Effects of immediate-release opioid on memory functioning: a randomised-controlled study in patients receiving sustained-release opioids

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To cite: Kamboj, S.K. et al (2014) Effects of immediate-release opioid on memory functioning: a randomised-controlled study in patients receiving sustained-release opioids. Published online: 3 APR 2014. DOI: 10.1002/j.1532-2149.2014.498.x

Effects of Immediate-release Opioids on memory, Eur J Pain, *in press*

Abstract

Background: The effects of opioid medication on cognitive functioning in patients with cancer- and non-cancer pain remain unclear. **Method**: In this mechanistic randomised, double-blind, placebo-controlled, cross-over study of patients (n=20) receiving sustained-release and immediate-release opioid medication as part of their palliative care, we examine memory effects of an additional dose of participants' immediate-release medication (oxycodone or morphine) or placebo. Immediate prose recall and recall of related and unrelated word-pairs was assessed pre-and post-drug (placebo or immediate-release opioid). Memory for these stimuli was also tested after a delay on each testing occasion. Finally, performance on an 'interference' word-pair task was assessed on the two testing occasions since proactive interference has been posited as a mechanism for acute opioid-induced memory impairment. **Result**: Unlike previous work we found no evidence of memory impairment for material presented before or after individually-tailored, 'breakthrough' doses of immediate-release opioid. Furthermore, immediate-release opioid did not result in increased memory interference. On the other hand, we found *enhanced* performance on the interference word-pair task after immediate-release opioid, possibly indicating *lower* levels of interference. **Conclusion**: These results suggest that carefully titrated immediate-release doses of opioid drugs may not cause extensive memory impairment as previously reported, and in fact, may improve memory in certain circumstances. Importantly our findings contrast strikingly with those of a study using the same robust design which showed significant memory impairment. We propose that factors, such as depressive symptoms, education level and sustained-release opioid levels may influence whether impairment is observed following immediate-release opioid treatment.

Introduction

Ongoing moderate-to-severe pain is often effectively managed using a combination of long-acting (sustained release; SR) and short-acting (immediate release; IR) opioid formulations. This combination allows for control of background (chronic) pain as well as episodic increases in pain level that exceed a moderate intensity (breakthrough pain). Given the relatively frequent use of opioids with ambulatory, community dwelling patients – who may, for example, drive or perform other leisure or work tasks requiring intact cognitive functioning – the effects of opioids on cognition are increasingly relevant to patients and clinicians (Kendall, Sjøgren, Pimenta, Højsted, Kurita, 2010; Kurita, Lundorff, Pimenta, Sjøgren, 2009).

The effects of opioids on memory performance in clinical populations remain poorly understood because of a paucity of well-controlled studies (see Kendall et al., 2010; Kurita et al., 2009). The limited existing research suggests that ongoing SR opioid treatment leaves many areas of cognitive performance intact (Kendall et al., 2010; Kurita et al., 2009). This is perhaps unsurprising given the tendency to develop tolerance to opioid effects when doses are steady. Alternatively, studies in which memory impairment has been convincingly demonstrated have involved memory testing shortly after an increase in opioid medication through dose escalation (Bruera, Macmillan, Hanson, MacDonald, 1989) or the use of IR opioid medication on top of patients' SR medication (Kamboj, Tookman, Jones, Curran, 2005). These studies support the idea that acute, reversible memory impairments in pain patients arise as a result of cumulative opioid doses. In our previous study (Kamboj et al.., 2005) we investigated the effect of 'acute-on-chronic' (i.e. SR *plus* IR) opioid on memory functioning. Delayed recall was impaired for the prose stimuli presented

after a dose of IR morphine (anterograde amnesia) as well as *before* the dose (retrograde amnesia). Other studies suggest that cognitive performance can be enhanced by opioid treatment, although these findings are generally restricted to non-cancer patients and to relatively basic attentional or executive function tasks (see Kendall et al., 2010). We are not aware of any controlled study with patients showing *improvements* in memory performance following opioid treatment.

In the current study we retain the robust experimental design of our previous study (Kamboj et al., 2005) to examine mechanisms of possible memory impairments in patients receiving SR and IR opioid medication as part of their clinical management. By manipulating task-difficulty with related and unrelated word-pairs we examined whether impairment following IR opioid is related to task difficulty (cognitive load). Alternatively, since delayed memory performance can be impaired by learning new information we examined the tendency for newly learned information to interfere with previous learning (i.e. proactive interference), an explanation we posited for previously found memory impairment following IR opioid treatment (Kamboj et al., 2005).

Method

Participants and design

A randomised, placebo-controlled, double blind, cross-over design was used to compare the effects of a single dose of IR opioid with those of a matched placebo in patients taking sustained release opioids (Kamboj et al., 2005; see Figure 1). A concurrent study examined the effects of acute-on-chronic opioids on an emotional processing task (Carroll et al., 2011), which also served as a filler task required for

the memory assessment protocol described below. The study was carried out in a palliative care clinic serving a large UK city. Data collection occurred between Oct 2008 and April 2009, at which point the study was terminated due to meeting the target for participant recruitment.

The study was approved by University College London Hospital NHS ethics committee and all participants gave written, informed consent. The inclusion criteria were as follows: clinically stable outpatients or inpatients; older than 18 years; taking a stable SR opioid medication dose for at least 48 hours with no more than two appropriate doses of IR ('break-through') opioid analgesia per day in addition to their maintenance dose; good spoken English; basic literacy; normal or adjusted to normal vision/hearing. Exclusion criteria were contraindication to the prescription of morphine or oxycodone; history of psychosis or head injury.

Participants were recruited consecutively on the basis of recommendation by the clinical team who assessed them for inclusion criteria. Only participants who were deemed able to complete both testing occasions were recommended. Twenty participants were included and completed both testing session. No participant needed to be replaced due to dropout.

Participants were tested on two occasions no less than 48 hours apart. They completed cognitive assessments immediately before and then beginning 45 minutes after a single dose of IR opioid (morphine or oxycodone) or placebo. Participants were randomly allocated to drug condition (placebo or IR opioid on the first day) and received the alternative drug treatment on the next testing occasion. The allocation

was balanced so that 50% of participants were assigned to placebo and 50% to opioid on the first testing day. No other restrictions were applied to the randomisation code. The code was generated by a computerised random number generator and held by the senior authors (HVC and SKK) who were not involved in data collection. The authors involved in enrolling and testing participants were blind to treatment assignment.

Participants received the following SR opioid treatments: Fentanyl patch (n=2), Oxycontin (n = 10), oral morphine (n = 6), morphine sulphate via a syringe driver (n = 1) and codeine (n = 1). The daily equianalgesic morphine dose of SR opioid was 137.50 $\pm$ 208.58 (mean $\pm$ SD). All participants routinely required IR doses of morphine (n=7) or oxycodone (n=13). None required more than two IR doses per day: 17 required an IR dose once or twice a day; one required IR medication once a week and two less frequently than once a week. The mean equianalgesic morphine dose of IR opioid was 31.25$\pm$46.70 mg.

Eighteen participants had cancer and two, non-malignant chronic pain. Five participants were taking psychotropic medication at the time of the study: two diazepam, two citalopram and one venlafaxine. The dose/ timing of these drugs with respect to the time of the testing session did not differ between the two testing sessions. Seventeen were outpatients and three inpatients. Inpatients were admitted for respite care or for symptom management (i.e. nausea, breathlessness, under controlled pain.). Their condition at time of inclusion was not thought to be worse than that of out-patients at the time of testing.

Procedure

Assessments were carried out in the following order.

Pre-drug Assessments

Numerical Rating Scales (NRSs) for pain and mood, and the Hospital Anxiety-Depression Scale (HADS; Zigmond and Snaith, 1983) were used as general subjective measures. Participants then completed the first word-pair learning and recall task (pre-drug word-pair list; see below) followed by a prose task from the Rivermead Behavioural Memory Test (RBMT; pre-drug story; Wilson, Cockburn, Baddeley, 1985).

Drug Administration

Participants' usual IR opioid medication at its usual dose was individually prepared by a pharmacist. In order to conceal identity of treatment across different doses, drugs were administered in liquid form and flavoured with peppermint to disguise any taste differences between the opioid and placebo. Both the researcher and participant were blind to the drug condition.

No participant took an IR dose of morphine or oxycodone in the 8 hours preceding the testing session(s).

Post-drug Assessments

Forty five minutes after taking the placebo/IR opioid participants again completed pain NRS ratings. Participants then completed a second word-pair

learning and immediate recall task (post-drug word pair list) followed by a second RBMT prose task (post-drug story). A filler task lasting 20 minutes was then completed to prevent rehearsal (this was a non-memory tasks related to facial affect recognition). Then, performance on delayed recall for the pre-drug word-pairs was followed by the post-drug word-pair lists. The RBMT stories were then both recalled (delayed recall of the pre- and post-drug stories). Finally, participants were asked to complete a final related word-pair list (interference word-pair list) using similar instructions to those used for the first and second word-pairs.

Four versions of the memory tasks were required for pre-, and post- testing in both treatment occasions. Test versions were counterbalanced across participants and testing session.

At the end of each testing occasion participants guessed which drug treatment they had received (placebo or IR opioid).

Subjective measures: pain and mood

Pain. Patients rated their current pain on 0-10 NRS (British Pain Society, 2006): (i) intensity (no pain – extreme pain) (ii) distress (not distressing at all – extremely distressing) and (iii) interference (does not interfere - interferes completely). Pain relief following the drug treatment was rated on a 0-100% rating scale.

Mood ratings. Pre- and post-drug mood was assessed using three 100mm scales assessing anxiety (calm-anxious), general mood (sad-happy) and arousal (alert-sleepy). Assessment of depression and anxiety symptoms across testing days was obtained using the HADS which consists of 14 items (seven each for anxiety and

depression symptoms) scored on a 0-3 scale. A score of ≥8 indicates clinical levels of anxiety/depression. A pain catastrophizing questionnaire was administered on the first session only but is not reported here as it was only relevant to the emotional face-processing task (Carroll et al., 2011).

Memory Assessment: Prose and word pair recall

Prose recall was assessed using the RBMT. The RBMT (Wilson et al., 1985) assesses everyday memory performance and contains four versions of a prose task, as required by our protocol. Previous studies have found prose recall to be sensitive to opioid-induced impairments (Curran et al., 2001; Kamboj et al., 2005). Standard scoring was applied with 1 point received for a correctly recalled 'idea unit' or exact synonym and half a point for partial recall or synonym (Wilson et al., 1985). Story versions were balanced across time (pre- and post-drug) and drug condition.

Word-pair recall was tested using material from Curran and Hildebrandt (1999) and Frishkoff (2007). Individual word-pairs were presented for 5s on a laptop computer using MS Power Point (2003, Microsoft Corporation, Silicon Valley, CA, USA). Participants were instructed to attend carefully to the words and read them aloud. They were told that they would be required to recall the *second* word of each pair after being cued by the first word of the pair. Each word list contained 12 word-pairs with intermingled related (n=6 words, e.g. 'letter – post' from Curran and Hildebrandt, 1999) and unrelated (n=6 words, e.g. 'bean – closet' from Frishkoff, 2007) word-pairs in each. There were three learning trials for each word-pair list and in each trial, word pair order was different (i.e. pseudo-randomly presented). After learning, participants were cued with the first word from each pair followed by a '?'

symbol and instructed to recall the second word. The final test trial served as the dependent variable in the analysis.

Four different word-pair lists (pre- and post-placebo and pre- and post-opioid), each with six different related and unrelated word pairs were used so that participants received different word lists on each testing interval (pre-placebo, post-placebo; pre-IR opioid, post-IR opioid). Version order was balanced across testing occasion.

To explore whether any impairment caused by IR opioid treatment was due to difficulties distinguishing temporal context of encoding we used two versions of an additional 'interference list' which contained 12 related word-pairs, consisting of the first words from the two previously presented related word-pair lists (i.e. the six pre- and six post-drug related words), paired with new related words (e.g. 'letter – post' becomes 'letter – envelope'). This combination was required in order to have enough stimuli for the task, although a combination of pre- and post-drug words means that this task cannot be considered a traditional 'A-B, A-C' proactive interference paradigm (*cf.* Lezak, 1995). There was only a single learning trial for this task. Correct recall, as well as the number of intrusions (responses that were words from a previously presented list) and errors (responses which were words that had not been previously presented) was recorded.

Statistical Analyses

The data were analysed using the Statistical Package for Social Sciences (SPSS, Version 20). Tests of normality were carried out prior to conducting parametric tests. Analyses involving one within-subjects factor (i.e. drug treatment: opioid versus placebo) were carried out using a paired samples t-test. Three-way ANOVA was used in tests with three within-participants factors (i.e. drug treatment: placebo and opioid, delay: immediate versus delayed, and word pair relatedness: related versus unrelated or drug treatment, trial number (1,2,3) and word pair relatedness).

Power analysis was conducted using G*Power (Faul, Erdfelder, Lang, and Buchner, 2007) with power set at 0.8 and alpha at 0.05. This indicated a sample size of n=20 was required to detect within-between factors interactions of medium to large effects (f=0.35) which was more conservative than the large effects seen in Kamboj et al., 2005. Means are presented throughout with $\pm$ standard deviations (SD) or $\pm$ standard error of the mean (SEM) as indicated.

Results

Demographics

The mean age of patients was 57.65 ± 10.16 years. They had 14.00 ± 3.03 years of education. Eight participants (40%) were employed and 12 (60%) were retired. Prior to the onset of their illness 15 participants were "skilled professionals," four were "semi skilled" and one was "unskilled."

Subjective Ratings: pain, mood and drug effects

Mood. HADS anxiety and depression scores did not change significantly over the two testing sessions (p values>0.1; Table 1). Furthermore, within session mood-VAS measures showed no main or interactive effects involving drug (placebo, opioid) or time (pre, post drug; p values > 0.1; Table 1).

Pain. Across testing occasions, pain intensity, distress and interference levels decreased significantly with time (pre- to post-; Table 2). However there were no main or interactive effects involving drug on ratings of these dimensions (all p values >0.1).

[Tables 1 and 2 about here]

Guess on treatment

Ten participants guessed their drug condition (placebo/ IR opioid) correctly on the first day and 11 correct on the second day. Eight participants correctly guessed their condition on both testing occasions. Thus blinding appeared to be achieved.

Adverse effects

No participant experienced any adverse effects on either drug treatment occasion. Based on clinical judgement there was no significant deterioration in clinical state or changes in treatment in any participant between the first and second testing sessions.

Immediate and Delayed Recall of Prose

Table 3 summarises these data.

[Table 3 about here]

Immediate prose recall. There were no main effects of drug (IR opioid versus placebo) [$F(1,19)=0.89$, $p=0.769$)] but a main effect of time (pre- versus post-drug) [$F(1,19)=6.35$, $p=0.021$] with fewer story ideas recalled post-drug following both drug treatments. There was no interaction between drug and time [$F(1,19)=0.02$, $p=0.90$].

Delayed prose recall. There were no significant main effects of drug [F(1,19)=1.28, p=0.27] or story (pre- or post-drug story[1]) [F(1,19)=3.12, p=0.094] and no interaction between drug treatment and story [F(1,19)=0.51, p=0.48].

Word-pair recall

There was no differences in learning rates between drug treatments (p>0.2).

Recall of pre-drug word pairs. Table 4 summarises drug treatment effects according to word-relatedness and test delay (immediate, delayed) on number of words recalled from the pre- (top panel) and post-drug wordlists (bottom panel). As expected, there was a main effect of word relatedness with more related than unrelated words recalled [F(1,19)=48.90, p<0.001]. There was also a main effect of test delay such that immediate recall was superior to delayed recall [F(1,19)=123.63, p<0.001].

A two-way interaction between word relatedness and delay was found [F(1,19)=10.714, p=0.004]. There was also a two-way interaction between word relatedness and drug treatment [F(1,19)=7.538, p=0.013]. However as shown in Table 4, this interaction seems to depend on worse performance in the IR opioid condition on unrelated words for delayed *as well as* immediate recall. Since the latter finding suggests baseline differences before the drug was administered (although the difference was non-significant: [t(19)=1.697, p=0.106]) the word relatedness x drug interaction is unlikely to represent a genuine effect of drug. There was no three-way interaction involving drug treatment.

[1] NB delayed recall was tested for both pre- and post drug stories in sequence.

Recall of post-drug word pairs. Likewise, for the post-drug word list, there were main effects of relatedness [$F(1,19)=26.221$, $p<0.001$] and delay [$F(1,19)=21.923$, $p<0.001$], but no other main effects or interactions.

Interference word list performance

There were 1.15 $\pm$ 1.39 prior-list intrusions after placebo and 1.70 $\pm$ 1.98 after opioid during recall of the interference list [$t(19)=1.18$, $p>0.2$].

Errors occurred at floor level: placebo: 0.65 $\pm$ 1.09, opioid: 0.60 $\pm$ 0.88. These data were not analysed further.

Participants recalled a *greater* number of words (out of 12) from the interference list after IR opioid (9.40 $\pm$ 2.28 words) than after placebo (8.1 $\pm$ 2.81 words) [$t(19)=2.41$, $p=0.026$]. This enhancement was not correlated with any pain-related or mood variables (e.g. pain relief levels, opioid dose; HADS scores: p values>0.1).

[Figure 2 about here]

Discussion

In this double-blind, randomised placebo-controlled study we examined memory functioning and factors that might contribute to memory impairment in palliative care patients receiving SR opioids after receiving an additional (non-pain-contingent) dose of their IR opioid. In particular, we examined the effects on immediate and delayed verbal memory performance of a proactive interference task and of varying cognitive load (by manipulating task difficulty with related and unrelated words). Our main findings were that IR opioid treatment did not seem to result in impairment of immediate or delayed recall of verbal material learned before IR opioid treatment (retrograde amnesic effect) or after (anterograde amnesic effect). Secondly instead of showing evidence of greater interference, IR opioid treatment was actually associated with increased recall from the interference list.

There are still a relatively small number of studies examining the effects of opioids on cognitive functioning in patients with chronic pain. Well-controlled trials are still rarer and existing studies show widely varying effects (improvement, no change, deterioration). Moreover, critical areas of cognitive functioning that are required for everyday social and occupational functioning (e.g. delayed recall) have been neglected. As such it is perhaps unsurprising that there is no agreement about which factors might account for the varying results seen across studies. Below we outline some factors that may explain this divergence, focusing primarily on differences in participant characteristics. In particular we discuss the main findings of this study (lack of effect of IR opioid on delayed and immediate episodic memory) and those reported in Kamboj et al. (2005; namely, large effects on delayed episodic

memory) to highlight potential factors that may contribute to the range of effects observed across other studies of opioids and cognition.

An absence of impairment in delayed recall for material presented after IR opioid administration (anterograde memory impairment) in the current study was somewhat surprising. While retrograde amnesia associated with opioid administration has only been reported in Kamboj et al. (2005), anterograde memory impairment seems to be a more reliable finding in 'acute-on-chronic' or dose escalation studies (Bruera et al., 1989; Kamboj et al., 2005; see also Curran et al., 2001 for an acute-on-chronic study with participants in a methadone maintenance programme). Indeed effects on anterograde memory are relatively common in studies of drugs that have a dampening effect on arousal (although such memory effects tend to be independent of arousal; see e.g. Curran, 2000).

The absence of memory impairment in this study may follow from lower levels of (cumulative) 'pre-morbid' demographic, medical and psychological risk factors among participants. Conversely, the more general effects on memory found in Kamboj et al. (2005; i.e. anterograde and retrograde impairment) may have arisen because those participants possessed a number of risk factors that were not present in the current sample. It is therefore instructive to compare participant characteristics between the current study and those in Kamboj et al. (2005), especially since both studies used the same tightly-controlled design and identical experimental material (the RBMT).

The average *age* of participants in Kamboj et al. (2005) was 65.2 years compared to 57.7 years in the current study. While a recent controlled study with healthy middle-aged and older adults showed similar impairment following IR oxycodone (Cherrier, Amory, Ersek, Risler, Shen, 2009), a large multi-site cross-sectional study found that older age was a risk factor for poorer general cognitive functioning in patients using opioids for cancer pain (Kurita, Sjøgren, Ekholm, Kaasa, Loge, Poviloniene, and Klepstad, 2011). Nonetheless, the age difference between the two studies seems insufficient to account for the differences between the two sets of results and in both cases the mean age of participants was considerably lower than that typically associated with episodic memory decline (Buckner, 2004).

Other differences between the two studies included the *mean number of years of education* received (a protective factor). In the current study participants had 14 years compared to only 11.4 in Kamboj et al. (2005). Participants in the current study also had lower average *HADS depression scores* (<7) compared to the previous study (~9). Scores of ≥8 on HADS-depression are potentially indicative of clinical disorder and major depressive disorder is itself associated with impairments in episodic memory (Burt, Zembar and Niederehe, 1995). SR morphine-equivalent doses were 190.7 mg in the Kamboj et al. (2005) study compared to 137.7 mg in the current study. Kurita and colleagues have found that high morphine-equivalent doses (>400 mg) were associated with greater cognitive impairment compared to lower (<80 mg) doses.

Baseline memory performance (pre-drug treatment performance on immediate episodic prose memory[2]) also differed in the two studies. This may have been a function of 'pre-morbid' memory ability, or a result of the aforementioned risk factors (age, SR opioid dose, education level and depression),. In Kamboj et al. (2005) baseline memory was ~7 'idea units' whereas in the current study this value was ~9 (Table 3).

Finally, participants in the current study differed from those in Kamboj et al (2005) in terms of both placebo response, and pain relief following IR opioid. In Kamboj et al (2005) we found that patients reported a significantly larger reduction in pain following IR opioid treatment, whereas in the current study there was no difference between groups in pain relief. As such, it may be that impairment in memory is only seen when there is a concomitant increase in pain relief. Such an association should be investigated in future studies.

One way to think about these differing results is in terms of 'cognitive reserve capacity,' a concept borrowed from neuropsychology and used to explain why different sets of patients with identical levels of brain pathology may or may not show neurological signs (e.g. of Alzheimer's or stroke; see Stern, 2002). Applying the simplest version of this concept to opioid-induced impairment, average *pre-morbid* cognitive reserve of patients (which depends on brain size, synaptic organisation etc) experiences additional load from chronic risk factors (e.g. depression and SR opioid treatment). These chronic factors may be sufficient for the threshold to be breached, resulting in, for example, lower baseline memory

[2] Pre-drug performance on immediate episodic prose memory (pre-placebo and pre-opioid) represents a baseline level of memory performance in the absence of additional IR opioid (but in the presence of patients' usually circulating SR opioid) that was measured in both studies

performance following IR opioid (Kamboj et al., 2005). Alternatively, additional acute load – in the form of the pharmacological effects of IR opioid – may be required for (additional) impairment to become evident (the 'acute-on-chronic' impairment seen in Kamboj et al., 2005). It is possible that neither of these conditions apply to the participants of the current study. In particular, even when cognitive load was ostensibly highest (unrelated word recall following IR opioid) there was no obvious statistical effect.

The second finding of the current study was the *enhanced* performance on the interference list following IR opioid. Reduced recall from this list (as well as prior list intrusions) after IR opioid would have indicated proactive interference. This opposite finding may therefore represent 'release from' proactive interference after IR opioid. The possibility that opioids have paradoxical memory effects has not specifically been investigated in any previous study that we are aware of. Benzodiazepines, which have more traditional amnestic effects, do produce paradoxical enhancement of memory, although this is for material presented *before* the drug is taken (Weingartner, Sirocco, Curran and Wolkowitz, 1995).

Improvements in cognitive performance in the context of opioid treatment are actually quite commonly reported. For example Haythornthwaite and colleagues found that compared to baseline, a period of treatment with long-acting opioid resulted in a marginal improvement in digit-symbol substitution performance (Haythornwaite, Menefee, Quatrano-Piacentini, Pappagallo, 1998). Opioid treatment was also associated with reductions in anxiety and hostility in that study, although the association between cognitive performance and mood/pain variables was not

reported. Other studies with non-cancer pain patients have also shown longitudinal (rather than acute) improvement with opioid treatment, especially on attentional and executive function measures (e.g. Jamison, Schein, Vallow, Ascher, Vorsanger, Katz, 2003; Rowbotham, Twilling, Davies, Reisner, Taylor, Mohr, 2003). Indeed, in a review of opioid effects on cognitive performance in non-cancer patients, Kendall et al. (2010) show that the majority of studies in fact either showed no impairment or actual improvement following opioid treatment. However, there are significant limitations in the extant research with non-cancer patients (e.g. lack of appropriate control groups and non-randomised trials). Of more direct relevance to the current study in terms of sample characteristics, Kurita et al.'s review of cognitive effects of opioids in cancer patients generally found impairment following opioid administration (Kurita et al., 2009). As such the improvement seen here is inconsistent with the majority of existing findings. Further work is required to add to the currently limited evidence on opioid effects on cognition before a clear picture can emerge regarding the conditions under which impairment and potential improvement in cognitive functioning occur.

In summary, the current study suggests that the use of IR opioid does not result in acute deterioration in memory performance, and may even be associated with specific improvements in memory in patients who also use SR opioids. We suggest that one or more 'cognitive risk factors' were absent (or protective factors were present) in the current set of participants, accounting for an absence of impairment after IR opioids. While the results suggest that under some circumstances patients may not experience memory decline after IR opioid, it should be noted that for ethical reasons we did not conduct this study in the context of breakthrough pain

(since there is a 50% chance of receiving placebo during an acute pain episode). As such, while we mimicked the clinical situation as closely as possible with regard to using the patient's usual IR opioid, at the usual dose, the effects of IR opioid use on cognition in the context of pain remains unanswered.

We suggest that future research should focus on discovering the factors that determine the occurrence of opioid-induced cognitive impairment in patient groups with characteristics that vary along the key dimensions we outlined above (mood, education levels and SR opioid levels). Controlled experimental studies with non-pain patients may be a valuable first step to determining the role of such factors, although longitudinal work (e.g. Kurita et al., 2011) is likely to be the most feasible.

Acknowledgements

The researchers would like to thank the staff and patients at the research unit and Hospice where their research was conducted for their support with this project. We also thank the two anonymous reviewers for their helpful comments on this paper. The work was entirely funded by University College London.

Author contributions

All authors contributed substantially to the project. The specific contributions were as follows. Conception: HVC, SKK, LC, AT. Design: SKK, HVC, LC, AT, LJ. Recruitment: AT, LJ. Data collection: LC, EC. Data analysis and paper writing: SKK. All authors discussed the results and commented on the manuscript.

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Effects of Immediate-release Opioids on memory, Eur J Pain, *in press*

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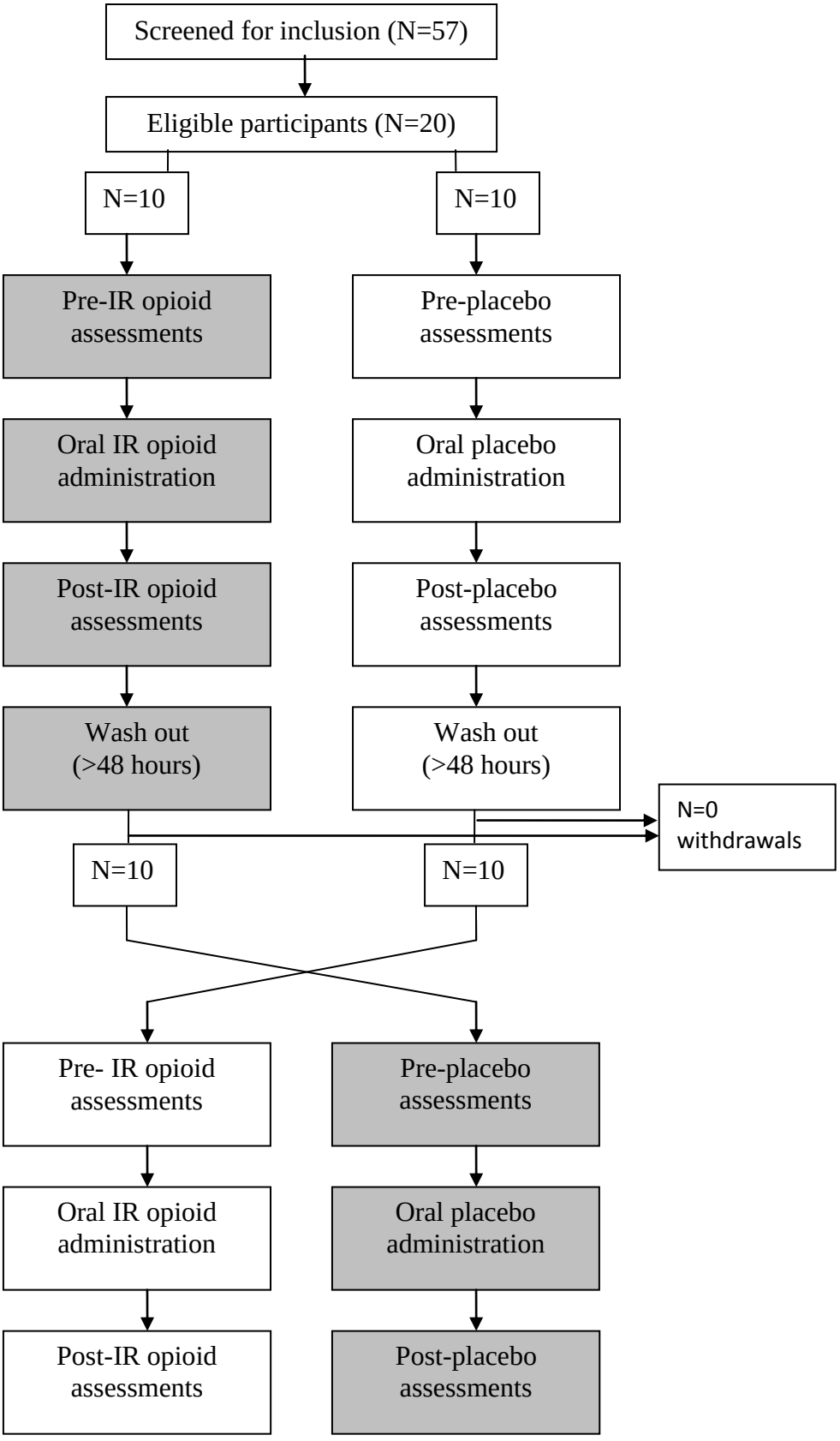

Figure 1: Protocol flow chart. Please refer to methods section for details.

Figure 2. Immediate cued recall from the interference list word-pairs (mean number of words ± SEM)

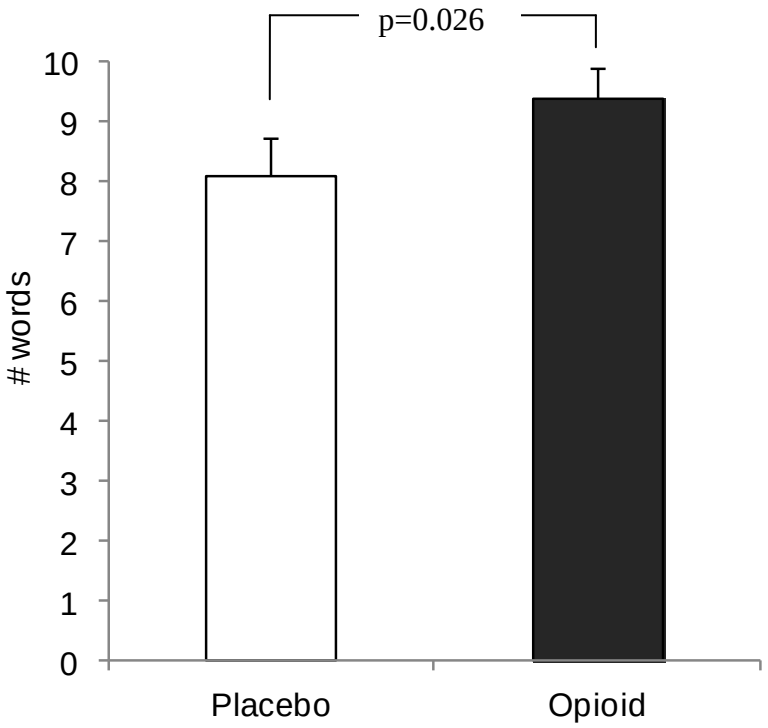

Table 1: Subjective mood (mean ± SD), pre- and post-drug treatment, except for HADs scores which were only recorded pre-drug on the two testing occasions.

	Placebo		Opioid	
	Pre	Post	Pre	Post
HADS Anxiety	7.30 ± 4.60		8.76 ± 4.60	
HADS Depression	6.55 ± 4.16		6.83 ± 4.34	
Calm-anxious	2.78 ± 2.76	2.58 ± 2.39	2.72 ± 2.68	2.25 ± 2.67
Sad-happy	6.20 ± 1.85	6.20 ± 2.28	5.83 ± 2.39	6.15 ± 2.53
Alert-sleepy	4.98 ± 2.47	5.33 ± 1.89	5.25 ± 3.16	4.68 ± 2.76

Table 2: Pain-related ratings (mean ± SD) pre- and post- placebo and opioid, except for relief which was only recorded post-drug on both testing occasions.

	Placebo		Opioid	
	Pre	Post	Pre	Post
Intensity*	3.15 ± 2.62	2.23 ± 2.44	2.85 ± 2.76	2.25 ± 2.33
Distress*	2.95 ± 2.74	2.23 ± 2.47	2.63 ± 2.83	1.60 ± 1.69
Interference**	4.78 ± 3.10	3.50 ± 2.88	5.48 ± 3.49	2.97 ± 2.19
Relief		60 ± 35.36		47.19 ± 40.25

* Main effect of time: p=0.01; ** p=0.03

Table 3: Immediate and delayed prose recall performance (mean number of idea units recalled on the Rivermead Behavioural Memory Test ± SD) pre- and post-drug on the two testing occasions.

	Placebo		Opioid	
	Pre	Post	Pre	Post
Immediate recall	9.35 ± 3.52	8.60 ± 3.62	9.55 ± 3.79	8.70 ± 3.12
Delayed recall	5.82 ± 3.41	6.75 ± 4.19	6.67 ± 4.04	6.95 ± 3.51

Table 4: Recall of the pre-drug and post-drug wordlists: Immediate and delayed cued recall of related and unrelated words presented before drug treatment (top) and the word list presented after drug treatment (bottom). Mean number of words (± SD) is presented.

	Pre-placebo wordlist		Pre-opioid wordlist	
	Related	Unrelated	Related	Unrelated
Immediate	5.70 ± 0.57	4.25 ± 1.65	5.85 ± 0.37	3.75 ± 1.89
Delayed	4.90 ± 1.17	2.70 ± 1.87	5.00 ± 0.97	2.05 ± 1.43

	Post-placebo wordlist		Post-opioid wordlist	
	Related	Unrelated	Related	Unrelated
Immediate	5.40 ± 1.14	3.75 ± 2.14	5.70 ± 0.57	3.85 ± 1.76
Delayed	5.00 ± 1.34	3.20 ± 2.07	5.10 ± 1.07	3.15 ± 1.95