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Effects of methadone plus alcohol on cognitive performance in methadone-maintained volunteers

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Abstract

Background—Methadone maintenance patients (MMP) often abuse other drugs, including alcohol. The combined use of methadone and alcohol could impair performance and daily functioning.

Objective—To examine the effects of methadone in combination with alcohol, as well as acute increases in methadone, on performance outcomes.

Method—This double blind, double-dummy, crossover study included 8 opioid dependent participants stabilized on methadone. Participants completed 6 inpatient sessions corresponding to methadone (100% or 150% of daily dose) and beverage (placebo, 0.25 or 0.50 g/kg alcohol). Performance tasks were completed before and after drug administration. Area under the timecourse values were analyzed by a 2 (methadone dose) by 3 (alcohol dose) repeated measures analysis of variance.

Results—Main effects of methadone were observed for two attention outcomes, suggesting reduced accuracy and slowed responding at an elevated methadone dose. In addition, main effects of alcohol were observed for episodic memory (false alarms and response bias) suggesting more

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Declarations of Interest

The authors have no declarations of interest.

All authors contributed in a significant way to the manuscript and have read and approved the final manuscript. Drs. Mintzer, Bigelow, and Strain designed the study. Dr. Vandrey and Dr. Mintzer wrote the protocol. Dr. Kleykamp and Dr. Mintzer managed the final data analysis, literature searches, and summaries of previous related work. Dr. Kleykamp wrote the first draft of the manuscript. All authors contributed to editing the manuscript.

impulsive responding as alcohol dose increased. No robust interactions of methadone and alcohol were observed for any outcome.

Conclusions—Study findings indicate that an acute increase in methadone (150%) and a moderate dose of alcohol (2–3 drinks) can impair distinct aspects of performance, although no significant interactive effect between methadone and alcohol was found. Future studies with larger sample sizes, larger doses, and more clinically informative tasks could expand on the present findings and further explore the cognitive consequences of concurrent opioid and alcohol use.

Keywords

methadone; alcohol; performance; cognition; attention

Introduction

Approximately 25–35% of methadone maintenance patients (MMP) continue to use and/or abuse alcohol after entering treatment^{1,2,3}. Alcohol use can worsen concomitant health conditions that are common among MMP (e.g., liver disease; hepatitis C)⁴ or increase the risk of overdose when combined with opioids^{5,6}. Both methadone and alcohol can impair aspects of cognitive performance when administered alone^{7,8}. Thus, performance-impairing effects might be exacerbated when the drugs are used in combination. This hypothesis is supported by reports that methadone-related performance impairments are potentiated by sedatives (e.g., diazepam)^{9,10}. In addition, because methadone dose increases can be associated with performance impairment^{9,11–13}, the potential exists for alcohol to cause unexpected performance impairments when a patient abuses methadone by taking more than the prescribed dose (e.g., by using diverted or take-home doses) or uses other opioids in addition to their usual methadone dose.

To our knowledge, only one study has examined the effects of alcohol on performance in patients being maintained on methadone¹⁴. Although alcohol (0.70 ml/kg) impaired simulated driving performance in that study relative to a no-alcohol control condition, it did not differentially affect performance in the methadone group relative to a non-drug using control group. Conclusions from that work are limited by the relatively low methadone maintenance dose (40 mg), absence of an alcohol placebo control, and the limited number of performance assessments. Furthermore, the study did not provide information about the effects of additional methadone on top of the maintenance dose, in combination with alcohol. Thus, the purpose of the present study was to examine the dose effects of methadone (100% and 150% of a daily dose) on a range of psychomotor/cognitive performance outcomes in combination with alcohol (placebo, 0.25 and 0.50 g/kg) in opioid-dependent volunteers maintained on methadone. In addition to informing the case where a methadone maintenance patient abuses methadone in combination with alcohol, inclusion of the 150% methadone dose provides an experimental model of illicit opioid use among MMP. A well-controlled study of MMP found opioid abstinence rates of only 27% after 26 weeks of treatment, indicating that some continued opioid use is common among MMP¹⁵. A 150% methadone increase was selected because it is the lowest dose increase that has been shown to be associated with cognitive impairment in methadone maintenance patients (without alcohol)⁹. The selected alcohol doses reflect low to moderate levels of consumption, such as

would be common in social drinking scenarios (0.50 g/kg = approximately 2–3 standard drinks).

Predictions regarding the possible interactive effects of alcohol and methadone are difficult to make given the novelty of assessing both drugs in combination. Generally speaking opioids such as methadone tend to impair aspects of attention, speed of processing and psychomotor function, rather than memory outcomes^{10, 16} (but see also¹¹, whereas alcohol more consistently impairs a variety of performance outcomes including psychomotor function, memory, and attention¹⁶. Thus, it was anticipated that methadone alone would primarily impair attention and psychomotor function, alcohol alone would impair performance less specifically. As noted, research to date is very limited regarding the effects of the drugs in combination¹⁴; however, given their impairing effects in isolation we would expect the combination of drugs to produce greater impairment than either drug alone.

Method

Participants

Participants were 8 (4 male; 5 Caucasian/3 African American) opioid dependent (Diagnostic and Statistical Manual-IV [DSM] criteria¹⁷), social drinkers, who were either enrolled in methadone maintenance at the time of screening (n = 2, 100 mg maintenance dose, duration of treatment 1 and 1.5 years, respectively) or willing to begin methadone treatment (n = 6). Recruiting and screening procedures were similar to those described previously^{18,19}. Demographic details for participants include: age (31 to 54 years; mean = 43.3), education (8 to 14 years; mean = 11.8), and estimated IQ (83 to 107; mean = 96.4; Shipley Institute of Living Scale)²⁰. Participants must have used alcohol on at least 4 days out of the past month with at least two drinks per occasion (weekly drinks ranged from 2 to 12), but not be dependent on alcohol or non-opioid drugs (except nicotine) as determined by self-report using the timeline follow-back method²¹ and DSM Checklist^{17, 22,23}. Self-reported drug use in the 6 months prior to screening included (% of participants): cocaine (50%), heroin (88%), benzodiazepines (25%), and cannabis (75%). The Johns Hopkins School of Medicine Institutional Review Board approved the study. Participants gave written informed consent and were paid for their participation.

Procedures

Participants resided on a closed 14-bed residential unit for the duration of the study. Individuals who were not in methadone treatment at study initiation (n=6) completed an initial outpatient methadone induction and then were admitted to the unit after a week of 80 mg/day of methadone (the full induction period lasted approximately 2 weeks). After being acclimated to the unit, participants completed training on the cognitive battery prior to the first experimental session, to reduce potential practice effects (i.e., participants performed the tasks within 20% of their baseline performance after completing the task at least three times). Then, all participants completed six test sessions as described below.

Drug Administration—During sessions, participants received an oral methadone solution (METH) (100% or 150% of the participant's usual daily dose: 100 mg, n = 2; 80 mg, n = 6),

and a beverage (placebo, 0.25 or 0.50 g/kg alcohol) in a double-blind, double-dummy crossover design. Beverage administration occurred over a 10 minute interval beginning approximately 75 min after METH administration to synchronize the period of peak effect for both METH and alcohol (ALC)^{24–26}. ALC doses were administered as 95% ethanol (USP, FL Distillers Co., Lake Alfred, FL) mixed with fruit juice; placebo (PL) beverage consisted of fruit juice. Beverage was administered in a covered opaque cup and consumed through a straw wrapped with an ALC-soaked band to mask olfactory and gustatory cues. In addition, 2 ml of 95% ALC was added into the straw to mask taste differences between beverages²⁷. The order of the six drug conditions (METH 100%/PL, METH 150%/PL, METH 100%/ALC 0.25, METH 100%/ALC 0.50, METH 150%/ALC 0.25, METH 150%/ALC 0.50) followed a fixed, ascending order (as listed above) for the first three participants as a precaution to determine if dosing conditions were safe and tolerated. For the remaining five participants, the order was randomly selected from a Latin Square. Session dosing replaced daily METH dosing on session days; the usual METH dose was administered on non-session days. Sessions were 4–5 days apart to allow for the elimination of alcohol and return of methadone to maintenance levels.

Task Administration—Performance tasks were completed in a designated session room on the residential unit before drug administration and at time points after drug administration (from 50 to 265 min after oral solution administration; specific time points varied across tasks). In addition, breath alcohol levels were taken immediately before methadone dosing and a total of 8 times after administration. The performance testing battery included the following tasks:^{27–33}

- Psychomotor performance (circular lights, balance, simple reaction time): The circular lights tasks involved rapid hand-eye coordinated movements in which the participant pressed a series of 16 buttons (circularly arranged around a 54-cm diameter) as rapidly as possible in response to the randomly sequenced illumination of their associated lights. A standing balance task measured the ability to stand on one leg with eyes closed; the dependent measure was the number of seconds balanced on each leg (a maximum of 60 sec across both legs). Lastly, the simple reaction time task included single asterisks that appeared on the screen at random intervals, and participants clicked on the mouse as soon as they detected each asterisk.
- Sensory Acuity (Critical flicker fusion): Participants viewed a light stimulus across a range of frequencies and used a toggle switch to indicate, on increasing and decreasing frequency curves, the points at which the stimulus appeared respectively to stop and start flickering. The transition point on the ascending curve is called the threshold of fusion, and the transition point on the decreasing curve is called the threshold of flicker.
- Attention (computerized version of the digit symbol substitution test, DSST): During the task participants responded to randomly selected digits (1–9) appearing on the computer screen using a numeric keypad to reproduce a geometric symbol associated with that digit displayed continuously at the top of the screen.

- Divided attention: The divided attention task required the participant to perform a central visual tracking task (moving a mouse cursor to track a crosshair moving on a horizontal plane in the center of the screen) and a peripheral digit monitoring task (clicking a mouse whenever a number stimulus was presented that matched a target stimulus in the periphery of the screen). These tasks were performed both separately (single task condition) and concurrently (dual task condition).
- Executive function (Trail-Making Task): The trail-making task included two computerized trail-making tests analogous to the paper/pencil Trail-Making A and B Tests. During the tasks participants connected numbers in numerical sequence (Trails A) or alternated between numbers and letters (Trails B).
- Working Memory (N-back task): The N-back task assessed the participant's ability to recall letters presented n-positions back in a continuous string of letters (i.e., 1, 2, or 3 positions back; 0-back was a non-memory control condition in which participants were simply required to respond to a specified target letter in the continuous string).
- Episodic memory (Word Memory Paradigm) Following an initial study phase, episodic memory was tested via free recall and recognition tests. During the task a list of words was presented in a study list at the beginning of the testing session, then following an 80-minute delay participants provided responses).

Data Analysis

The data were prepared for analysis by calculating percentage of pre-drug values for all outcomes except the trail-making tests (difference scores used because pre-drug error rates were 0 in some cases) and the word memory task (raw scores used because the task was administered one time only). Percent change data were calculated to account for baseline differences in performance between participants. In addition, due to repeated data collection over multiple timepoints and the varying timecourse profiles for the cognitive effects of alcohol and methadone, area under the timecourse curve (AUC) data transformation was completed for all data (except the word memory task, which was administered one time only). The AUC transformation (method of trapezoids) involves calculating values for each participant that represent the total drug exposure over time for each outcome measure. AUC values were then analyzed by a 2 (methadone dose; METH 100% and 150%) by 3 (alcohol dose; PL, 0.25g/kg ALC, and 0.50 g/kg ALC) repeated measures analysis of variance (ANOVA). The only exception was the n-back task which was analyzed by analysis of covariance (ANCOVA) with the non-memory control condition as a covariate and memory load (1-back vs. 2-back) as an additional factor. Pairwise comparisons were only conducted for variables with significant F-values (Fisher's LSD)³⁴. Comparisons for significant interactions were limited to the following pairs (due to sample size limitations on statistical power): METH100%/PL vs. METH100%/0.50 (to test the effect of alcohol at the participant's usual methadone dose), METH150%/PL vs. METH150%/0.50 (to test the effect of alcohol at an increased methadone dose), and METH100%/PL vs. METH150%/PL (to test the effect of a methadone dose increase). Alpha was set at 0.05.

Results

Blood alcohol levels and descriptive data for all performance outcomes are shown in Table 1. Significant findings are described below. No significant effects were observed for circular lights, balance, simple reaction time, DSST, trail-making, free recall, or n-back.

Methadone alone

Two outcomes yielded significant main effects of METH: attention/dual task proportion correct (a measure of accuracy) [100% mean= 94.19, SE=2.95, 150% mean= 84.39, SE=3.33; $F(1, 7) = 3.98$; $P<0.05$] and attention/single task tracking moves (a measure of speed) [100% mean= 98.87, SE=1.62, 150% mean= 93.30, SE=1.57; $F(1, 7) = 3.98$; $P<0.05$]. For both outcomes, the higher dose of METH was associated with greater impairment (decreased proportion correct/accuracy and increased tracking moves/slowing). No other significant main effects of METH were observed for any other outcome.

Alcohol alone

Two outcomes yielded significant main effects of ALC: recognition memory false alarms [PL mean= 0.20, SE=0.04, 0.25g/kg mean= 0.33, SE=0.03, 0.5g/kg mean= 0.36, SE=0.04; $F(2, 14) = 6.19$; $P<0.05$] and response bias [PL mean= 0.39, SE=0.11, 0.25g/kg mean= 0.04, SE=0.11, 0.5g/kg mean= -0.04, SE=0.12; $F(2, 14) = 6.10$; $P<0.05$]. Note that lower scores for response bias indicate increased responding of “yes” when asked to indicate whether a test word had been studied previously. Thus, lower scores indicate less discretion in distinguishing words that were actually studied from new words, and thus indicate impaired recognition memory. For both outcomes, the highest dose of alcohol was associated with greater impairment. No other significant main effects of ALC were observed for any other outcome.

Methadone and alcohol interaction

A significant interaction of methadone and alcohol was observed for the critical flicker fusion task [see Table 1 for means; $F(2, 14) = 3.98$; $P<0.05$]. However, pairwise comparisons revealed no significant differences among means. No other significant interactions were observed for any other outcome.

Discussion

The present study modeled a potential scenario of methadone or illicit opioid abuse in methadone patients with concurrent consumption of a low-moderate dose of alcohol, in a residential laboratory setting that controlled for the use of other drugs (e.g., heroin, cocaine, benzodiazepines). To our knowledge, this is the first study to examine effects of additional methadone in combination with alcohol on cognitive performance in opioid-dependent volunteers maintained on methadone. Overall, no clear interaction between methadone and alcohol could be discerned for any outcome (a significant interaction for sensory acuity showed no significant pairwise comparisons). In contrast to these null effects, a subset of attention and episodic memory outcomes were impaired when methadone and alcohol were examined separately. The elevated dose of methadone (150% of normal dose) decreased

accuracy on a dual task attention task (when competing responses were required for task completion) and slowed responding during a single task tracking task. These findings correspond to previous research showing psychomotor and attentional impairment after an acute, 150% dose of methadone⁹ (i.e., reaction time and DSST performance). Thus, an acute increase in methadone associated with treatment changes or opioid abuse is likely to impair attentional performance. Such impairments have the potential to negatively influence everyday behaviors such as driving or interacting effectively with others.

In contrast to methadone alone, alcohol in isolation did not influence attention outcomes, but did impair aspects of episodic memory with increased rates of false alarms and response bias for the episodic memory task as alcohol dose increased. These findings correspond to a previous study demonstrating alcohol-related impairment for MMP taking their usual dose of methadone relative to a no-alcohol condition, although that study found impairment on a simulated driving task and did not specifically measure episodic memory¹⁴ The alcohol-related impairments observed in the present study could be interpreted as reduced inhibitory control (i.e., inability to inhibit a “yes” response) suggesting a tendency towards impulsive behavior. Such impulsivity would have the potential to influence driving and other behaviors adversely. However, this speculation requires further testing using more refined measures of inhibitory control and/or impulsivity. Also, with regards to alcohol, it is important to note that the mean blood alcohol level in the present study was only 0.035% when impairment was observed. Thus, these results demonstrate that, independent of methadone dose, alcohol can impair performance at relatively low doses (approximately 2–3 drinks), as recently demonstrated in a driving simulator study of moderate alcohol use.³⁵

Some important study limitations should be considered when interpreting the present results. First, it should be noted that we chose to model illicit opioid use or abuse in the present study by increasing the methadone dose, as the most straightforward and logistically simple design in MMP. However, a design in which a shorter acting opioid agonist is administered in combination with alcohol could be used in future studies to provide additional clinically relevant information. In addition, given the relatively low dose of alcohol used in the study, future studies with higher alcohol doses (and in heavier drinkers) might better model concurrent alcohol abuse. Lastly, and potentially most importantly, the limited number of significant findings across multiple study outcomes could indicate that within the low-to-moderate dose ranges studied here there is only limited performance disruption related to the single or combined use of these drugs. However, the small sample size of the study provides only limited statistical power, especially when examining complex drug interactions across complex cognitive outcomes where effects are likely to vary between participants. Thus, the limited or null interaction effects observed in the present study could be due to type II error rate (failing to detect an effect that truly exists).

In sum, the present study provides preliminary evidence that additional use of an opioid by MMPs, as modeled by an acute increase in methadone dose, is associated with attentional impairment, and that moderate alcohol use is associated with episodic memory impairment/impulsive responding. The clinical relevance of these findings is qualified in that the tasks used to measure performance tasks were experimental in nature, and they lack normative standards that could allow these results to be compared to healthy, non-drug using persons.

However, the presently used tasks are important for parsing apart the specific cognitive processes associated with drug impairment, although they do not readily translate to everyday functioning. Thus, future studies examining the interaction of methadone and alcohol could expand on the present findings by assessing performance on more clinically applicable tasks that model everyday functioning (e.g., driving simulator) using a larger sample of MMP and higher drug doses.

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Table 1

Outcomes as a function of drug condition

	100% METH PL		150% METH PL		100% METH 0.25g/kg ALC		150% METH 0.25g/kg ALC		100% METH 0.50g/kg ALC		150% METH 0.50g/kg ALC		Pairwise Comparisons	
	Mean	(SE)	Mean	(SE)	Mean	(SE)	Mean	(SE)	Mean	(SE)	Mean	(SE)		
Blood Alcohol Level (g/dl)	0.000	(0.00)	0.000	(0.00)	0.013	(0.00)	0.015	(0.00)	0.035	(0.00)	0.036	(0.00)	–	
Psychomotor Performance														
Circular Lights (# responses)	100.13	(4.84)	95.53	(2.10)	96.95	(2.09)	97.95	(2.46)	95.50	(4.01)	93.89	(3.51)	–	
Balance (# sec balanced)	109.49	(19.87)	113.47	(17.61)	133.08	(35.10)	110.14	(16.82)	104.62	(13.68)	103.77	(13.91)	–	
Simple Reaction Time (sec)	115.35	(6.91)	107.87	(3.38)	110.88	(3.77)	119.03	(6.40)	107.88	(3.85)	106.10	(6.52)	–	
Sensory Acuity														
Critical Flicker Fusion (threshold)#	96.12	(1.65)	96.87	(1.47)	97.32	(2.00)	91.41	(2.11)	92.14	(2.71)	94.45	(0.93)	NS	
Attention														
DSST														
Number of trials attempted	103.98	(6.30)	93.93	(1.78)	93.57	(3.26)	93.01	(4.05)	97.71	(4.86)	93.63	(3.53)	–	
Proportion correct	102.13	(3.36)	100.08	(1.58)	101.48	(1.99)	97.14	(3.43)	100.06	(0.95)	99.17	(1.17)	–	
Divided Attention														
Dual Task														
Tracking moves (speed)	98.80	(1.04)	96.87	(2.42)	94.69	(1.33)	94.42	(4.60)	95.32	(2.18)	86.92	(4.18)	–	
Tracking accuracy	88.21	(2.78)	84.21	(2.30)	84.36	(3.95)	81.36	(5.47)	85.81	(4.69)	75.94	(5.79)	–	
Mean RT (monitoring)	113.25	(12.30)	115.32	(6.02)	122.13	(6.38)	114.84	(9.42)	113.89	(7.16)	130.68	(14.75)	–	
Proportion correct (monitoring)*	93.05	(1.52)	88.35	(4.93)	89.82	(3.65)	88.68	(5.75)	99.70	(7.94)	76.15	(6.12)	M:100>150	
Single Task (tracking)														
Tracking moves (speed)	98.00	(1.47)	93.52	(2.16)	96.24	(1.83)	94.57	(2.67)	102.36	(4.16)	91.80	(3.47)	M:100>150	
Tracking accuracy	90.60	(2.71)	86.52	(2.63)	87.75	(2.72)	85.91	(5.09)	89.08	(4.21)	81.21	(3.95)	–	
Single Task (monitoring)														
Mean RT	120.32	(5.67)	115.94	(4.42)	114.19	(6.48)	122.81	(6.18)	119.81	(9.50)	120.37	(8.74)	–	
Proportion correct	97.12	(2.07)	96.67	(2.12)	101.68	(2.23)	94.32	(3.49)	92.61	(2.19)	92.27	(3.48)	–	
Executive Function														
Trail-making A														
Running time (sec)	0.51	(3.81)	0.95	(3.41)	1.59	(3.49)	–0.21	(2.82)	–3.56	(3.76)	2.68	(4.61)	–	

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	100% METH PL		150% METH PL		100% METH 0.25g/kg ALC		150% METH 0.25g/kg ALC		100% METH 0.50g/kg ALC		150% METH 0.50g/kg ALC		Pairwise Comparisons
	Mean	(SE)	Mean	(SE)	Mean	(SE)	Mean	(SE)	Mean	(SE)	Mean	(SE)	
Total Errors	-0.19	(0.27)	0.06	(0.42)	0.06	(0.31)	0.94	(0.42)	-0.13	(0.23)	0.44	(0.27)	-
Trail-making B													
Running time (sec)	3.50	(3.76)	7.86	(5.52)	-8.34	(10.32)	16.33	(12.44)	-0.64	(9.26)	-0.55	(6.72)	-
Total Errors	0.81	(0.25)	-0.06	(0.22)	0.44	(0.27)	0.31	(0.19)	-0.25	(0.49)	0.44	(0.54)	-
Working Memory													
Median RT	100.64	NA	108.04	NA	106.20	NA	111.94	NA	109.44	NA	112.25	NA	-
d' (sensitivity)	83.35	NA	86.30	NA	86.12	NA	71.86	NA	85.30	NA	84.31	NA	-
Episodic Memory													
Recognition task													
Hit rate	0.58	(0.09)	0.53	(0.08)	0.59	(0.08)	0.63	(0.08)	0.67	(0.07)	0.67	(0.08)	-
False alarm rate *	0.19	(0.05)	0.22	(0.05)	0.30	(0.04)	0.30	(0.04)	0.36	(0.06)	0.43	(0.06)	A: PL<0.25,0.50
d' (sensitivity)	1.22	(0.31)	0.94	(0.28)	0.81	(0.23)	0.95	(0.22)	0.93	(0.24)	0.71	(0.26)	-
C (response bias) *	0.38	(0.17)	0.40	(0.16)	0.16	(0.13)	0.09	(0.15)	-0.07	(0.16)	-0.18	(0.17)	A: PL=>0.50
Gamma (metamemory)	0.35	(0.13)	0.39	(0.12)	0.34	(0.14)	0.18	(0.11)	0.25	(0.13)	0.19	(0.14)	-
Free Recall													
Number recalled	7.88	(3.41)	4.75	(0.88)	4.50	(1.25)	4.00	(1.41)	5.38	(1.99)	4.25	(1.19)	-

Note:

* significant main effect,

significant interaction, A=alcohol, M=methadone, PL=placebo. Analyzed data were percentage of predrug values for all except the trail-making task (difference scores; predrug error rates were 0 in some cases) and the word memory task (raw scores; task was only administered at one time point, during the expected time of peak effect); for all data except the word memory task, area under the curve (AUC) values were calculated for each participant by the method of trapezoids. Data for the n-back task are adjusted ANCOVA means (for which no SEs are available) with the non-memory control condition as covariate, collapsed across memory load (1-back and 2-back conditions).