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Decision-making ability in current and past users of opiates: A meta-analysis

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Highlights

- Opiate users are consistently impaired on a range of different aspects of decision-making
- Severe deficits were still present in opiate-users even after cessation of use
- Deficits could not be accounted for by co-morbid conditions such as polydrug use and head injury

Abstract

Opiate use is associated with deficits in decision-making. However, the impact of abstinence and co-morbid factors, like head injury and poly-substance abuse, on this ability, is currently unclear. This meta-analysis aimed to assess 1) the magnitude of decision-making deficits in opiate users; 2) whether co-morbid factors moderate the severity of these deficits; 3) whether ex-opiate users demonstrate smaller decision-making deficits than current users; and 4) whether the length of abstinence is related to the magnitude of decision-making deficits. We analysed 22 studies that compared the performance of current and ex-opiate users to healthy controls on decision-making measures such as the Iowa Gambling Task. Current users demonstrated a moderately strong impairment in decision-making relative to controls, which was not significantly moderated by co-morbid factors. The magnitude of the impairment did not significantly differ between studies assessing current or ex-users, and this impairment was not related to length of abstinence. Thus, it appears that opiate users have relatively severe decision-making deficits that persist at least 1.5 years after cessation of use.

Key words

Decision-making, opiate users, orbitofrontal cortex, abstinent, co-morbid

1. Introduction

Long term opiate use is associated with a range of problems in everyday life, including poor physical and mental health, impaired social functioning, and high unemployment rates (De Maeyer et al., 2010; De Maeyer et al., 2011; Meulenbeek, 2000). These difficulties may be linked to deficits in cognitive functioning, with a number of cognitive processes including attention, verbal memory, and executive functions shown to be impaired in both heroin and prescribed opiate users (see Baldacchino et al., 2012; and Wang et al., 2013 for reviews). Of the cognitive processes negatively impacted by opiate use, decision-making ability appears to be one of the most consistently and severely affected (Baldacchino et al., 2012).

While it is relatively well-established that decision-making is compromised in opiate users (Baldacchino et al., 2012), little is known about which individuals within this heterogeneous population are most at risk. Similarly, the trajectory of the decision-making impairment following treatment is currently unclear. In particular, it is not known whether decision-making deficits abate during periods of abstinence. Such information has the potential to improve understanding of the difficulties that opiate users face and to assist policy makers and service providers to develop effective support services.

A more detailed understanding of the relationship between opiate use and decision-making ability has been limited by the fact that most available studies in this field have relatively small sample sizes, and findings have been inconsistent, making it difficult to draw reliable conclusions. Therefore, the current study used a meta-analysis to pool and re-examine available data to investigate the temporal trajectory of decision-making deficits in opiate users, and examine the potential influence of individual factors on the severity of these deficits.

In the current context, effective decision-making refers to the ability to avoid making choices that result only in small or short-term benefits, and/or choices that carry a high risk of adverse outcomes. Studies of decision-making have shown that, compared to non-drug-using controls, opiate users tend to select options with short-terms gains but long term losses (e.g., Lemenager et al., 2011; Mintzer et al., 2005; Mintzer and Stitzer, 2002; Verdejo-Garcia and Perez-Garcia, 2007) as well as smaller immediate rewards over larger delayed rewards (i.e. delay discounting, Kirby and Petry, 2004; Kirby et al., 1999). In addition, opiate users generally choose riskier options, such as choosing a large but unlikely reward, over a smaller, but likely reward (Brand et al., 2008; Ersche et al., 2006; Ersche et al., 2005b). The magnitude of these decision-making difficulties is substantial, with medium to large effect sizes (Cohen's $d = 0.70$) reported in studies that compare opiate users to non-drug-using controls (Baldacchino et al., 2012). These decision making difficulties have the potential to impact on real life choices about money, housing, and health related behaviours (e.g. Wilson and Vassileva, 2016).

Compromised decision-making ability in this population is not surprising given that opiate use is associated with abnormalities in the orbitofrontal cortex (OFC) and associated neural networks. The OFC supports the integration of sensory and emotional inputs when calculating the value of rewards (Elliott et al., 2000; Krawczyk, 2002; Rolls, 2000; Wallis, 2007). The OFC is also part of a larger neural network involving the dorsolateral prefrontal cortex (dlPFC) and nucleus accumbens (Cohen et al., 2005; Ernst and Paulus, 2005; Krawczyk, 2002) which is particularly important for planning behaviour that leads to distant, as opposed to immediate, rewards (Bechara, 2004, 2005; Bechara et al., 2000a; Bechara et al., 2000b; Gläscher et al., 2012; Wallis, 2007). Opiate users show evidence of reduced OFC and dlPFC grey matter density (Lyoo et al., 2006; Yuan et al., 2010) and damage to white matter (Li et al., 2016; Liu et al., 2008; Lyoo et al., 2004; Qiu et al., 2013a).

Abnormal functional connectivity in OFC networks has also been found in opiate users (Cheng et al., 2013; Liu et al., 2009; Ma et al., 2010), and this has been linked to poorer decision-making performance (Qiu et al., 2011). In addition, in comparison to controls, users of different types of opiates have demonstrated either hyper- or hypo-activation of the OFC while making risky decisions during a gambling task (Ersche et al., 2006). Furthermore, reductions in dopamine and serotonin transmission systems are also evident amongst opiate users (Liu et al., 2013; Shi et al., 2008; Yeh et al., 2012; Zaaijer et al., 2015). Although the relationship between neurotransmitters and decision-making has not been specifically investigated in opiate users, abnormalities, for example in dopamine transmission, have been linked to reduced performance in other aspects of cognitive functioning in opiate users (Liang et al., 2016). Taken together, the research reveals that there are abnormalities in relation to OFC and dlPFC structure, function, and neurotransmission in opiate users that might underpin, at least to some extent, their impaired decision-making ability. Although it should be noted that the extent to which neural pathology precedes opiate use is currently unclear, a recent longitudinal brain imaging study by Li et al. (2016) showed that opiate use was associated with white matter degeneration over the period of one year. This research has confirmed that at least some measurable degeneration occurs over a period of active opiate use.

If neural pathology does contribute to the decision-making deficit in opiate users, it may be anticipated that people with a longer history of opiate use will display more severe decision-making impairments, given that structural brain changes have been shown to be greater in people who have used opiates for longer periods of time (Yuan et al., 2010; Yuan et al., 2009). However, findings from the five available studies directly addressing this relationship have been mixed. Some have reported a negative association between duration of opiate use and decision-making ability (Cheng et al., 2012; Yan et al., 2014), whereas others failed to detect such a relationship (Brand et al., 2008; Clark et al., 2006;

Lemenager et al., 2011). The limited number of these studies however, makes it difficult to make firm conclusions regarding the relationship between decision-making and duration of opiate use. It is nevertheless possible to investigate this issue further by considering other studies of decision-making in opiate users that do not *directly* investigate this relationship. More specifically, because the mean duration of opiate use across such studies varies, we were able to collate the data from these studies in the current meta-analysis and use meta-regression to further examine whether the size of the decision-making deficit varies as a function of the duration of opiate use.

Over and above opiate use duration, co-morbid conditions may also affect the severity of decision-making deficits in opiate users. For example, a large proportion of people who use opiates are also dependent on other street drugs (Astals et al., 2008). In addition, many long term opiate users have experienced neurological damage, either as a result of overdose, or physical trauma (Darke et al., 2012b). To the best of our knowledge, the potential impact of poly-substance abuse and head injury on decision-making has not been examined in this group to date (Darke et al., 2000; Loeber et al., 2012). However, in opiate users, poly-substance abuse and head injury are both associated with greater levels of impairment in other cognitive domains including memory, information processing, verbal learning, and executive and general cognitive function (Darke et al., 2012b; Darke et al., 2000; Henry et al., 2012; Loeber et al., 2012). Thus, it is possible that poly-substance abuse and head injury may also detrimentally affect decision-making. In the current meta-analysis, we compared the size of the decision-making impairment reported in studies that included only opiate users who were free of co-morbid issues, to that reported in studies that included people with poly-substance abuse and head injuries.

A further issue that lacks clarity in relation to the decision-making ability of opiate users is whether deficits in this capacity abate when opiate-users enter a period of abstinence. There is evidence that there is some recovery of neurotransmitter receptor availability and function after opiate cessation (Shi et al., 2008; Yeh et al., 2012), and therefore some improvement in decision-making might be anticipated. However, abnormal neural connectivity has been observed in abstinent ex-users (Cheng et al., 2013; Liu et al., 2009), perhaps reflecting permanent opiate-related damage to dlPFC regions, or abnormalities that predated drug use. On this basis, any improvement in decision-making would be expected to be limited. No research has yet tracked a cohort of opiate users from a period of active use through to a period of abstinence. However, some group comparison studies have reported that decision-making ability in ex-users is equivalent to that of non-drug-using controls (Zeng et al., 2013; Zhang et al., 2011), implying that recovery may occur. Contrary to this, other studies have reported that decision-making ability in ex-users is poorer than controls (Ahn et al., 2014; Clark et al., 2006; Li et al., 2013; Verdejo-Garcia and Perez-Garcia, 2007; Yan et al., 2014). In the current meta-analysis, we brought together available group comparison studies to investigate whether decision-making deficits in ex-users (relative to controls) are smaller than decision-making deficits in current users (relative to controls). Such a pattern of results would imply that some recovery of decision-making ability following abstinence does occur. In addition, we also considered the possibility that functional brain changes may occur gradually following cessation of opiate use. If this is the case, decision-making ability may not improve immediately, but may instead improve slowly over a period of time. The current meta-analysis allowed us to investigate the extent to which any recovery of decision-making ability is related to length of abstinence.

In summary, we expected that the current meta-analysis would show that (1) the magnitude of decision-making deficits (relative to controls) would be greater in studies that included opiate users with poly-substance dependence and head injury, than in studies that included only opiate users who were free from these co-morbidities; (2) the length of time using opiates would moderate the magnitude of the decision-making deficits (relative to controls), such that participants who had used opiates for longer would have more severe decision-making deficits; (3) the magnitude of the decision-making deficits (relative to controls) would be greater in current users than in ex-users; and (4) in ex-users, the length of abstinence would moderate the magnitude of the decision-making deficits (relative to controls) such that longer periods of abstinence would be associated with smaller decision-making deficits.

2. Method

2.1 Literature Search and Study Selection

This meta-analysis was conducted following PRISMA guidelines (Liberati et al., 2009; Moher et al., 2009). We searched for studies that measured decision-making and which compared a control group to a group that was dependent on opiates (*current users*) at the time of testing, and/or a group that had been dependent in the past but was now abstinent (*ex-users*). We used search terms related to opiate dependence, and specific decision-making measures commonly used in neuropsychological literature (see inclusion criteria), as well as terms related more broadly to decision-making and cognitive impulsivity. The following databases were searched: MEDLINE Complete, PsychINFO, CINAHL

Complete, Scopus, and Web of Science Core Collection. Final searches were performed in February 2016. Reference lists of included articles were screened to identify other studies that met criteria for inclusion. However, this did not result in any additional eligible studies.

2.2 Inclusion Criteria

Studies were eligible for inclusion if they: (a) included a comparison between an opiate group (*current* or *ex-users*) and healthy control group; (b) reported on participants aged between 18 and 65 years; (c) were available in full text format; (d) described quantitative results; (e) provided statistics from which an effect size could be calculated; for example, group means, standard deviations, *F*, *t*, or *X* statistics; and (f) were published in English.

Additional inclusion criteria relating to the participant groups (current users, ex-users, controls) were applied. Specifically: (a) current opiate users had to have been dependent on opiates at the time of testing; (b) current opiate users were required to have been regularly using heroin and/or an opiate substitute (such as methadone, buprenorphine or suboxone) in the month prior to testing; (c) ex-users had to have been dependent on opiates in the past; (d) ex-users had to have been completely abstinent from all drugs of abuse (except alcohol and nicotine) and not have used any opiate (including substitutes such as methadone) for a minimum average of one month.

Studies were excluded if: (a) healthy controls had a significant history of drug or alcohol use, i.e. had been diagnosed with substance dependence or abuse (although past experimental use of illicit substances was tolerated); (b) healthy controls were using illicit substances at the time of testing; or (c) participants in any of the three groups had a concurrent psychiatric diagnosis (with the exception of depression and/or

anxiety that was not being treated with medication). It is important to note that studies were *not* excluded if opiate user groups were concurrently using (or had concurrently used) other drugs, as poly-substance use is prevalent in this population (Veilleux et al., 2010). However, poly-substance *use* and poly-substance *dependence* were coded separately in analyses. Furthermore, unlike other reviews (Baldacchino et al., 2012), this meta-analysis did not exclude based on head injury as this was a variable of interest.

2.3 Decision-Making Measures

To be included in the meta-analysis, papers had to report on a decision-making measure that assessed the ability to make choices with a favourable long-term outcome, despite potential short-term losses. In the wider literature, such measures are sometimes referred to as tests of *cognitive impulsivity* (e.g. Baldacchino et al., 2012) because more impulsive individuals tend to select options that provide some immediate reward, but which also tend to have more negative long term consequences. Specifically, the tasks that were included assessed decision-making under conditions of ambiguity where outcomes are unknown or cannot be predicted (e.g. Iowa Gambling Task (IGT); Bechara et al., 1994), or under conditions of risk where probabilities may be estimated (e.g. Game of Dice Task (GDT); Brand et al., 2008; Balloon Analogue Risk Task (BART); Lejuez et al., 2002; Cambridge Gambling Task (CGT); Rogers et al., 1999). Tasks that assessed inadequate reflection before a choice is made (Information Sampling Task (IST); Clark et al., 2006) or where the value of a delayed reinforcer is worth less than an immediate (albeit smaller) reinforcer (i.e. delay discounting; Bickel and Marsch, 2001) were also included.

2.4 Data Screening and Extraction

For each study, the following participant data for opiate and control groups were extracted: number of participants in each group; duration of opiate use for both current users and ex-users; duration of abstinence for ex-users; and poly-substance use and head injury status for current users. For decision-making measures, data extracted were group means (and standard deviations) of the main outcome measure or statistics that effect sizes could be calculated from (e.g. *t, F*). The first author (KB) extracted all data, and where needed, contacted the first or corresponding author of each article to request missing information. Three attempts were made to contact authors, after which studies were excluded if necessary data could not be obtained (the authors of the following studies could not be contacted: Heyman and Dunn, 2002; Robles et al., 2011; Zhang et al., 2011). Similarly, articles were excluded if data to calculate effect sizes were not available or not retained (Fishbein et al., 2007; Petry et al., 1998; Rogers et al., 1999). Data was extracted a second time by an independent reviewer (see acknowledgements). Discrepancies between the first and second reviewers were resolved by a third independent reviewer (SM). Studies where the same data were published across multiple publications were combined to avoid reporting overlapping data (authors were contacted where appropriate to determine whether data overlapped; Ahn et al., 2014; Dai et al., 2015; Ersche et al., 2005a; Ersche et al., 2006; Qiu et al., 2011; Qiu et al., 2013a; Sun et al., 2015a; Verdejo-Garcia et al., 2007; Wilson and Vassileva, 2016).

Where articles reported more than one control group, and one of these controls groups included some illicit drug use (Rotheram-Fuller et al., 2004), only the control group that reported no drug use was included. Where articles reported on multiple groups of current opiate users, these data were collapsed into a single group (Ersche et al., 2005b; Pirastu et al., 2006; Rotheram-Fuller et al., 2004). In studies that reported on

groups that had been abstinent for an average of less than one month, these groups were classified as current users (Cheng et al., 2012; Kirby and Petry, 2004). For studies that reported baseline and follow-up testing using a behavioural measure, only the baseline values were entered into analyses (Baldacchino et al., 2015; Zhang et al., 2012). For studies that reported data for two or more decision-making measures (Ahn and Vassileva, 2016; Li et al., 2013; Upton et al., 2012), effect sizes for each separate decision-making measure were pooled to create a combined decision-making effect size estimate.

2.5 Data Analyses

The data were run using Comprehensive Meta-Analysis Version 2 software (CMA; Borenstein et al., 2005). All analyses were conducted using random-effects models, including calculations of effect sizes, subgroup and moderator analyses, and assessment of publication bias. Random-effects models were used because of known variation amongst populations (Hedges and Olkin, 1985) and because this type of modelling has a less restrictive set of statistical assumptions. Effect sizes were calculated as *Cohen's d* (standard difference in means; Cohen, 1992). Heterogeneity was assessed using the I^2 statistic, which describes the percentage of total variation across studies due to heterogeneity rather than chance (Higgins et al., 2003).

To address the question of whether longer duration of opiate use is associated with greater decision-making deficits, meta-regression was run (with a Method of Moments correction for random-effects variance). To address the questions of whether current opiate users with head injury or poly-substance dependence have greater decision-making deficits than current opiate users without these co-morbidities, subgroup

analyses using a *Q*-test for heterogeneity were run ($Q_{between}$; Borenstein et al., 2009). Studies were grouped by participants' head injury status (*yes, no*) and poly-substance dependence status (*dependent, intermittent use*), and effect sizes for each group were compared. It should be noted that it is rare that an established opiate user exclusively uses opiates (Darke, 2011). More often than not, they concurrently use other drugs (Astals et al., 2008). Therefore, all participants in the opiate groups were coded as either users of, or dependent on, other drugs. Studies that did not explicitly specify criteria regarding poly-substance dependence status or head injury status were coded in the positive (*dependent* for poly-substance use or *yes* for head injury).

To address the question of whether the magnitude of the decision-making deficit (the degree of difference from the control group) was smaller for ex-users than for current users, a subgroup analysis was run using the dichotomous predictor of *ex-users* versus *current users*. Additionally, a meta-regression was run (restricted to the studies involving ex-users) to assess the impact of years of abstinence on decision-making differences.

2.6 Publication Bias and Outliers

Publication bias was assessed by visually inspecting funnel plots and by calculating Orwin's fail-safe N (Orwin, 1983; Zakzanis, 2001). The fail-safe N (N_{fs}) value provides a hypothetical number of unpublished studies with nonsignificant results ($d \leq 0.2$) which would need to exist (outside of published literature) to call the current findings into question (Rosenthal, 1979; Zakzanis, 2001). A larger N indicates more confidence in the findings (McLennan and Mathias, 2010).

The presence and influence of outliers was assessed by examining the standardised residual for each study (Viechtbauer and Cheung, 2010). In cases where a study had a z-score of greater than ±1.96, its influence was examined using the "one study removed" method. Studies were retained in the overall analyses if they did not substantially change the overall effect size.

3. Results

3.1 Included Articles

After an initial literature search, a total of 4635 articles were found, which was reduced to 3537 articles once duplicates were removed. Their titles and abstracts were screened, and 192 articles were retained. These were examined to determine whether they met the inclusion criteria for the study. From this, 38 articles were subjected to a full-text analysis. Following full-text analysis, 22 studies were deemed to meet inclusion criteria (see Figure 1 for a summary of the screening process). Fifteen reported data for current users and 7 reported on ex-users.

[FIGURE 1 ABOUT HERE]

3.2 Participant and Study Characteristics

Table 1 presents a summary of the main characteristics of each study. Cohen's *d* represents the magnitude of the difference between the opiate and control groups on the decision-making measures. Overall, a total of 512 current users and 513 ex-users were compared to 969

controls. The majority of participants in both the current and ex-user groups were dependent on, or had been dependent on, heroin (93.46%). Most (71.23%) current users were also using an opiate substitute, such as methadone or buprenorphine. The most commonly used opiate substitute was methadone (68.77% of all opiate-substitute participants).

[TABLE 1 ABOUT HERE]

3.3 Influence of Individual and Temporal Factors on Decision-Making in Current Users

To assess the influence of outliers, the standardised residual was examined for all studies involving current users. One study was identified as an outlier in this group (Ersche et al., 2005b). However, results of the "one study removed" analysis indicated that it did not significantly influence the overall effect size and was therefore included in further analyses. Figure 2 presents the forest plot for studies assessing current users.

Fifteen studies reported data for current users. The mean age of current users was 34.55 years (14 studies). The overall effect size for the magnitude of the difference in decision-making performance between current users and controls was significant (d = -0.70, 95% CI = -0.89, -0.51, $p < .001$). There was moderate heterogeneity (I^2 = 52.07) and the fail-safe N was 37.58.

Eleven studies reported data for duration of opiate use for current opiate users. The mean duration of opiate use was 10.34 years (11 studies). There was moderate heterogeneity (I^2 = 60.63) and the fail-safe N was 25.36. Meta-regression indicated that there was no significant

relationship between years of opiate use and the magnitude of the difference in decision-making performance between current opiate users and controls: Q_{model} = 0.73, $Q_{residual}$ = 10.19, Z = 0.85, p = 0.39.

Ten studies excluded participants based on head injury, while 5 studies did not exclude opiate users based on this criterion (or did not report it as an exclusionary criterion). Subgroup comparison indicated that the magnitude of the difference between current opiate users and controls for studies which included participants with head injury (d =-0.68, 95% CI = -0.93, -0.42) did not significantly differ from studies which did not include participants with head injury (d = -0.73, 95% CI = -1.00, -0.45; $Q_{between}(1)$ = 0.07, p = 0.80). Heterogeneity was low for studies with head injury (I^2 = 28.78) and the fail-safe N was 11.88, while for studies without head injury, heterogeneity was moderate (I^2 = 61.83) and the fail-safe N was 26.25.

Eight studies reported data for current opiate users without current dependence on other substances (i.e. those coded as intermittent users), while 7 reported data for current opiate users who had other drug dependencies. Subgroup analysis indicated that there was no significant difference between studies that reported data for opiate users who *did* have a current or past poly-substance dependence (dependent: d = -0.64, 95% CI = -0.82, -0.46) compared to studies which reported data for opiate users who did not have a current or past poly-substance dependence (intermittent use: d = -0.77, 95% CI = -1.12, -0.41; $Q_{between}(1)$ = 0.40, p = 0.53). Heterogeneity was very low for studies with poly-substance dependence (I^2 = 4.63) and the fail-safe N was 15.33, while for studies without poly-substance dependence heterogeneity was moderate (I^2 = 68.81) and the fail-safe N was 22.68.

[FIGURE 2 ABOUT HERE]

3.4 Decision-Making in Ex-Users

To assess the influence of outliers, the standardised residual was examined for all studies involving ex-users. One study was identified as an outlier in this group (Zeng et al., 2013). However, "one study removed" analysis indicated that it did not appear to significantly influence the overall effect size and it was therefore included in further analyses.

Seven studies reported data for ex-users. The mean age of ex-users was 31.88 years (6 studies), and mean duration of heroin use in ex-users was 8.00 years (6 studies). The mean duration of abstinence was 0.89 years (6 studies). Heterogeneity was relatively high for studies that assessed ex-users (I^2 = 80.53) and the fail-safe N was 7.98. Figure 2 presents the forest plot for current and ex-users. The analysis of overall effect size for ex-users was significant (d = -0.43, 95% CI = -0.73, -0.13, p = .006). However, the subgroup analysis comparing studies which assessed current users to studies which assessed ex-users was not significant ($Q_{between}(1) = 2.23$, $p = 0.136$). Duration of abstinence was not significantly associated with decision-making performance: $Q_{model} = 0.15$, $Q_{residual} = 4.01$, $Z = 0.38$, $p = 0.70$. Heterogeneity was relatively high for studies reporting duration of abstinence (I^2 = 83.63) and this finding was associated with a fail-safe N of 6.48.

4. Discussion

The primary aim of this meta-analysis was to explore the influence of co-morbidities and temporal factors on the decision-making ability of opiate users. We identified 15 studies that compared the decision-making abilities of current opiate users with controls. Consistent with an earlier meta-analysis, which applied stricter inclusion criteria (Baldacchino et al., 2012), we found that the size of the deficit in decision-making in opiate users relative to non-drug-using controls was moderate to large. This confirms that when opiate users are faced with choices, they find it difficult to avoid making risky decisions, or to forgo small short-term gains in order to achieve larger gains in the long term. In real life, this pattern of decision-making behaviour has the potential to negatively impact many areas of life. Poor decision-making in the real world could play out as difficulty resisting non-essential purchases in order to save up a deposit for accommodation, or even difficulty forgoing the short-term benefits of drug use in order to maintain abstinence. Although the real world sequela of decision-making deficits in opiate users has received little research attention, a recent study by Wilson and Vassileva (2016) found that poor decision-making in opiate users predicted sexually risky behaviour, putting users at risk of contracting HIV. In other drug-using populations, poor performance on the lab-based decision-making tests considered in this meta-analysis has been linked to dropout from drug treatment services (Stevens et al., 2013; Stevens et al., 2015b) and higher rates of relapse (Stevens et al., 2015a).

Having confirmed decision-making as an area of substantial impairment in opiate users, we then assessed the influence of comorbid conditions on this ability. To do this, we included studies that reported on opiate users who had head injuries and those who had dependencies on other drugs. These co-morbidities are very common in this group, and thus including these studies (which were excluded from the previous meta-analysis; Baldacchino et al., 2012), allowed us to examine a more representative sample. We had anticipated that people with these co-

morbidities may exhibit even more severe decision-making deficits than other opiate users. However, the magnitude of the deficit did not differ significantly between opiate users with poly-substance dependence or head injury, and those without these co-morbid issues. Although relatively few studies were available for these subgroup analyses and, as such, they may have been underpowered, the magnitude of the deficit between the opiate users and controls was similar (moderate to high) regardless of whether co-morbidities were present or not. These findings therefore suggest that poly-substance use and head injury do not play a key role in influencing the level of decision-making deficit in opiate users. This raises the possibility that the observed impairment in decision-making relates more directly to opiate use, possibly through its impact on brain function (Cheng et al., 2013; Lyoo et al., 2006).

Over and above co-morbidities, the current study also investigated whether decision-making deficits are related to the duration of opiate use. More specifically, given the established links between opiate use and brain abnormalities (Cheng et al., 2013; Ersche et al., 2006; Liu et al., 2009; Liu et al., 2013; Lyoo et al., 2006; Ma et al., 2010; Shi et al., 2008; Yeh et al., 2012; Yuan et al., 2010; Zaaijer et al., 2015), and findings showing that structural brain changes are more severe in people who have used opiates for longer periods of time (Yuan et al., 2010; Yuan et al., 2009), it was anticipated that the size of the decision-making deficit might increase in line with the length of opiate use. Our meta-regression did not show such a relationship. However, the duration of opiate use reported in the 11 studies included in this analysis ranged from a mean of 7.58 years (Baldacchino et al., 2015) to a mean of 15.5 years (Lemenager et al., 2011). One possible interpretation of these findings is that brain changes may happen relatively early in the trajectory of opiate use. It is therefore possible that, if opiate use is associated with brain changes (for example, in the OFC; Ersche et al., 2006; Liu et al., 2009; Ma et al., 2010), then such neuropathology may be well established at least within 7

years, with further adverse effects being minimal. Future studies investigating the trajectory of decision-making ability across the earlier years of opiate use, such as from the first week to 7 years post-initiation of opiate use, would help clarify this issue.

The final question addressed in the current study was the impact of abstinence on the decision-making ability of opiate users. To do this, we examined decision-making deficits in ex-users who had previously been addicted to opiates, and found that abstinence from opiates (for an average of just under a year) was not associated with a smaller deficit in decision-making. More specifically, while the effect size for the difference in decision-making performance between ex-users and non-drug using controls was smaller than the effect size for the difference between current users versus controls, the difference between these effect sizes was minimal and failed to reach significance. These results suggest that decision-making deficits appear to continue even after opiate use ceases. These results are consistent with those of Mintzer et al. (2005) who found no significant difference in decision-making performance between current and ex-users on the IGT.

In addition, the duration of abstinence was not significantly associated with the magnitude of the decision-making deficit in opiate users. The period of abstinence in the available studies ranged from just over four and a half months (Sun et al., 2015b) to just over one and a half years (Ahn and Vassileva, 2016). Although previous research suggests recovery of decision-making ability may occur after extended periods of time (e.g. Zhang et al., 2011), the results of this meta-analysis suggest that, at least for the first 1.5 years of abstinence, improvements may be minimal. This is consistent with neuroimaging research conducted within the first 18 months of abstinence from opiates, which has found lasting impairments in the functional connectivity of the dlPFC and OFC, as well as reduced dopamine transmission (Cheng et al., 2013; Liu et al., 2009; Shi et al., 2008; Yeh et al., 2012). However, given that only 7 studies of ex-users were included in the analyses, and all but one of these

focused on users who had been abstinent for a relatively short time, additional longitudinal research is needed in order to gain a clearer understanding of whether, and by what magnitude, decision-making abilities improve after longer periods of abstinence.

This meta-analysis has confirmed an association between opiate use and decision-making deficits, but it cannot address the direction of causality. Indeed, there are at least two possible causal pathways that may explain the current results. First, long-term opiate use may lead to decision-making deficits via structural brain changes. While not definitive, research showing an association between the duration of opiate use and the severity of structural abnormalities (Yuan et al., 2010; Yuan et al., 2009), as well as research showing measurable white matter degeneration in opiate users over a period of a year (Li et al., 2016), is consistent with the pathway of structural brain changes. Furthermore, most (Harvey-Lewis et al., 2012; Kieres et al., 2004; Schippers et al., 2012), although not all (Harty et al., 2011), animal studies have demonstrated that decision-making impairments can be experimentally induced by administering opiates. Additional research also shows that opiate administration in animals reduces function of the OFC (Sun et al., 2006), an area known to play a significant role in decision-making (Krawczyk, 2002; Wallis, 2007). A second possible pathway, however, may also be in operation, whereby people with long-standing poor decision-making ability may be more likely to begin, and to continue using opiates (Bechara, 2005). This may be due to an overactive impulsive system which weakens the influence of the executive control system in the PFC, leading to a focus on immediate, rather than delayed, consequences of drug use (Bechara, 2005; Bickel et al., 2007). Longitudinal studies provide support for this model, with delayed discounting in childhood and adolescence predicting higher rates of drug use in adulthood (Audrain-McGovern et al., 2009; Ayduk et al., 2000). Additionally, people with developmental disorders characterised by decision-making deficits, such as Attention Deficit Hyperactivity

Disorder (ADHD; see Mowinckel et al., 2015, for a meta-analysis), demonstrate a higher propensity for drug use (Biederman et al., 1998; Biederman et al., 1995; Wilens et al., 1997). Therefore, at least for a subgroup of opiate users, poor decision-making seems to predate drug abuse. The results of the current meta-analysis are consistent with either, or indeed both, of these pathways. Clarification of their relevant influence, however, awaits further empirical research. Nevertheless, given that there was no clear indication of recovery after drug use was discontinued, and no effect of co-morbidities on decision-making differences, the results of the current study provide strong evidence that the observed decision making deficits were not merely a result of transient drug effects or of co-morbid conditions.

Although this meta-analysis provides new insights into the decision-making impairment in opiate users, results may not translate to all opiate-using groups. For example, studies were excluded from the current meta-analysis if they included opiate-users who had a concurrent serious psychiatric diagnosis. Co-morbid psychiatric disorders are common in opiate users (Astals et al., 2008) and decision-making deficits are likely to be present in these groups as well, but may be more severe (e.g. Vassileva et al., 2007). Additionally, not enough studies were available to separately analyse the effect of different types of opiates (i.e. methadone, buprenorphine, or street heroin). While some studies suggest there may be differences in decision-making ability depending on the specific opiate used (Ersche et al., 2005b; Pirastu et al., 2006), other research suggests different opiates do not differentially affect cognitive function (Darke et al., 2012a; Soyka et al., 2008). Similarly, there were too few studies available to investigate the differences between different decision-making measures, with the majority of studies assessing performance on the IGT, and only a few studies using other measures. Future research should take both the opiate type and the decision-making measures used into consideration when investigating decision-making ability in opiate users.

Taken together, the results of this meta-analysis provide clear evidence that opiate-users display decision-making deficits. Furthermore, these deficits appear to be relatively consistent, even when comparing opiate users who have other substance dependencies or head injury, to those without these co-morbid problems. Perhaps most importantly, the current research show that decision-making deficits persist even after drug use is discontinued, which may put opiate users at risk of drug use relapse (Passetti et al., 2008) and other risky behaviour (e.g. Wilson and Vassileva, 2016). Treatment programs for opiate users typically focus on the reduction, and eventual cessation of illicit drug use, and on reducing associated harms (such as crime, drug-related disease and mortality; Darke et al., 2007; Ford et al., 2011; Nicholls et al., 2010). However, the current research demonstrates that opiate users would benefit from support that goes beyond simply reducing their drug use or achieving abstinence. Even when this aim has been achieved, ex-opiate users are likely to struggle with making decisions in high-risk situations, and are likely to benefit from ongoing support. There is now a firm basis for treatment programs to consider decision-making difficulties in order to provide more relevant and targeted support to people seeking treatment for current or past opiate addiction. If decision-making is taken into account this may increase opiate users' success in remaining in treatment and maintaining abstinence, as well as achieving broader life changes.

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6. Appendix

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8. Figure captions

Fig. 1. Summary of studies excluded from the meta-analysis (with reasons for exclusion and number of studies in each category)

Fig. 2. Forest plot of all studies included in the meta-analysis. Studies involving current opiate users are presented at the top, and those involving ex-users are presented below. Each plot point represents the magnitude of the difference (effect size) between the opiate user group and control group on decision-making measures. The open diamond represents the pooled effect size for each subgroup and the closed diamond represents the pooled effect size for all studies.

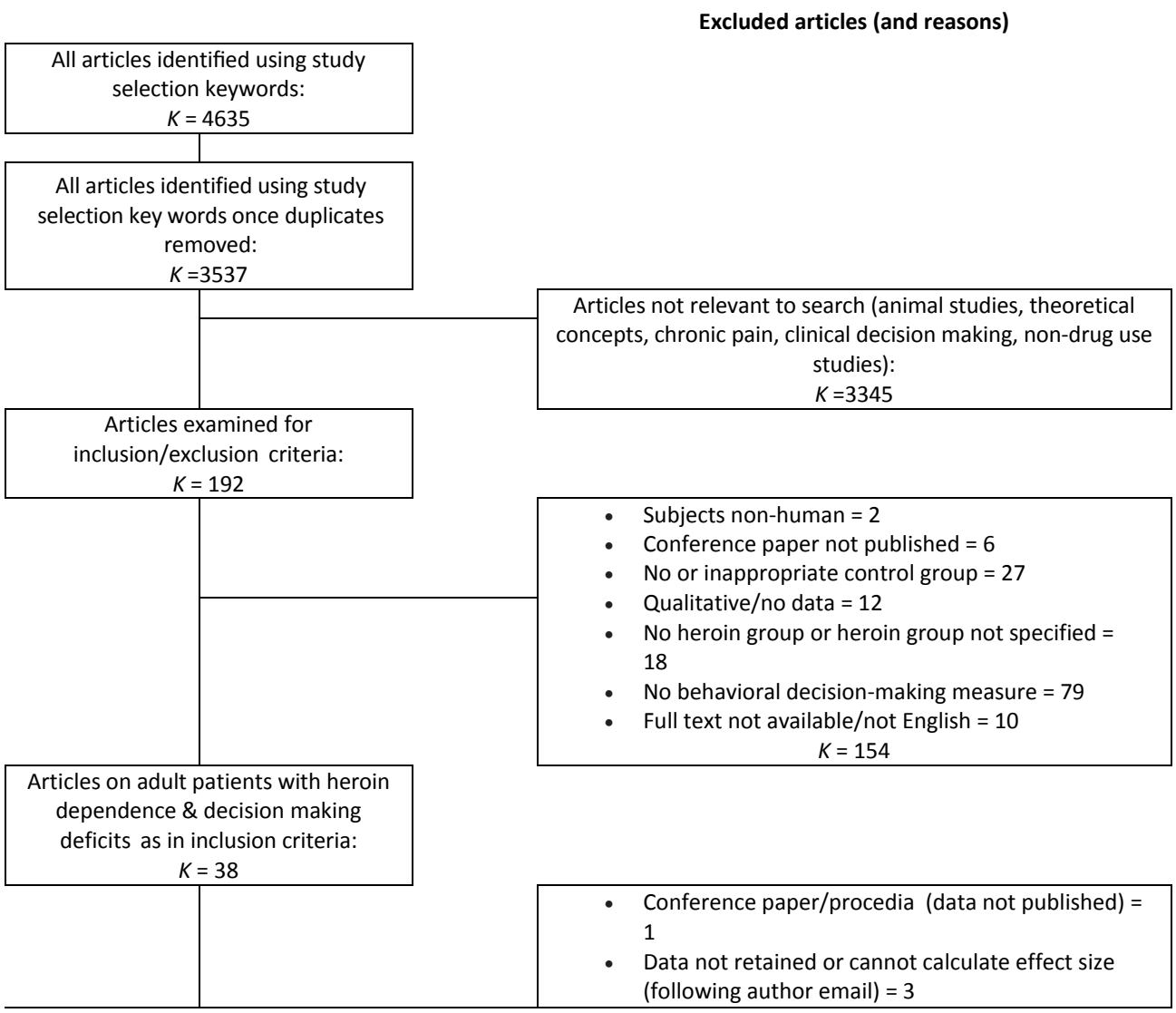
9. TablesTable 1

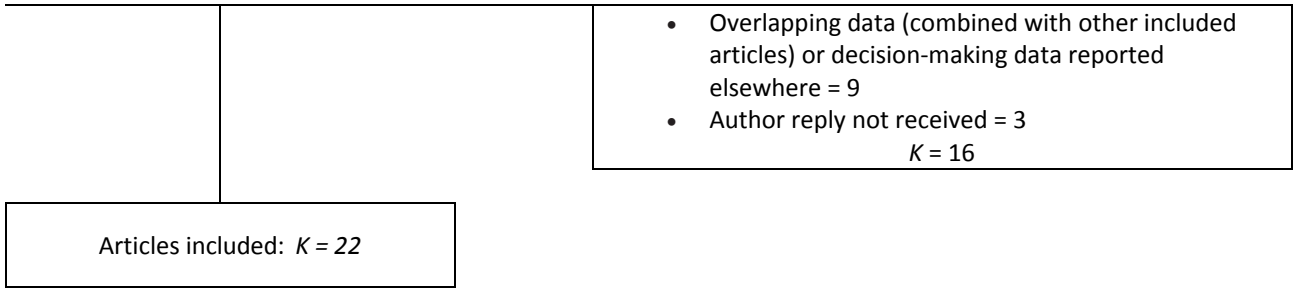
Sample characteristics of studies included in the meta-analysis and effect sizes for decision-making measures (Cohen's *d*).

				Features of opiate group				
Author (year)	**DM measure**	**Opiate group *n***	**Control group *n***	**Opiate use (years)**	**Abstinence (years)**	**Head injury included**	**Poly-substance use pattern**	**Cohen's d (95%CI)[a]**
Current Opiate Users								
Baldacchino et al. (2014)	CGT	53	28	7.58	NA	No	Dependence	-0.66 (-1.12, -0.19)
Barry and Petry (2008)	IGT	28	37	-	NA	Yes	Dependence	-0.57 (-1.07, -0.07)
Brand et al. (2008)	GDT	18	18	11.64	NA	No	Intermittent use	-1.02 (-1.72, -0.33)
Cheng et al. (2012)	DDT	56	56	7.60	NA	No	Intermittent use	-0.96 (-1.35, -0.56)
Clark et al. (2006)	IST	40	26	11.00	NA	No	Intermittent use	-0.86 (-1.38, -0.35)
Ersche et al. (2005b)[c]	CRT	39	27	9.93	NA	No	Intermittent use	0.13 (-0.36, 0.63)
Khodadadi et al. (2010)	BART	25	50	-	NA	Yes	Intermittent use	-1.08 (-1.59, -0.57)
Kirby et al. (2004)	DDT	27	44	-	NA	Yes	Dependence	-0.91 (-1.41, -0.41)
Kirby et al. (1999)	DDT	56	60	8.30	NA	Yes	Dependence	-0.55 (-0.92, -0.18)
Lemenager et al. (2011)	IGT	46	43	15.50	NA	No	Dependence	-0.53 (-0.95, -0.11)
Ma et al. (2015)	IGT	14	14	8.79	NA	No	Intermittent use	-1.58 (-2.43, -0.74)
Madden et al. (1997)	DDT	18	38	9.40	NA	No	Dependence	-1.19 (-1.79, -0.58)
Pirastu et al. (2006)[c]	IGT	48	21	14.69	NA	No	Intermittent use	-0.30 (-0.82, 0.22)
Rotheram-Fuller et al. (2004)[c]	IGT	18	10	-	NA	No	Intermittent use	-0.79 (-1.59, 0.01)

Upton et al. (2012)[b]	IGT, SGT	26	27	9.35	NA	Yes	Dependence	-0.31 (-0.85, 0.23)
Ex Opiate Users								
Ahn and Vassileva (2016)[b]	IGT, CGT, DDT, BART	44	81	7.10	1.74	NA	NA	-0.13 (-0.50, 0.24)
Li et al. (2013)[b]	IGT, DDT	124	43	6.42	1.06	NA	NA	-1.06 (-1.42, -0.69)
Sun et al. (2015b)	IGT	121	103	15.16	0.39	NA	NA	-0.47 (-0.74, -0.21)
Verdejo-Garcia and Perez-Garcia (2007)	IGT	27	36	-	-	NA	NA	-0.52 (-1.03, -0.02)
Yan et al. (2014)	IGT	58	60	7.50	1.09	NA	NA	-0.58 (-0.95, -0.21)
Zeng et al. (2013)	IGT	86	88	4.30	0.98	NA	NA	0.18 (-0.12, 0.48)
Zhang et al. (2012)	IGT	53	56	7.54	0.44	NA	NA	-0.47 (-0.85, -0.09)

[a] Represents the magnitude of the difference between the opiate and control groups on the decision-making measures, with negative values indicating poorer performance by the opiate group (compared to controls)
[b] Where more than one decision-making measure was reported, a combined effect score was computed
[c] Where more than one opiate group was reported, a combined decision-making score was computed and used for calculating effect size
Abbreviations: BART = Balloon Analogue Risk Task; CGT = Cambridge Gambling Task; CRT = Cambridge Risk Task; DM = decision-making; DDT = Delay Discounting Task; IGT = Iowa Gambling Task; IST = Information Sampling Task; NA = not applicable; SGT = Soochow Gambling Task





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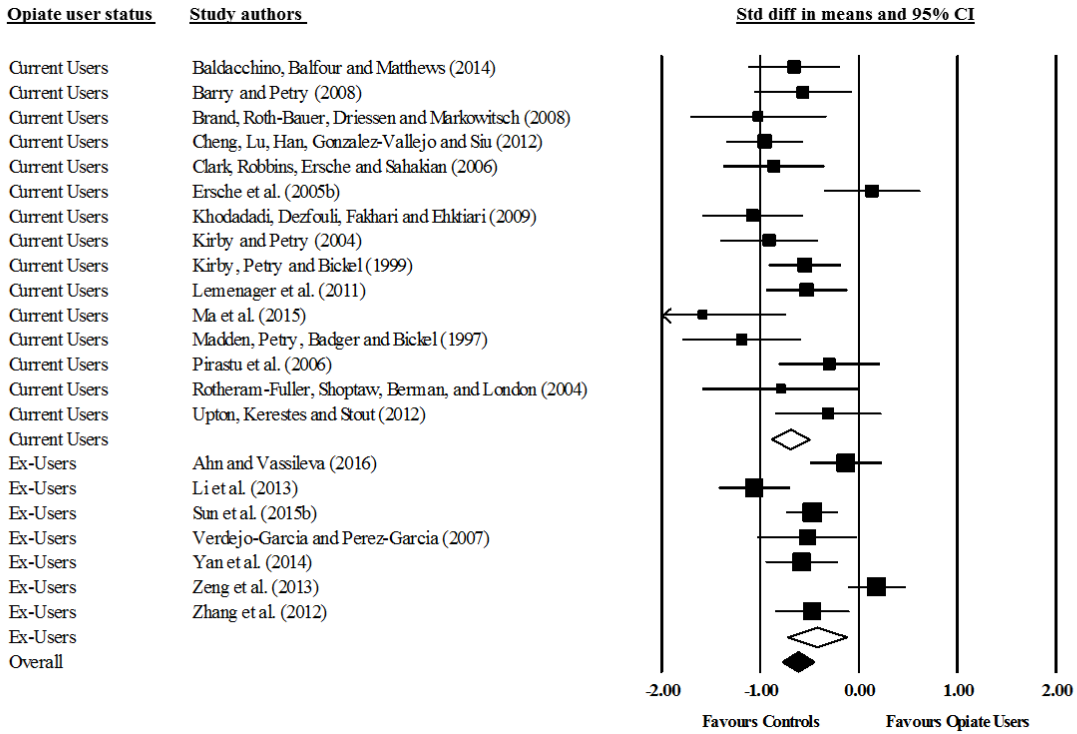

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