Department of Psychiatry and Behavioral Sciences, Behavioral Biology Research Center, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

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Effects of Opioid Pharmacotherapy on Psychomotor and Cognitive Performance: A Review of Human Laboratory Studies of Methadone and Buprenorphine

Miriam Z. Mintzer

Summary

Opioid pharmacotherapy can provide the stability necessary to initiate lifestyle changes, obtain steady employment and function in society. Thus, a critical question is the extent to which pharmacotherapy is associated with impairment in psychomotor and cognitive performance that might affect functioning. In this article, I review human laboratory studies of the effects of the most common opioid pharmacotherapies, methadone and buprenorphine, on psychomotor and cognitive performance (both observational group comparison and experimental drug administration studies) and the effects of withdrawal from opioid pharmacotherapy on performance. I then outline some recommendations for further study in this area.

Key Words: Opioid Pharmacotherapy - Cognitive Performance - Methadone - Buprenorphine

The most widespread single intervention for opioid dependence is pharmacological treatment (primarily opioid substitution pharmacotherapy) [(1)]. An important benefit of pharmacotherapy is that it can provide the stability necessary to initiate lifestyle changes, obtain steady employment and function in society. Thus, a critical question is the extent to which pharmacotherapy is associated with impairment in psychomotor and cognitive performance that might affect functioning. In this article, I review the literature on the effects of the most common opioid pharmacotherapies, methadone and buprenorphine, on psychomotor and cognitive performance. Methadone, a long-acting

Address for reprints: Miriam Z. Mintzer, Department of Psychiatry and Behavioral Sciences, Behavioral Biology Research Center, Johns Hopkins University School of Medicine, 5510 Nathan Shock Drive, Baltimore, Maryland 21224. phone (410) 550-0529 fax (410) 550-0030, mmintzer@jhmi.edu

mu opioid agonist that is well absorbed orally, has been used as a pharmacotherapy for opioid dependence since the mid-1960's [2]. Buprenorphine, a mu opioid partial agonist and kappa antagonist, is currently used as an analgesic and as a treatment for opioid dependence [3]. As a treatment for opioid dependence, buprenorphine was first approved in France in 1995 and is currently approved in 44 countries worldwide (Dr. Rolley E. Johnson, Reckitt Benckiser, personal communication, June, 2006). Buprenorphine is approved for sublingual administration alone (Subutex) and in combination with the opioid antagonist naloxone (Suboxone; as a treatment for opioid dependence, United States, Australia and New Zealand). The buprenorphine/naloxone sublingual combination product was designed to minimize intravenous abuse of buprenorphine by dependent opioid abusers. Because naloxone has poor sublingual bioavailability [4], use of buprenorphine/naloxone tablets by the therapeutic sublingual route produces a predominantly buprenorphine effect; however, when the tablets are dissolved and injected by a dependent opioid abuser, naloxone precipitates a withdrawal syndrome [5-8]. After reviewing human laboratory studies of the effects of opioid pharmacotherapy on performance (both observational group comparison and experimental drug administration studies) and the effects of withdrawal from opioid pharmacotherapy on performance, I outline some recommendations for further study in this area.

Effects of opioid pharmacotherapy on performance: Group comparison studies

This section reviews group comparison studies that examined performance (using standardized neuropsychological batteries or other measures of cognitive and/or psychomotor performance) in methadone-maintenance patients (MMP) or buprenorphine-maintenance patients (BMP) relative to various control groups.

MMP/BMP vs. non-drug abusing controls. A number of studies have examined the performance of MMP or BMP relative to non-drug abusing controls (i.e., individuals with no known history of drug abuse). Rothenberg et al. [10] compared 12 MMP who reported having had little or no drug use (other than methadone) for at least one month prior to testing (confirmed via urinalysis), to 12 non-drug abusing controls in a similar age range. Relative to controls, MMP were unimpaired on a continuous performance test (measuring sustained attention) and actually exhibited shorter reaction times on a simple visual reaction time (RT) task. While these results provide no evidence for impairment in MMP, interpretation is somewhat limited by the absence of information about matching of the two groups on variables that might affect performance (e.g., years of education, IQ) and the limited range of measures. Grevert et al. [11] tested the memory performance of 30 MMP (and 31 patients being maintained on LAAM) at three separate timepoints: prior to beginning pharmacotherapy, and following one and three months of pharmacotherapy. A control group of 26 non-drug abusers who were matched to individual MMP participants with respect to age, gender, education, ethnicity, and employment status were tested at similar intervals. There were no significant differences among groups at any of the three timepoints and no differences

within either pharmacotherapy group at the later timepoints relative to pre-treatment performance.

Using a standardized neuropsychological battery, Darke et al. [12] examined the performance of 30 MMP relative to 30 non-drug abusers matched with respect to age, gender, and years of education. The battery included measures of premorbid intelligence, psychomotor performance, information processing, attention, short-term memory, long-term memory, and problem solving. While the groups did not differ with respect to premorbid intelligence, MMP performed significantly worse than controls on all other measures. The wide range of impaired functions is striking. However, conclusions based on this study are limited for the following reasons. First, a urine drug screen was not performed prior to neuropsychological testing. A larger proportion of MMP than controls in the study reported current use of a variety of drugs, including benzodiazepines which have well-documented performance-impairing effects [13]; thus, it is difficult to differentiate effects of opioid use from other acute drug effects. Second, there was an exceptionally high prevalence of reported head injury in the MMP group (67% compared to only 20% for controls), which may also have contributed to impaired performance in MMP. Third, testing was conducted prior to daily methadone dosing, raising the possibility that some MMP may have been in early withdrawal during testing.

Using a standardized battery developed by the Austrian Road Safety Board to assess driving-related skills (Act & React Test System), Specka et al. [14] examined the performance of 54 MMP relative to 54 non-drug abusers matched with respect to age, gender, and years of education. An important strength of the study is the relatively large sample size. MMP were impaired relative to controls on a tachistoscopic perception task, a 7-min task in which participants are asked to decide whether comparison patterns are identical to or different from target patterns, and a task requiring the capacity to integrate information under high-pressure conditions. On a choice reaction time task, MMP were faster than controls but produced more errors. On two tasks requiring visual tracking, MMP were more accurate but slower. Although a urine drug screen was performed prior to performance testing, MMP with a positive drug screen (38 out of 54 MMP) were not excluded, again making it difficult to differentiate effects of opioid use from other acute drug effects. It is important to note, however, that analyses comparing MMP with positive drug screens versus negative drug screens at the time of performance testing revealed no significant differences in performance.

In a study conducted in our laboratory [15], we examined the performance of 18 MMP relative to 21 non-drug abusers matched with respect to gender, race, age, years of education, current employment status, current reading level, and estimated IQ score. Recent drug abstinence was verified by urinalysis. MMP exhibited impairment relative to controls in psychomotor speed (as assessed by the Digit Symbol Substitution test: DSST, and computerized trail-making tests), working memory (as assessed by the two-back task, which requires participants to temporarily maintain in memory and continuously update the identity and order of the two previous letters in a sequence of

letters presented consecutively on the screen), decision making [as assessed by a computerized version of the gambling task [16-18], which requires the evaluation of long-term consequences of current decisions], and metamemory (awareness and knowledge of one's own memory). Results also suggested possible impairment in inhibitory mechanisms (Stroop color-word task), although the effect was not statistically significant. MMP did not exhibit impairment in time estimation, conceptual flexibility or episodic memory. Like the Darke et al. [12] study, these results provide evidence for impairment in a wide range of functions.

A few recent studies have specifically examined decision-making in opioid-pharmacotherapy patients. Rotheram-Fuller et al. [19] examined performance on a version of Bechara's gambling task as well as the Wisconsin Card Sorting Task (WCST; a measure of conceptual thinking and flexibility) of four groups, matched with respect to age, gender, and estimated IQ score: Methadone-maintained tobacco smokers (N = 9) and non-smokers (N = 9), and control (non-drug abusing) smokers (N = 9) and non-smokers (N = 10). While there were no significant differences among groups in WCST performance, methadone-maintained smokers (but not non-smokers) were significantly impaired on the gambling task relative to both control groups. An analysis comparing the two MMP groups indicated that the smokers were also significantly impaired relative to the non-smokers. These results are consistent with Mintzer and Stitzer's [15] findings with the gambling task, but additionally suggest that tobacco smoking may be a risk factor for decision-making impairment in MMP. Interestingly, the differences among groups disappeared when participants performed the gambling task a second time after being informed of the optimal strategy for performing the task. This pattern suggests that the impairment in smoking MMP is related to deficient strategy learning rather than to continued use of sub-optimal decision-making strategies despite awareness of consequences. Although MMP were encouraged to abstain from other drug use throughout the study, participants who reported drug use were not excluded, again making it difficult to differentiate effects of opioid use from other acute drug effects.

Madden et al. [20] and Petry, Bickel, & Arnett [21] examined decision-making in BMP. Using the delay-discounting task, Madden et al. [20] compared the rate of temporal discounting of monetary rewards in 18 BMP to that of 38 non-drug abusing controls matched with respect to age, gender, education, and estimated IQ. BMP discounted the subjective value of hypothetical delayed monetary rewards significantly more (reflecting greater impulsivity) than did controls. Petry et al. [21] compared the performance of 34 BMP to that of 59 non-drug abusing controls matched with respect to age, gender, education and estimated IQ on a version of Bechara's gambling task and on the Future Perspective Task (FTP) in which participants are asked to make predictions about the timing and ordering of future events. BMP were less likely than controls to predict events far into the future and to systematically organize events in the future on the FTP (suggesting a shortened time horizon) and were impaired relative to controls on the gambling task [consistent with the Mintzer & Stitzer [15] and Rotheram-Fuller et al. [19] studies described above]. No information is provided about the current drug use of

the BMP and no urine drug screens are reported prior to testing in these studies, again making it difficult to differentiate effects of opioid use from other acute drug effects.

MMP/BMP vs. abstinent opioid abusers. In the studies reviewed above, MMP/BMP were compared to non-drug abusing controls only, making it difficult to differentiate the effects of current opioid pharmacotherapy treatment from the effects of a history of long-term opioid abuse. This section reviews studies that included abstinent opioid abusers (i.e., individuals with a history of long-term opioid abuse, but with no current use) as controls.

Using a broad range of measures, Gritz et al. [22] examined the performance of 10 MMP relative to a control group of 10 former opioid abusers residing in an abstinence colony. The groups did not differ significantly with respect to level of education. Recent drug abstinence was verified in both groups via urinalysis. MMP were impaired relative to controls on measures of perception, story memory (assessed via recall), and memory for difficult pairs of words, but unimpaired on immediate digit span, story memory (assessed via recognition), object recognition memory, memory for easy pairs of words, and the DSST. Robinson and Moskowitz found that MMP were unimpaired, relative to abstinent opioid abusers in a similar age range, on tracking [23], divided attention, and visual search tasks [24], but that the rate of processing of tachistoscopically-presented information was reduced in the MMP [24]. Recent drug abstinence was verified in both groups via urinalysis. Gordon and Appel found that MMP were unimpaired relative to control groups of abstinent opioid abusers and non-drug abusing controls on the DSST [25] and the continuous performance task [26], and exhibited comparable or shorter reaction times relative to controls on visual reaction time tasks [27]. Recent drug abstinence was verified via urinalysis.

Davis et al. [28] examined performance on a neuropsychological battery (which included measures of attention, spatial and verbal learning, immediate and delayed spatial and verbal recall, verbal fluency, and conceptual flexibility) of 15 MMP relative to 16 abstinent opioid abusers enrolled in drug-free treatment programs and 14 non-drug abusing controls (pain management patients). The MMP and abstinent opioid abusers did not differ significantly in terms of age or estimated IQ score, and had similar histories of drug abuse. MMP were significantly impaired relative to abstinent opioid abusers on the verbal fluency task (a measure of semantic memory), and the overall incidence of impaired performance (defined as a score of two or more standard deviations below published norms on two or more neuropsychological measures) in the abstinent opioid abusers (31%) fell between that in the MMP (60%; highest incidence of impairment) and that in the non-drug abusing controls (7%; lowest incidence of impairment). The incidence of impairment was significantly different in the MMP vs. control groups, but no other paired comparisons were significant. Although the incidence of impairment in the abstinent opioid abuser group was not significantly different from that in the MMP group, the pattern of results suggests that current methadone maintenance may be associated with additional impairment over and above that associated with long-term opioid abuse. It should be noted that no information is provided about the current

drug use of the MMP and no drug urine screens are reported prior to testing, making it difficult to differentiate effects of methadone from other acute drug effects.

In our laboratory [29], we compared performance of a control group of 21 currently abstinent, formerly dependent opioid abusers retrospectively to our earlier groups (MMP and non-drug abusing controls;[15]; cf. MMP/BMP vs. non-drug abusing controls, above) on the same battery of performance measures. Consistent with the Davis et al. [28] study, performance of the abstinent opioid abusers fell between that of the MMP and non-drug abusing controls on most measures, although MMP were only significantly impaired relative to the abstinent opioid abusers on one measure (conceptual flexibility). While conclusions based on retrospective comparisons are inherently limited, it is important to note that the MMP and abstinent opioid abusers did not differ significantly with respect to gender, race, mean age, years of education, current reading level or estimated IQ, and had similar histories of drug abuse.

Verdejo et al. [30] examined the performance of 18 MMP relative to 23 abstinent opioid abusers on a neuropsychological battery that included semantic and phonological fluency, working memory, Stroop color-word, measures of processing speed, visuo-spatial attention, cognitive flexibility, response inhibition, and analogical reasoning, and the WCST. The groups were matched with respect to age, education, pre-morbid IQ, and employment status. Recent drug abstinence was verified by urinalysis. Relative to abstinent opioid abusers, MMP exhibited slower performance on tests of processing speed, visuo-spatial attention, and cognitive flexibility, as well as reduced accuracy on tests of working memory and analogical reasoning.

In a recent study, Prosser et al. [31] examined the performance of 29 MMP relative to 27 abstinent opioid abusers and 29 non-drug abusers matched with respect to gender. Recent drug abstinence was verified by urinalysis. After differences between groups in level of education and age were statistically controlled, MMP exhibited impairment relative to non-drug abusing controls on the WAIS-R Vocabulary Test (an estimate of general IQ) and on the Benton Visual Retention Test (BVRT; a test of visual memory and visual construction), but not on the Controlled Oral Word Association test (COWA; a test of verbal fluency). Interestingly, MMP did not exhibit impairment relative to abstinent opioid abusers on any measure and actually performed significantly better than the abstinent abusers on the Benton Visual Retention Test.

MMP vs. BMP. A few studies have compared the performance of MMP and BMP. As a partial agonist, buprenorphine may produce less performance impairment than methadone. Soyka et al. [32] retrospectively compared the performance of 28 BMP to that of 13 MMP who had been previously tested on the same standardized battery developed by the Austrian Road Safety Board to assess driving-related skills (Act & React Test System; ART-90). MMP exhibited significant impairment relative to BMP on a 7-min task in which participants are asked to decide whether comparison patterns are identical to or different from target patterns, a task requiring the capacity to integrate information under high-pressure conditions, and a choice reaction time task. Although these results support the hypothesis of less performance impairment with buprenorphine

than methadone, conclusions are limited due to the absence of controlled procedures and matching of patients in the two groups.

Schindler et al. [33] also used a version of the Act & React Test System (ART 2020) to examine the performance of 15 MMP and 15 BMP. Each maintenance group participant was matched with a group of non-drug abusing controls (n = 3-56; the median performance score for the control group was then compared to that of the matched maintenance group participant) with respect to age, gender, and score on a measure of intelligence. The controls were selected from a sample of people who had previously completed the ART 2020 battery. The combined MMP and BMP group exhibited significantly longer mean reaction and decision times relative to controls on a task in which participants are required to respond as quickly as possible to specific stimuli appearing in a video sequence of a city drive from the driver's perspective. In addition, the percentage of incorrect responses was significantly higher in the combined MMP and BMP group relative to controls on a 7-min task in which participants are asked to decide whether comparison patterns are identical to or different from target patterns. However, the overall number of responses and the number of correct responses were also significantly higher in the combined groups, making this result somewhat difficult to interpret. There were no significant differences between the combined group and the controls on the other four tasks of the ART 2020 battery.

Analyses comparing each pharmacotherapy group separately to controls revealed that the MMP group exhibited the same pattern of impairment relative to controls as described above in the combined group, whereas the BMP group exhibited significant differences relative to controls only on the 7-min pattern-comparison task (increases in percentage of incorrect responses only). The authors suggest that MMP (and BMP to a lesser degree) may sacrifice accuracy for speed. Although these results support the hypothesis of less performance impairment with buprenorphine than methadone, conclusions are limited for the following reasons. First, the MMP and BMP groups were not directly compared because they were not matched. Second, conclusions regarding differences between MMP and BMP are complicated by the fact that testing began 22 hours after last medication dosing; given the half-life differences between methadone and buprenorphine, it is more likely that MMP than BMP may have started to experience opioid withdrawal symptoms during the test battery, making it difficult to differentiate drug effects from early drug withdrawal effects. Third, although a urine drug screen was performed prior to performance testing, participants with positive drug screens for other drugs were not excluded, making it difficult to differentiate effects of opioid use from other acute drug effects. In fact, MMP/BMP with positive drug screens at the time of neuropsychological testing exhibited greater impairment relative to controls than those with negative drug screens.

In a well-designed study, Pirastu et al. [34] directly compared 30 MMP and 18 BMP, matched with respect to gender, age, and level of education. Consistent with the hypothesis of less impairment with buprenorphine, MMP were significantly impaired relative to BMP on Bechara's gambling task. Both MMP and BMP were impaired relative to

non-drug abusing controls on WAIS-R full-scale IQ and the Benton Visual Retention Test, and there were no differences between MMP and BMP on these measures or on the WCST.

Summary. The results of group comparisons of MMP/BMP to non-drug abusers or abstinent opioid abusers are inconsistent, with some studies showing impairment in a wide range of functions and some providing no evidence for impairment. However, two conclusions that are supported by several different studies may be drawn. First, opioid pharmacotherapy patients appear to exhibit impairment in processing information when performing at high speeds. Given Schindler et al.'s [33] suggestion that MMP (and BMP to a lesser degree) may sacrifice accuracy for speed, this conclusion is not inconsistent with reports of shorter RTs for MMP in some RT tasks [10,27]. Second, opioid pharmacotherapy patients appear to exhibit impairment in decision-making tasks. The results of a few studies that compared MMP and BMP provide some support for the hypothesis of less impairment with buprenorphine than methadone, although conclusions are limited due to methodological issues and further research is needed.

It is important to note that although group comparison studies can provide valuable, clinically relevant information about performance impairment, the conclusions that can be drawn are limited due to difficulties in differentiating impairments attributable to acute opioid pharmacotherapy dosing, chronic opioid pharmacotherapy dosing, poly-drug abuse, and other confounding factors (e.g., differences in personality, brain dysfunction, environment). Furthermore, group comparison studies do not enable differentiation of impairments that are a consequence of opioid abuse versus impairments that predated the opioid abuse. In the case of the observed decision-making deficits, it is possible that the impairment may have predated the opioid abuse and in fact even played a role in its development, rather than being a consequence of the abuse. The next section reviews experimental studies involving performance testing following administration of additional acute doses of methadone to MMP or additional acute doses of methadone or buprenorphine to dependent opioid abusers being maintained experimentally on methadone or buprenorphine respectively, and experimental studies involving performance testing following chronic administration of methadone or buprenorphine to dependent opioid abusers.

Effects of opioid pharmacotherapy on performance: Drug administration studies

Rothenberg et al. [10] found that an additional dose of up to 10 mg had no effect on simple visual RT or sustained attention in 12 MMP being maintained on 20-70 mg methadone/day. Using a battery of tasks that included finger tapping, simple visual RT, the DSST, digit cancellation (measuring sustained attention), and immediate and delayed prose recall, Curran and colleagues examined the effects of increasing MMP's daily dose. They found that increasing patients' usual dose by 33% did not affect performance in 18 MMP being maintained on 20-80 mg methadone/day [35] (mean daily dose:

44 mg; N = 18). However, administering the full daily dose on a single occasion to 20 MMP accustomed to receiving 50% of their dose at each of two occasions during the day significantly impaired delayed recall of prose in a task that has been shown to be a good predictor of everyday memory performance [36] (mean daily dose: 33 mg, range: 10-50 mg; N = 20). Acute methadone (15-60 mg) did not impair DSST or short-term memory performance in 13 dependent opioid abusers being maintained on 30 or 60 mg methadone/day [37]. Likewise, acute buprenorphine (4-16 mg intramuscular) did not impair DSST or short-term memory performance in 8 dependent opioid abusers being maintained on 8 mg sublingual buprenorphine/day [38].

Results of an early study in which 15 non-dependent opioid abusers were given doses of up to 400 mg methadone/day for a period ranging from 28 to 186 days show that following chronic methadone administration, participants performed arithmetic and coordination tests at similar rates of speed as at baseline, but with substantially more errors, and that participants' mean IQ (measured by the Otis intelligence test) decreased by 7 points relative to baseline [39]. Although this is the only published experimental study to provide information about chronic dosing effects of methadone at such high doses, results must be interpreted cautiously due to lack of statistical analysis and controlled procedures (e.g., daily dose, duration of treatment were not consistent across participants).

A study in our laboratory [40] evaluated the chronic dose-effects of buprenorphine/naloxone (8/2, 16/4, 32/8 mg, sublingual tablets) in dependent opioid abusers on performance of a broad range of psychomotor and cognitive tasks, following a period of 7-10 days of repeated dosing at each dose, in a double-blind, within-subject, crossover design. Results indicated only one significant effect: Impairment in episodic memory performance for 32/8 relative to 8/2 and 16/4 mg buprenorphine/naloxone. The absence of impairment on most measures, and the finding of impairment in episodic memory only at the highest dose (32/8 mg; doses of 4-24 mg buprenorphine are recommended for opioid pharmacotherapy) support the hypothesis of limited impairment with buprenorphine. However, these null effects should be interpreted cautiously due to the absence of a placebo condition or control group.

Lenne et al. [41] used an independent groups design to test dependent opioid abusers randomly assigned to three months of daily dosing of methadone (n = 10; mean daily dose: 48 mg) or buprenorphine (n =11; mean daily dose: 14.4 mg) on simulated driving, and found no performance differences between the methadone and buprenorphine groups. In addition, neither pharmacotherapy group performed significantly worse than a group of non-drug abusing age-matched controls. While these results support the hypothesis of limited impairment with buprenorphine, conclusions are limited by the lack of impairment in the methadone group (possibly due to the low methadone doses).

Soyka et al. [42] tested dependent opioid abusers randomly assigned to daily dosing of either methadone (N = 24) or buprenorphine (N = 22) on the Act & React Test System (ART-90) after 8-10 weeks of treatment. There were no significant differences

between the groups with respect to age, gender, level of education, or duration of opioid dependence. On a task in which the participant is instructed to press a button when a particular tone and light signal appear, participants in the methadone group produced significantly more false positive errors than those in the buprenorphine group. Although this finding provides some support for the hypothesis of less impairment with buprenorphine, it should be noted that there were no significant differences between the groups on any other measure of this large battery. In addition, the authors note that 85% of the patients were using cannabis, benzodiazepines or opioids at the time of testing but do not indicate whether the percentage differed between groups, making the results difficult to interpret.

Effects of opioid pharmacotherapy withdrawal on performance

Two studies have examined effects of withdrawal on performance in MMP [43, 44]. To our knowledge, no performance studies of withdrawal have been conducted in BMP. Using a within-subject design, Kelley et al. [43] examined the performance of 30 MMP (mean daily methadone dose: 63 mg, range: 20-120; mean duration of methadone maintenance treatment: 240 days, range: 28-874) tested 1 hr vs. 25 hr (short-term abstinence) after daily methadone dosing. The battery included measures of auditory threshold, distance perception, reaction time, time perception, digit span, and attention span. The only measure that showed an effect of time of testing was distance perception, and interpretation of the direction of the effect is ambiguous. Using an independent groups design, Lyvers and Yakimoff [44] compared performance on the WCST of a group of MMP tested 90 min after daily methadone dosing (N = 21; peak methadone effect) and a group tested 24 hr after daily methadone dosing (N = 18; short-term abstinence). For both groups, participants had to be stabilized on at least 25 mg daily methadone (mean = 66.9) for at least one month prior to testing. MMP with excessive alcohol consumption, recent use of drugs other than methadone, or a history of treatment for alcohol or non-opioid drug-related problems were excluded from participation. MMP tested 24 hr after methadone dosing exhibited significantly higher rates of perseverative responses and errors (considered measures of impaired frontal lobe functioning) relative to MMP tested 90 min after methadone dosing. There were no differences in rates of non-perseverative errors.

Withdrawal effects on performance have also been examined using opioid antagonists to precipitate withdrawal in dependent opioid abusers being maintained on methadone. The opioid antagonist naloxone administered 20 hr or more after methadone dosing in opioid abusers maintained on daily methadone has been shown to precipitate symptoms of withdrawal as assessed by standard objective and subjective scales, but not to impair performance as assessed by the DSST [7, 45-49], immediate digit recall [7, 45-49], the Maddox Wing test [50], the Stroop test, or the digit span test [51].

Recommendations for further study

Use of controlled longitudinal designs. To better understand the effects of opioid pharmacotherapies on performance, there is a need for studies that test performance in dependent opioid abusers prior to beginning opioid pharmacotherapy and at multiple timepoints during the course of opioid pharmacotherapy treatment. To our knowledge, the only study that used a longitudinal design in opioid pharmacotherapy patients was an early study that only tested memory performance [11].

Studies of high-dose methadone. The original methadone dose recommendation made by Dole and colleagues [52] was 80-120 mg/day (with some patients requiring higher doses), and the superior efficacy of doses ≥ 80 mg relative to lower doses was supported by subsequent clinical research [53, 54; cf 55]. In the 1980's, there were attempts to reduce methadone doses in many clinics, such that a survey conducted in 1988 found that the average maintenance dose was 50 mg/day or less at 68% of U.S. methadone maintenance treatment clinics [56]. Although the issue of optimal methadone dosing is still controversial [57-61], recently there has been a trend towards using increasingly higher maintenance doses. An informal national survey found that the average daily methadone dose in U.S. clinics increased from 45 mg in 1988 to 56.6 mg in 1993 to 69.4 mg in 1998 [62]. This trend is supported by recent clinical data suggesting that some patients require doses considerably higher than the 100 mg "glass ceiling" common in the 1980's (higher than 200 mg/day, and as high as 1100 mg/day in some cases; [63-65]. Increasingly higher doses may also be needed due to higher dependence levels resulting from increased purity of street heroin [66]. Given that patients being maintained on high methadone doses would be expected to be most vulnerable to performance impairment, information about the effects of methadone at high doses is now needed. Yet, with the exception of the Isbell et al. [39] study that examined effects of doses as high as 400 mg, most studies of methadone have examined low to moderate doses, and none has examined multiple doses to provide information about performance dose-effect functions.

Dose-transition studies. Opioid pharmacotherapy patients are likely to be at increased risk for performance impairment following dose escalation. Yet, to our knowledge, there are little or no data on the effects of specific methadone or buprenorphine dose increases on performance in MMP or BMP (cf. Effects of opioid pharmacotherapy on performance: Drug administration studies). Results of the few studies that have been conducted in MMP suggest that acute increases of up to 33% of the daily maintenance dose do not impair performance, whereas increases of 100% of the daily dose may impair performance [35, 36]. There is a need for studies in which the effects of specific opioid pharmacotherapy dose increases and decreases on performance are examined. Data from such studies may aid clinicians in making decisions about opioid pharmacotherapy dosing schedules, particularly in patients with additional risk factors for impairment.

Interaction studies of opioid pharmacotherapy with alcohol and benzodiazepines. Polydrug abuse is common in dependent opioid abusers. Clinical surveys indicate that

rates of alcohol and benzodiazepine abuse are particularly high in MMP [67-70]. Relative to other MMP, patients who abuse benzodiazepines and/or alcohol exhibit a more severe profile of symptoms including greater psychopathology, more HIV risk-taking behavior, poorer health and social functioning, and a greater mortality risk [67, 71-75]. For both alcohol and benzodiazepines, patients commonly report using the drugs to "boost" the effects of their daily methadone [69, 76, 77]. These clinical observations are supported by evidence that experimental administration of the benzodiazepine diazepam potentiates the subjective and physiological (e.g., pupil constriction) effects of methadone and decreases methadone self-administration in MMP [78, 79].

Given that alcohol and benzodiazepines are both known to profoundly impair performance after acute administration [cf. 13, 80], potentiation of performance-impairing effects of opioid pharmacotherapies could have serious consequences. In fact, results of an epidemiological study of suspected drug-impaired drivers indicated that all methadone-positive samples were also positive for an additional drug, raising concerns about possible functional performance impairment associated with methadone/drug combinations [81]. To our knowledge, only one laboratory study has examined interactive effects of alcohol on performance in MMP and BMP [41], and only one has examined interactive effects of a benzodiazepine [82]. As noted earlier, Lenne et al. [41] reported that opioid abusers receiving daily chronic dosing of methadone or buprenorphine were unimpaired on simulated driving relative to controls. Although acute alcohol dosing impaired simulated driving in all three groups, it did not differentially affect performance of the pharmacotherapy groups relative to controls. While these results do not provide support for the hypothesis of additive interactions between methadone/buprenorphine and alcohol, conclusions are limited by the lack of impairment in the pharmacotherapy groups in the absence of alcohol and the relatively low alcohol dose (at or below .05% blood alcohol). Linnoila and colleagues [83,84] demonstrated that another opioid, codeine, potentiated the performance-impairing effects of alcohol on simulated driving, supporting the hypothesis of additive interactions between opioids and alcohol. Lintzeris et al. [82] examined the effects of acute doses of the benzodiazepine diazepam (10 and 20 mg, placebo) in 8 MMP (mean daily dose: 55 mg) and 8 BMP (mean daily dose: 10.5 mg). Diazepam produced significant impairment relative to placebo on cancellation time, reaction time, and DSST performance in the MMP but only on cancellation time in the BMP. While these results suggest that interactive effects with benzodiazepines may be greater for MMP, conclusions are limited because the two groups were not directly compared to each other due to the small sample size.

Comparison of effects of opioid pharmacotherapy versus alcohol and other drugs. A critical issue is the extent to which opioid pharmacotherapy may be associated with functional impairment in a patient's natural environment. One way to address the issue of functional impairment is to estimate the degree of expected impairment in the environment by directly comparing the performance deficits to those produced by other drugs that have already been established as producing clinically significant impairment. The World Health Organization has recommended that alcohol (which

has a well-established association with traffic accidents and driving impairment) be used as a reference drug against which to compare other drugs with respect to performance impairment [85]. Likewise, the International Council on Alcohol, Drugs and Traffic Safety has proposed that categories of drug-induced driving-related impairment be defined in reference to specific blood alcohol levels, and researchers have recommended that alcohol be included as an active drug control when evaluating effects of drugs on driving [86]. This approach of using alcohol as a reference drug for assessing performance impairment has been employed by researchers to estimate the impairment associated with opioid analgesics and other drugs used as anesthetics during ambulatory surgical procedures [87, 88]. However, to our knowledge, it has not been applied to pharmacotherapies for opioid dependence. Some investigators have also argued for the usefulness of establishing a hierarchy of performance impairment in which drugs are ranked relative to each other with respect to their performance-impairing effects [89, 90]. Such a hierarchy was attempted with alcohol, benzodiazepines, antihistamines, caffeine, and nicotine, but opioids were not included [89].

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