2.941) but not gender (Schlosser, Abdallah, Callahan, Bradford, & Cottler, 2008).

A peer-driven HIV prevention intervention ('Risk Avoidance Partnership') reduced drug use ($p = 0.001$) and sex-risk outcomes ($p = 0.010$) at 6-months follow-up in a sample of $n = 523$ drug injectors and/or inhalers (including a majority of crack users); improvements in attitude outcomes were also observed. There were no major outcome differences between the peer-health advocates delivering the intervention and intervention participants (Weeks et al., 2009).

An experimental ('Safety Counts') HIV prevention intervention, compared to a standard NIDA intervention, resulted in greater reductions in sexual activity (effect size ration (ESR) = 0.78; $p < 0.001$), unprotected sex (ESR = 0.58; $p < 0.001$); drug injection risks (ESR = 0.93; $p < 0.001$); crack use frequency (ESR = 0.90; $p < 0.001$); and other drug use frequency (ESR = 0.93; $p < 0.001$) among $n = 875$ opiate and crack (35.3%) users in a cross-over design study. Risk reduction effects were associated with intervention adherence (Rotheram-Borus, Rhodes, Desmond, & Weiss, 2010).

An experimental, brief group ('Positive Choices') intervention, compared to a standard intervention, found select positive change results – specifically regarding the number of sex partners, number of paid & casual sexual partners, condom use practice and attitudes, and HIV disclosure – at 3-months follow-up, among $n = 347$ heterosexual African-American crack users living with HIV which however were not sustained at the 9-months follow-up (Williams et al., 2012).

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Material/environmental interventions: Drug consumption facilities and 'safer crack use paraphernalia distribution'

Since the 1990s, some 100 so-called 'Drug Consumption Facilities' (DCFs) – with the main objectives to reduce morbidity (e.g., BBV transmission) or mortality (e.g., overdose) risks, reduce public order problems, and to connect users with other social, health and treatment services (Hunt, 2006a; Schatz & Nougier, 2012; Zobel & Dubois-Arber, 2004) – have been implemented in Australia, Canada and Europe (Hedrich, Kerr, & Dubois-Archer, 2010; Hunt, 2006a; Kimber, Dolan, & Wodak, 2005). The majority of DCFs aim primarily at injection drug users (IDUs) and injection-related risks. While few DCFs have been systematically evaluated, available studies demonstrate reductions in injection risks and overdose fatalities, as well as improvements in health status and treatment utilization among DCF users (Hedrich et al., 2010; Schatz & Nougier, 2012; Wood, Kerr, Tyndall, & Montaner, 2008). A minority of DCFs (primarily in Europe) include facilities services targeting drug inhalers (e.g., crack smokers); these have been proposed but remain to be implemented elsewhere (e.g., in North/South America) (Hedrich, 2004; Hunt, 2006b; Kothner, Langer, & Klee, 2011; Shannon et al., 2006). A series of Canadian studies – conducted in Vancouver, Toronto and Ottawa – have found that largely majorities (ranging from 28% and 71%) of street-involved crack and other drug inhalers would use DCF services if offered, but did not measure any impacts of such interventions (Bayoumi et al., 2012; Collins et al., 2005; DeBeck et al., 2011; Shannon et al., 2006). Unfortunately, overall no rigorous evaluations on the discernable impacts of DCF programs targeting drug inhalers – including crack users – exist (Hedrich et al., 2010; Strathdee & Navarro, 2010).

Based on the evidence for distinct injury/morbidity risks associated with crack use (Faruque et al., 1996; Fischer, Powis, Firestone Cruz, Rudzinski, & Rehm, 2008; Haydon & Fischer, 2005; Porter, Bonilla, & Drucker, 1997), 'safer crack use paraphernalia' (SCUP) distribution initiatives have been implemented in select locales as targeted efforts to reduce such risk outcomes. SCUP programs are typically offered as community-based outreach initiatives, distributing simple 'kits' of basic materials (e.g., break-safe glass stems, rubber mouthpieces, metal screens for safer crack pipe assembly; (Haydon & Fischer, 2005; Malchy, Bungay, Johnson, & Buxton, 2011) – plus basic information and health promotion elements – to facilitate safer crack use practices.

In a mixed-methods pilot study among $n = 97$ poly-substance using crack users in Vancouver, most respondents (~80%) reported 'unsafe' crack use practices (e.g., crack pipe sharing; unsafe paraphernalia material use; 'shot-gunning') and acute health and legal risks (e.g., oral burns/lesions and respiratory problems; sex or drug trade involvement); 89% expressed a willingness to utilize a SCUP program if available (Malchy, Bungay, & Johnson, 2008).

A qualitative study of $n = 200$ women crack users in Vancouver found that involvement in SCUP assembly created a 'safe space' supporting the sharing of safer use and health 'relevant information' and 'facilitated community development' among participants (Bungay et al., 2009).

A mixed-methods assessment of two SCUP programs among $n = 31$ crack users – a majority of which had an IDU history – in Victoria, Canada, reported reductions in the sharing and/or use of risky crack paraphernalia; increased health risk awareness; and reduced crack paraphernalia access problems; however barriers to SCUP utilization included limited availability; lack of fitting materials; absence of protected crack use spaces; and police interference (Ivsins, Roth, Nakamura, Krajden, & Fischer, 2011).

A cross-sectional evaluation of a SCUP initiative in Ottawa, Canada, among $n = 550$ IDUs with regular crack (injection or non-injection) use found a non-significant increase in SCUP utilization (from 80% to 94%) over the 12-month study period. The prevalence of injecting crack use decreased (96% to 78%; $p < 0.001$), but was substituted by oral crack use. The overall prevalence of crack use paraphernalia sharing remained high (e.g., 80% or higher), while high-frequency crack paraphernalia sharing declined from 37% pre- to 14% post-SCUP initiative ($p = 0.001$) (Leonard et al., 2008).

A pre-post study of a Vancouver SCUP program found an increase in finding access to 'safer' crack use paraphernalia, including pipes ($p = .010$), and mouthpieces ($p < 0.001$), among $n = 356$ – mostly daily – crack users. However, the majority of participants continued to use unsafe paraphernalia materials, and the sharing of paraphernalia, including used pipes ($p < 0.001$), and mouthpieces ($p = 0.005$), increased post-implementation (Malchy et al., 2011).

Among $n = 914$ crack users in Vancouver, 33% reported difficulty accessing SCUP. Factors independently associated with access difficulty included: sex work involvement (OR = 1.69; $p = 0.03$), crack paraphernalia sharing (OR = 1.69, $p < 0.01$), police presence (OR = 1.47, $p < 0.01$), difficulty accessing services (OR = 1.74; $p < 0.01$); crack use-related health problems (OR = 1.37; $p = 0.02$). Reasons given for difficulty accessing pipes included sources being closed (48%) and no one around selling pipes (18%) (Ti et al., 2012).

Treatment interventions

The literature identified on treatment interventions for crack/cocaine abuse/dependence was heterogeneous, comprising three main clusters: (1) psycho-social (e.g., including cognitive-behavioral and/or contingency management), (2) ancillary/adjunct treatment interventions and (3) pharmacotherapy, which were reviewed and structured accordingly.

Psycho-social treatment

A case management intervention, focusing on psycho-social service provision, resulted in a mean of 6.9 (range 0–37) months of drug free time among $n = 120$ crack abusing pregnant or postpartum women. In a stepwise regression analysis, aftercare management ($p < 0.0001$), vocational services ($p < 0.02$) and residential treatment enrollment ($p < 0.03$) predicted drug-free time ($R^2 = 0.46$ in final model) (Lanehart & Clark, 1994).

A randomized study of different psychosocial (including individual, group or standard therapy) treatment combinations in a sample of $n = 184$ predominantly African-American crack users found overall reductions in crack/cocaine use ($x^2 = 5.1$; $p < 0.05$), other drug use ($x^2 = 5.6$; $p < 0.05$), alcohol use ($x^2 = 23.4$; $p < 0.01$) and illegal activities ($x^2 = 8.6$; $p < 0.05$) at 12-months follow-up. Treatment outcomes were associated with treatment retention, which were predicted by individual and drug use characteristics (Hoffman et al., 1996).

Among $n = 8241$ out-of-treatment crack-cocaine, heroin and poly-substance (injection) users in 22 US sites, treatment entry was significantly associated with reduced crack use ($t = -2.77$; $p = 0.0057$) and reduced injection risk behavior ($t = -4.90$; $p < 0.0001$), but not sex risk behaviors or sharing/re-use of drug paraphernalia at 6-months follow-up (Hoffman, Klein, Clark, & Boyd, 1998).

Participants randomized to a 12-week cognitive behavioral therapy (CBT) intervention, compared to a 12-step program, were more likely to achieve four consecutive crack use-free weeks ($p = 0.04$; OR = 2.51) and abstinence at various study point measures ($p = 0.01$) up to 26-weeks post-intervention among $n = 128$ crack abusing US military veterans (Maude-Griffin et al., 1998).

Among $n = 72$ African-American – primarily crack-dependent – mothers in a comprehensive residential psycho-social treatment program, 'treatment completers' had the smallest proportion (15%) of substance use relapse, compared to 'early' (<30 days of treatment) and 'late dropout' (>30 days) groups (50% and 61%, respectively; $x^2 = 11.97$; $p = 0.003$) (Conners, Bradley, Whiteside-Mansell, & Crone, 2001).

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In a prospective cohort of $n = 496$ crack (34%) and other drug users, significant reductions ($x^2 = 93.01$; $p < 0.0001$) in crack use among crack users, yet also significant increases ($x^2 = 71.01$; $p < 0.0001$) in crack use among original non-crack users, were found at 4–5 year follow-up. Crack use at follow-up was associated with: crack use (OR = 3.02; $p < 0.001$); other illicit drug use, including heroin (OR = 8.83; $p < 0.001$), benzodiazepine (OR = 1.81; $p < 0.05$), and cocaine use (OR = 5.76; $p < 0.001$); mental health problems (OR = 1.33; $p < 0.05$); and criminal involvement (OR = 2.51; $p < 0.001$) at baseline (Gossop, Marsden, Stewart, & Kidd, 2002).

Siegal, Li, and Rapp (2002) identified (1) a sustained abstinence group (31%), (2) an inconsistent abstinence group (40%) and (3) a non-abstinent group (29%) among $n = 229$ primary crack/cocaine abusers at 18-month post-treatment discharge. Based on Addiction Severity Index (ASI) domains, abstinence outcomes were predicted by better participant employment ($F = 11.25$; $p < 0.001$), family ($F = 5.64$; $p < 0.01$), legal ($F = 6.11$; $p < 0.05$) and psychiatric ($F = 4.15$; $p < 0.05$) indicators and associated with longer periods of aftercare (OR = 2.14; $p < 0.01$) and 12-step program attendance (OR = 1.89; $p < 0.05$).

Among $n = 347$ primary crack/cocaine abusers, 44% – after an average period of 2.6 years – returned to treatment and had an average of 2.6 treatment episodes within five years of their index treatment. Treatment re-entry was associated with: African-American ethnicity (OR = 1.84; $p < 0.01$), marital status (OR = 2.14; $p < 0.01$), frequent cocaine use (OR = 1.84, $p < 0.05$) and higher level of service needs (OR = 1.18; $p < 0.05$) (Grella, Hser, & Hsieh, 2003).

In a prospective cohort of $n = 1658$ women crack/cocaine (49.6%) and other drug users, treatment exposure was associated with lower rates of sexual activity (Adjusted Odds Ratio (AOR) = 0.83; $p < 0.001$), but not with consistent condom use, except for those exposed to multiple treatment episodes (AOR = 1.40; $p = 0.05$) over a multi-year study period; crack/cocaine use (AOR = 1.36; $p < 0.05$) was a predictor of higher sexual risk behaviors (Latka et al., 2005).

An outreach treatment program (OTP), compared to standard care, resulted in intensive (e.g., near-daily; average lenght of enrollment: 6.2 months) treatment engagement, among $n = 94$ chronic high-risk crack abusers in the Netherlands. The OTP group indicated stronger physical health, living condition and psychiatric health improvements and higher treatment satisfaction yet no differences in substance abuse, legal or employment indicators; on-the-spot incentives and provider rapport were associated with treatment compliance (Henskens, Garretsen, Bongers, Van Dijk, & Sturmans, 2008).

In a prospective cohort involving $n = 182$ mainly crack/cocaine-and/or heroin-dependent (including co-use) residential treatment enrollees, 25% dropped out of treatment; dropouts had higher depressive (OR = 1.20; $p < 0.05$) and/or anxiety (OR = 1.54; $p < 0.05$) symptoms and were less likely (OR = .38; $p < 0.01$) to have been court-ordered into treatment (Lejuez et al., 2008).

In a series of follow-up studies on $n = 131$ crack/cocaine users at 2, 5, and 12 years post-detoxification treatment, almost half – and 63% of those who had been abstinent at 2-years – remained abstinent at 5-years. The abstinent group was still the most prevalent at 12 years. 21% ($n = 27$) of patients had died by the 12-year follow-up, with homicide being the most common cause ($n = 16$) (Dias et al., 2008; Ribeiro, Dunn, Laranjeira, & Sesso, 2004; Ribeiro, Dunn, Sesso, Dias, & Laranjeira, 2006).

In a sample of $n = 14{,}656$ crack (52%) and/or heroin users who had received at least 6 months' of primary (psychosocial or pharmacological) community treatment, 52% of crack users reported abstinence in the pre-study compared to the pre-treatment period. Crack use days were reduced by an equivalent of 61%, and crack use abstinence was higher (OR = 1.24; $p < 0.0001$) among crack-only users compared to co-users; outcomes for psychosocial interventions were superior to pharmacological interventions (Marsden et al., 2009).

A case management intervention resulted in significant improvements between baseline and end-of-treatment in relation to a number of factors, including: frequency of crack use ($t = 8.62$; $p < 0.05$), alcohol use ($t = 3.29$; $p < 0.05$) and illicit drug use ($t = 8.84$; $p < 0.05$), frequency of depression ($t = 3.01$; $p < 0.05$) and anxiety ($t = 3.24$; $p < 0.05$), and employment status ($Z = 2.27$; $p < 0.05$) among $n = 149$ predominantly African-American and Hispanic crack-using women (Corsi, Rinehart, Kwiatkowski, & Booth, 2010).

Both (1) motivational interviewing with skills building and (2) a video-based education with debriefing intervention (8-weeks in duration) – with no inter-group differences – increased Highly Active Antiretroviral Therapy (HAART) adherence (Effect Size (ES) = .45), and reduced days of crack/drug use-related problems (ES = .259) among $n = 54$ – mostly dependent – crack users with <90% HAART adherence at 3-months follow-up; effects were maintained at 6-months (Ingersoll et al., 2011).

Psycho-social treatment involving contingency management (CM)

Enhanced day treatment plus abstinent-contingent work therapy and housing, compared to usual treatment care, resulted in significantly fewer positive cocaine toxicologies at 2 (36% difference), 6 (18%) and 12-months (4%) follow-up ($p = 0.003$), as well as superior housing ($p = 0.01$) and employment outcomes ($p = 0.026$) in a sample of $n = 131$ homeless substance (primarily crack) abusers (Milby et al., 1996).

In two randomized experiments with a sample of $n = 90$ mostly (88%) crack-cocaine users enrolled in cognitive-behavioral therapy, (1) the provision of contingent vouchers did not impact on treatment participation or cocaine abstinence; (2) immediate versus delayed contingent voucher provision resulted in higher levels ($F(1,21) = 5.65$; $p = 0.03$) and longer duration ($F(1,21) = 6.47$; $p = 0.02$) of cocaine abstinence (Kirby, Marlowe, Festinger, Lamb, & Platt, 1998).

In a study involving $n = 70$ outpatients with cocaine dependence – half of which were mainly crack-cocaine smokers – in community-based treatment, contingent versus non-contingent voucher incentive provision resulted in achieving continuous abstinence for 12 or more weeks in a significantly larger proportion of patients ($x^2(1, N = 70) = 5.60$; $p = 0.02$), but not for 8 or more weeks or 16 or more weeks (Higgins, Wong, Badger, Ogden, & Dantona, 2000).

Enhanced behavioral day treatment including contingency and housing components, compared to standard treatment, resulted in higher treatment attendance ($p = 0.0006$) which was associated with higher rates of positive treatment outcomes (i.e., abstinence) at 6-months (OR = 1.30; $p = 0.0002$) and 12-months follow-up (OR = 1.29; $p = 0.0007$) among $n = 141$ homeless crack-cocaine abusers (Schumacher, Usdan, Milby, Wallace, & McNamara, 2000).

In a randomized controlled trial among $n = 110$ homeless and co-morbid crack-cocaine abusers, behavioral day treatment plus abstinence contingent housing and work therapy, compared to behavioral day treatment alone, achieved greater abstinence at 2- and 6-months (ES = 0.74; $p < 0.0001$ and ES = 1.06; $p = 0.0009$), and more days housed ($p = 0.016$) at 6-months follow-up (Milby et al., 2000).

Day treatment plus contingency management, compared to day treatment-only (DT), was 2.1 times ($p = 0.034$) more likely to result in positive treatment outcomes in a randomized sample ($n = 127$) of homeless and mainly African-American crack-cocaine abusers, at treatment completion; concordance between substance use disorder diagnosis and treatment outcome was found (Schumacher et al., 2003).

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In a sample of $n = 141$ homeless individuals primarily with crack-cocaine abuse randomly assigned to either (1) basic day treatment (DT) or (2) day treatment plus contingency management (DT+), both groups showed improvements in drug abstinence at all follow-ups ($p < 0.01$), and housing ($p < 0.01$) and employment outcomes ($p = 0.006$ and $p = 0.003$) at 12-months follow-up; however no inter-group differences were found (Milby et al., 2003).

Among $n = 196$ crack/cocaine-dependent individuals receiving either day treatment and no housing (NH), housing contingent on drug abstinence (ACH), or housing not contingent on abstinence (NACH), the ACH and NACH groups demonstrated superior treatment outcomes (e.g., abstinence) over the NH group at different follow-up assessments; however, no inter-group differences were found and all 3 groups showed significant improvements in maintaining employment and housing (Milby, Schumacher, Wallace, Freedman, & Vuchinich, 2005).

In a meta-analysis of the above five RCTs (Milby et al., 1996, 2000, 2003, 2005, 2008) assessing CM interventions in conjunction with various treatment conditions of drug-abstinent housing and work therapy and day treatment (DT) involving a total of 644 homeless crack-cocaine dependent individuals, CM-DT and CM-only indicated superior benefits over DT-only (pairwise tests for abstinence at 6-months $p < 0.006$) (Schumacher et al., 2007).

In a randomized controlled study of a 'therapeutic workplace' intervention where salary was contingently linked to drug-free urine-tests involving $n = 40$ pregnant or postpartum opioid dependent women with mostly crack/cocaine abuse ($n = 30$), the intervention was associated with a doubling with urine-test results free of opiates and cocaine (33% vs. 59%; $p < 0.05$). While 40% of women in the intervention group had drug-free urine-tests on at least 75% of testing occasions, only 10% of controls did so ($R(18) = .99$; $p < 0.01$) (Silverman, Svikis, Robles, Stitzer, & Bigelow, 2001).

In a randomized study involving $n = 79$ marginalized participants with mainly crack abuse in day/outpatient treatment, contingent voucher incentives for cocaine-negative urine toxicology screens did not result in screen result differences between the treatment conditions; the level of exposure to individual counseling accounted for about 41% of the observed variance ($R^2 = .406$; $F(1,61) = 42.35$; $p < 0.0001$) in continuous abstinence (Marlowe et al., 2003).

In a small feasibility study based on 'within-subject reversal design' examining voucher-based reinforcement therapy with African-American crack-cocaine using veterans, escalating voucher provision resulted in increased cocaine-free urine samples, yet only in the first two weeks of the 4-week intervention (Roll, Chermack, & Chudzynski, 2004).

A comparative study utilizing different experimental conditions among 12 predominantly crack-cocaine dependent patients in MMT found superior efficacy for cash over voucher incentives ($p < 0.05$), as well as for high-magnitude over low-magnitude cash incentives (all $p < 0.05$), towards achieving short-periods of cocaine-abstinence (Vandrey, Bigelow, & Stitzer, 2007).

In a 2×2 design study involving contingent versus non-contingent/yoked vouchers combined with either community reinforcement therapy or 12-step-facilitation among $n = 145$ crack/cocaine using women, contingent voucher provision was associated with greater proportions and durations of abstinence ($F(1,141) = 8.43$ and $F(1,141) = 7.76$, respectively; both $p < 0.01$); there were no differences between the two treatment modes (Schottenfeld, Moore, & Pantalon, 2011).

In a within-subject randomized crossover design study among 15 mostly long-term crack-cocaine users, predictable monetary reinforcement was superior to probabilistic reinforcement – and mostly so at high magnitude – in averting cocaine choice (Greenwald, Ledgerwood, Lundahl, & Steinmiller, 2014).

Adjunct/ancillary treatments

Of the adjunct therapies: (1) acupuncture, (2) anti-craving medication, and (3) brainwave stimulation, compared to no adjunct treatment, dosage ($F = 6.44$; $p < 0.001$) and frequency of neurobehavioral treatment sessions ($F = 7.51$; $p < 0.0001$) were associated with treatment attendance but not outcomes in a randomized sample of $n = 196$ African-American crack-dependent users undergoing C-B-based outpatient treatment (Richard, Montoya, Nelson, & Spence, 1995).

Among $n = 25$ young adult crack-dependent males (16–28 years), therapeutic cannabis use resulted in the ceasing of crack use in the majority of participants (68%), who also reported reduced craving symptoms and positive behavior changes (Labigalini, Rodrigues, & Da Silveira, 1999).

A systematic review of the effectiveness of acupuncture use in the treatment of crack/cocaine addiction treatment – including six RCTs – found no significant associations between ancillary acupuncture use and treatment outcomes ($p = 0.11$) (D'Alberto, 2004).

The delivery of adjunct electro-encephalographic operant conditioning training (EEG-OC) was associated with significant improvements in urinalysis results, self-report measures, length of residence, and depression scores ($t = 7.38$, $p < 0.005$) at 12-months post-completion among $n = 87$ crack-cocaine dependent males (Burkett, Cummins, Dickson, & Skolnick, 2005).

In a randomized controlled study of $n = 121$ crack and other drug abusers, subjects receiving EEG biofeedback sessions were more likely to be retained in treatment ($x^2 = 6.29$; $p < 0.05$), had longer treatment duration ($t = -3.07$; $p < 0.005$) and more abstinence ($x^2 = 7.78$; $p < 0.01$) at 12-months follow-up; they also demonstrated superior cognitive improvements (Scott, Kaiser, Othmer, & Sideroff, 2005).

In an exploratory 2-week study of cellphone use for 'ecological momentary assessments' (EMA) among $n = 30$ homeless crack/cocaine-dependent patients in outpatient treatment, 80% ($n = 24$) completed the EMA protocol. 77% reported craving, 27% reported ongoing crack use. While 50% reported the procedure to be irritating, and that they would ignore calls when using drugs, 30% stated that EMA increased their self-awareness and supported abstinence (Freedman, Lester, McNamara, Milby, & Schumacher, 2006).

A small exploratory study among regular crack users in Salvador, Brazil found that 'pitilho' use (the co-smoking of crack and cannabis) helped to reduce the negative pharmaco-behavioural and physical effects of crack use, vulnerability for violence, expenditures for crack, and benefits for behavior control (Andrade, Santiago, Amari, & Fischer, 2011).

Pharmaco-therapeutic interventions

Based on crack/cocaine's evidenced impact on the brain's reward and other neurotransmitter systems and processes related to cognition, memory, and other neuro-behavioral functions. (Volkow, Fowler, Wang, & Goldstein, 2002) a large number of pharmacotherapeutic treatment intervention agents have been tested which can essentially be categorized into three main categories: (1) 'treatment' medications aiming to remedy the biological processes responsible for cocaine dependence, (2) 'substitution' like medications, (3) immunotherapy/vaccination (Karila et al., 2008; Nuijten, Blanken, van den Brink, & Hendriks, 2011). Recent detailed and authoritative reviews exist on the feasibility, safety and outcomes of these interventions (e.g., Ciccarone, 2011; Kampman, 2010; Karila et al., 2011; Nuijten et al., 2011; Shorter & Kosten, 2011; Somaini et al., 2011); hence, the evidence – focusing on effectiveness outcomes in human studies – is summarized only cursorily below.

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Among glutamine agents, *N*-acetyl-cysteine resulted in reductions of cocaine craving and use in some smaller studies but not others (Amen et al., 2011; LaRowe et al., 2007, 2013; Mardikian, LaRowe, Hedden, Kalivas, & Malcolm, 2007). Several RCTs have found *Modafinil* – also in conjunction with CBT – to reduce cocaine use and craving (Anderson et al., 2009; Dackis, Kampman, Lynch, Pettinati, & O'Brien, 2005); a meta-analysis concluded that modafinil was superior to placebo in achieving cocaine abstinence (Castells et al., 2010). Mixed effects on cocaine use and craving have been documented in studies involving *Topiramate* (also combined with CBT; (Kampman et al., 2004; Nuijten et al., 2011; Reis, Castro, Faria, & Laranjeira, 2008), results for *Acamprosate* or *Memantine* have been largely negative (Bisaga et al., 2010; Kampman, 2010).

Various GABA agents (e.g., *Vigabatrin*, *Baclofen*, *Taigabine*) have shown no or mixed effects at best (e.g., Brodie et al., 2009; Shoptaw et al., 2003; Winhusen et al., 2007), and both a systematic review/meta-analysis and a Cochrane review, each involving 15 studies, concluded that there was no current evidence supporting the use of anti-convulsants for cocaine dependence treatment (Alvarez, Farré, Fonseca, & Torrens, 2010; Minozzi et al., 2008).

Among Dopamine agents, several clinical studies involving *disulfiram* – some combined with CBT and potentially dose-related – resulted in reduced cocaine use or abstinence in cocaine- or co-drug dependent patients; however, concerns regarding various potential adverse effects of *disulfiram* exist (Carroll et al., 2004; Malcolm, Olive, & Lechner, 2008; Oliveto et al., 2011; Pettinati et al., 2008). Similarly, some evidence for the efficacy, yet also concerns about potential adverse effects, exist for *varenicline* (Eggertson, 2012; Plebani et al., 2012; Poling, Rounsaville, Gonsai, Severino, & Sofuoglu, 2010). Little positive evidence has been found for *bupropion* and *levadopa* in different patient groups (Poling et al., 2006; Shoptaw et al., 2008). Two systematic reviews (involving 16 and 23 studies, respectively) concluded that select psychostimulant drugs may help towards cocaine abstinence outcomes but that the overall "evidence of efficacy . . . is inconclusive" (Castells et al., 2010) and ". . . does not support the use of dopamine agonists" for cocaine dependence treatment, even combined with psycho-social interventions (Amato et al., 2011). Similarly, a Cochrane review (comprising 37 RCTs involving 3551 patients) concluded that there was no support for efficacy of antidepressant use for cocaine dependence (Pani, Trogu, Vecchi, & Amato, 2011).

Among antipsychotics, clinical trials involving *risperidone* and *olanzapine* have not indicated positive outcomes for cocaine dependence (Grabowski, Shearer, Merrill, & Negus, 2004; Hamilton, Nguyen, Gerber, & Rubio, 2009; Kampman, Pettinati, Lynch, Sparkman, & O'Brien, 2003; Loebl et al., 2008); some positive effects for cocaine use of craving have been observed in small studies involving *quetiapine* and *aripiprazole* (Beresford et al., 2005; Meini et al., 2011; Vorspan, Bellais, Keijzer, & Lépine, 2008). A meta-analysis of studies using antipsychotics did not conclude any beneficial effects for cocaine dependence treatment (Amato, Minozzi, Pani, & Davoli, 2007).

Regarding agonist replacement therapy, several clinical studies involving *d-amphetamine* (potentially associated with treatment duration and/or dose) documented reductions in cocaine-seeking behavior or use (Grabowski et al., 2004; Greenwald, Lundahl, & Steinmiller, 2010; Rush, Stoops, & Hays, 2009; Shearer, Wodak, van Beek, Mattick, & Lewis, 2003). A singular RCT of immediate- and sustained-release methamphetamine indicated that the latter formulation reduced cocaine craving and use (Mooney et al., 2009). Mixed evidence for the therapeutic effects of methylphenidate among cocaine-dependent patients – especially those also suffering from ADHD disorders – have been observed; these may be more favourably associated with sustained over immediate release formulations (Arria & Wish, 2006; Levin, Evans, Brooks, & Garawi, 2007; Prudhomme-White, Becker-Blease, & Grace-Bishop, 2006; Schubiner et al., 2002; Somoza et al., 2004).

Several human studies have been conducted with cocaine antibody vaccine agents (primarily TA-CD). Evidence suggested that cocaine antibodies could be induced effectively, and resulted in decreased cocaine use among patients where higher antibody levels could be sustained; a main limitation is that these can only be achieved in partial sub-populations, and the effects are short-lived (Haney, Gunderson, Jiang, Collins, & Foltin, 2010; Kosten et al., 2002; Martell, Mitchell, Poling, Gonsai, & Kosten, 2005; Martell et al., 2009). A new vaccine compound has shown evidence for reduced cocaine seeking in animal models, yet remains to be tested in humans (Hicks et al., 2011; Wee et al., 2012).

Discussion

We comprehensively reviewed the English-language evidence on secondary prevention and treatment interventions for crack-cocaine users.

A fairly substantive body of largely controlled studies on innovative or tailored behavioral – largely brief/outreach based – targeted prevention measures targeting crack users focused mainly on HIV-risk and crack use outcomes, indicating mixed evidence on efficacy slightly in favour of experimental over standard/control (e.g., NIDA HIV) interventions. While some of the interventions produced discernable effects, and are relatively easy and economical to implement (e.g., in community-based settings), reduction effects for key risk or problem outcomes – based on largely high or intensive baseline problems levels – documented are largely partial and limited, and thus a form of 'harm reduction' at best. In addition, most interventions are limited to short-term effects, and the existence or potential – e.g., by intensive/repeat booster interventions – for longer-term effects remains largely un-examined in existing studies.

A very limited range of – largely observational and uncontrolled – studies exists on material/environmental prevention measures. While some reductions in risk behaviors (e.g., crack paraphernalia sharing, use of unsafe paraphernalia materials) have been observed in the few SCUP distribution evaluation studies conducted, these effects are limited at best and do not suggest potential for substantial reductions in tangible risk/harm burdens (as, for example, comparatively observed for needle exchange services [NES] or methadone maintenance therapy [MMT] (Amato et al., 2005; Hagan, Pouget, & Des Jarlais, 2011; MacArthur et al., 2012; Ritter & Cameron, 2006). The studies further indicate considerable problems with both the scope of and access to SCUP programs, yet also with substantive obstacles or interference (e.g., from law enforcement) to program implementation. Further and rigorous studies are needed to better understand the potential benefits of SCUP interventions. An even less empirically solid picture exists for DCF interventions aiming at crack users (or other drug inhalers/smokers). While DCF services aiming at IDUs – primarily in Australia and Canada – have been well-evaluated in regards to health and social outcome indicators, some intention/attitude studies on potential DCF utilization among crack users but no outcome evaluations or data exist. As DCF services have been implemented (in Europe) or discussed (in the Americas) in several jurisdictions, this is a major gap for evidence-based intervention development and implementation aiming at crack users. Rigorous studies should urgently be implemented to determine whether DCF services could constitute a potentially beneficial intervention for health and other outcomes, yet also for improving crack users' integration with the help system (Fischer et al., 2006; Hedrich et al., 2010; Strathdee & Navarro, 2010).

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On the treatment side, a substantive body of – fairly well-designed and controlled – studies suggests that psycho-social (e.g., cognitive-behavioral) treatment interventions can reduce drug use and health risks/harms, as well as improve social indicators for crack-cocaine use, at least to some extent. While studies are commonly limited in regards to treatment retention and a predominant focus on short-term effects, there appears to be a trend for tailored and more intensive interventions to result in superior efficacy. This reflects evidence that several systematic reviews focusing on psycho-social treatment measures for stimulant use more generally have found (Dutra et al., 2008; Lee & Rawson, 2008; Shearer, 2008), even though it needs to be considered that these populations may vary in terms of socio-economic, drug use and co-morbidity profiles. As such – and given the current status of pharmaco-therapeutic treatment options (see below) – psycho-social treatment options are likely the best, realistically available treatment option for crack/cocaine abuse currently available. While very little evidence – e.g., none for acupuncture, some for EEG biofeedback – exists for ancillary treatments, a key role in the effectiveness of psycho-social treatment may relate to the meaningful use and integration of contingency management (CM) in the design of treatment measures. CM measures have demonstrated superior efficacy over conventional treatment primarily for achieving periods of drug abstinence in crack user populations; this echoes the conclusions of several comprehensive reviews on CM interventions for cocaine or other drug using populations (Farronato, Dürsteler-Macfarland, Wiesbeck, & Petitjean, 2013; Knapp, Soares, Farrell, & Lima, 2007; Lussier, Heil, Mongeon, Badger, & Higgins, 2006; Prendergast, Podus, Finney, Greenwell, & Roll, 2006). Future work, here, needs to focus on developing and tailoring psycho-social treatment more effectively for the distinct high-risk and -needs population of crack users with the aim of increasing not just treatment efficacy, but also uptake and retention. Besides the creative use of CM tools to further explore the potential improvement of psycho-social treatment outcomes, the (personalized) combination of promising psycho-social and pharmaco-therapeutic treatment tools likely remain the primary frontier in treatment research for crack dependence (e.g., Ciccarone, 2011).

A large number of high-quality studies – mostly also involving extensive resources – have been conducted on both laboratory and human studies searching for potentially efficacious pharmacotherapy treatment options for cocaine/crack dependence. Numerous agents have been examined, yet the results have generally been "disappointing or, at best, equivocal" (Nuijten et al., 2011), and "no pharmacological treatment [to date] has proven to be effective" (Karila et al., 2011). The highest potential for benefit may currently rest in glutamatergic and GABA (e.g., topiramate or modafinil) as well as dexamphetine formulations, even though existing evidence for these agents is mixed and some addictive liability concerns (e.g., for dexamphetamine) exist (Kampman, 2010; Karila et al., 2011; Nuijten et al., 2011; Nuijten, Blanken, van den Brink, & Hendriks, 2014; Shorter & Kosten, 2011). While immunotherapy/vaccination has been hailed as a "new and promising" preventive-therapeutic approach, the evidence supporting potential clinical use of existing agents is highly selective and short in duration – rendering potential universal usage doubtful – while newer agents remain to be studied in humans (Herin, Rush, & Grabowski, 2010; Karila et al., 2011; Somaini et al., 2011; Wee et al., 2012). Commentators have proposed the likely futility of searching for a 'panacea'-like pharmacotherapeutic treatment agent, and instead emphasized the higher promise of more specific – e.g., related to distinct co-morbidities – of agent-patient matching along-side meaningful combinations with psycho-social treatment elements, offering potentially greater therapeutic benefits (e.g., Ciccarone, 2011; Dutra et al., 2008; Herin et al., 2010; Kampman, 2010; Lussier et al., 2006). In addition, a number of key – social and ethical – concerns and issues have been raised about the implementation of a potential cocaine/crack vaccine agent on a population level which remain largely unresolved (Ashcroft & Franey, 2004; Hall & Carter, 2004; Young, Sisti, Rimon-Greenspan, Schwartz, & Caplan, 2012).

A great majority of the studies reviewed were conducted in the US. While resource/funding discrepancies and challenges certainly exist in Latin/South American countries compared to North America and/or Europe, the relatively high prevalence of crack use/dependence, and extensive related health and social problems, dictate a distinct urgency as well as offer a timely opportunity to systematically investigate feasible and more effective prevention and treatment interventions for this marginalized risk-population. While crack use is as common as opioid and/or injection drug use in key global regions, 'gold standard' interventions like NES or OMT are currently lacking for this problem; concerted efforts towards the development and implementation of improved evidence-based targeted prevention and treatment interventions for crack-cocaine use should urgently be initiated.

This study has a number of important limitations. First, this overview is based on a series of comprehensive and structured literature searches focusing on the topical areas of interventions as described, yet did not follow the strict rules and procedures of a 'systematic review' due to resource limitations, as well as the heterogeneity of studies and data considered. It also included studies involving less rigorous methodologies (e.g., not restricted to randomized controlled trials), as well as heterogeneous populations (including poly-substance using populations, or populations to exclusively limited to crack-cocaine users) as well as intervention types (e.g., both different kinds of secondary prevention and treatment interventions). This may mean that certain literature items may have been missed due to the approach in literature searches and inclusion criteria applies; at the same time, the present overview likely considered and included literature that the highly rigorous terms and parameters of a systematic review may have otherwise excluded, and therefore offers distinct value in its breadth in scope. Based on limitations regarding study quality as well as the extensive heterogeneity of studies, interventions and data involved, meta-analyses were not possible, yet should be aimed for in future reviews with narrower and specific focus. This also means that specific results should really only be considered for each individual study, and cannot be synthesized or interpreted in 'pooled' fashion; rather, a primary purpose and value of the present review is a bringing together, and integrated presentation of relevant studies for the purposes of a 'big picture' overview as well as a comprehensive resource.

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