

Hot and cold executive functions in pure opioid users undergoing methadone maintenance treatment: Effects of methadone dose, treatment duration, and time between last methadone administration and testing

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Abstract

Context: Methadone maintenance is a standard treatment for opiate-dependent individuals. However, deficits in cognitive functioning have been associated with this treatment.

Aim: This study aimed to determine the dose and treatment duration-related effects of methadone on executive functions.

Setting and Design: Pure male opioid users with no considerable history of other drug abuse, undergoing methadone maintenance treatment (MMT) were recruited from a major government-run de-addiction center.

Methods: Hot executive functions including decision-making and emotion recognition were assessed using the Iowa gambling task and Ekman faces test, whereas cold executive functions including working memory (WM), cognitive flexibility, and response inhibition were assessed using n-back, Wisconsin card sorting test, and the GO/NOGO task, respectively.

Statistical Analyses Used: Descriptive statistics, Pearson's correlation coefficients, and multiple regression analysis were used to test the hypotheses of the study.

Results: Methadone dose and length of MMT were found to be associated with greater impairment in executive functions. Impairment in cognitive performance was also found to be inversely related to time since dosing. Regression analyses revealed that methadone dosage and time since dosing accounted for a significant proportion of the variance in cognitive flexibility, while the total amount of methadone administered was able to predict deficits in WM, methadone treatment duration predicted psychomotor speed, and time since dosing predicted decision-making ability.

Conclusions: To keep cognitive impairment at a minimum, methadone dose and treatment duration will have to be customized considering the history of opiate abuse so that impairment attributable to long-term opiate use may be differentiated from acute methadone dosing.

Key words: Cognitive impairment, executive functions, methadone dose, methadone maintenance

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Introduction

Opiate dependence is a serious health hazard worldwide, and in most countries, methadone substitution treatment is the standard evidence-based treatment for opiate-dependent individuals. Methadone maintenance treatment (MMT) is a comprehensive treatment program that involves the prescription of methadone as an alternative to the opioid on which the individual was dependent. Research has demonstrated that once the individual is stabilized at the right dose, long-term methadone prescription alleviates withdrawal symptoms, blocks euphoric effects, and reduces craving associated with opioids.^[1] Methadone has also been reported to improve physical and mental health, social functioning, and quality of life.^[2] In terms of benefits for society, MMT has the potential to reduce illicit drug use, criminal activity, and incidence of HIV infection.^[3-7]

Despite the potential benefits of MMT, some studies have indicated that chronic opiate use, whether naturally occurring or synthetic, is associated with several neuropsychological impairments both during active use and after a period of abstinence.^[8] The deficits in neuropsychological functioning reported for individuals undergoing MMT are prominent in what are called executive functions.^[9] Executive functions are defined as a set of higher-order abilities including initiation, inhibition, cognitive flexibility, shifting, switching, planning, speed of processing, and decision-making involved in the employment, monitoring, and regulation of goal-directed behaviors.^[10] Recent evidence suggests that these functions can be classified into two broad domains: (i) Cold executive functions that demand greater use of rationality and logic, such as working memory (WM), cognitive flexibility, response inhibition, and planning and (ii) hot executive functions that involve emotion, such as decision-making and emotion perception.^[11]

Methadone-associated cognitive impairment in both hot and cold executive functions such as attention, WM, processing speed, decision-making, and cognitive flexibility has been documented.^[12-22]

However, a number of studies have failed to replicate these findings, rendering them inconsistent. Rapeli suggested that cognitive deficits during early abstinence from opioid dependence are partly transient and related to neural dysregulation in the prefrontal cortex induced by withdrawal.^[22] Gruber claimed that MMT results in a significant improvement in the cognitive performance of opiate-dependent subjects.^[23] Soyka assessed the cognitive functioning of individuals during MMT and reported significantly improved concentration and executive functions after 8–10 weeks of stable methadone substitution treatment.^[17]

Studies of the effects of methadone dosing on the neuropsychological functioning of current methadone

users have also produced mixed results. Curran found that while a single dose of methadone may induce episodic memory impairment in patients who have a history of heroin use, methadone administered in divided doses does not.^[24] Similarly, Lyvers and Yakimoff found that patients in early methadone withdrawal made selectively more perseverative responses and errors than did recently dosed patients.^[25] Higher methadone doses were associated with worse cognitive function during peak state in two studies, while other studies have shown improved performance.^[26,27] For instance, Bracken compared short- and long-term methadone-maintained individuals.^[12] Their study showed that methadone-maintained individuals performed poorly on tasks of psychomotor speed and selective attention/impulsivity, but that performance improves with longer-term treatment, suggesting that with longer methadone maintenance, deficits in cognitive task performance may begin to normalize. Some researchers reported no association between methadone dose level and cognitive performance.^[28,29] More recently, Rass studied the effects of time relative to dosing and maintenance dose level on cognitive performance in methadone-maintained individuals. This study revealed that the effects of maintenance dose were mixed. Higher dose resulted in worse performance on attention and WM, but improved performance on executive function.^[16]

Given that the main aim of MMT for opioid-dependent individuals is to increase treatment retention and opioid abstinence, improve psychosocial functioning, and facilitate treatment of other co-morbid medical and psychiatric conditions, a thorough analysis of any dose-dependent impairment in the cognitive functioning of individuals undergoing MMT is essential so as to facilitate comprehensive rehabilitation of opioid-dependent individuals.^[30] However, with inconsistent research findings, the question of whether MMT, and in particular, the dosage and duration of methadone are associated with better or worse cognitive functioning is still unresolved and calls for further investigation.

Some researchers have speculated that the mixed effects of methadone dosage and duration on executive functions may be related to the plasma levels of methadone, which vary as a function of the time elapsed since the methadone dose. For example, performance in WM and cognitive flexibility tests were worse during peak levels of methadone (a couple of hours after methadone administration) whereas Lyvers and Yakimoff reported better executive cognitive performance among recently dosed individuals (90 min after methadone dose) than those in early withdrawal (24 h after methadone dose).^[16,17,25,31] These findings imply that methadone plasma levels must be considered while studying executive function deficits and improvements in patients undergoing MMT.

The intent of the present study was to explore the association of methadone dose, consumption, and treatment

duration with cognitive functioning in opiate-dependent individuals. As most previous studies reported findings based on data from poly substance users, in this study, individuals without a considerable history of other substance abuse were recruited. Furthermore, we studied the effect of total amount of methadone consumed by each participant (dose per day \times duration of treatment \times number of administrations per month), as we suspected, it might affect the cognitive functions of individuals undergoing MMT. Based on inconsistent findings from prior studies, we hypothesized that performance on the measures of executive functions would correlate with time since dosing, albeit with no certainty regarding the direction of the association.

Methods

Ethics statement

This research protocol was approved by the Ethics Committee of the University of Mohaghegh Ardabili, Iran, and informed consent was obtained from the study participants prior to administration of the questionnaires.

Participants

Thirty-four right-handed opioid-dependent men were recruited from two outpatient MMT clinics in Shahrekord, Iran. They were interviewed by two experienced clinicians, and individuals were included if they were pure opioid users in accordance with Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 criteria, on a stable dose of methadone in the last 2 months, able to read, and not used any substance other than methadone in the last 2 weeks. Individuals were excluded if they had hepatitis C or HIV virus infection, a history of head trauma, a neurodegenerative disease, or a psychiatric disorder based on DSM-5 criteria. All participants received detailed information about the study protocol, gave written informed consent, and were paid as reimbursement of travel costs incurred for participation in this study.

Forty-one males undergoing MMT volunteered to participate in the study. Seven participants were excluded as they failed to meet the inclusion criteria: One had a history of severe psychosomatic disorder including temporary blindness and paralysis, one had a seizure in the last month, one had Parkinson's disease, one had active hepatitis C virus, one reported having hallucinations, one had administered methadone during testing, and one did not complete all tests. Participants had no difficulty in completing the tests. Data were collected by the second author over a period of 60 days. The final sample comprised 34 opiate-dependent males undergoing MMT. Each participant completed the tests in one session with a 3 min break between tests. It took approximately two and a half to three hours for each individual to complete all the tests. The order of test administration was counterbalanced.

Neurocognitive measures

Decision-making

Decision-making was assessed with the Iowa gambling task (IGT).^[32] The aim of this task is to simulate real life decision-making using uncertainty, rewards, and penalties. In the game, players are given four decks of cards and an endowment of fake money. Players are instructed to select cards one at a time and try to lose the least amount of money and win the most. Turning a card results in a reward or a penalty, large in decks A and B and small (half as much) in decks C and D. Playing from decks A and B leads to an overall loss, whereas playing C and D leads to an overall gain. Players do not know how many cards will be in the decks. After encountering a few losses, normal participants begin to avoid the decks with large losses. The main dependent variable on this task was the net score on each block of the task. Net scores were calculated by subtracting the number of disadvantageous choices (decks A and B) from the number of advantageous choices (decks C and D) for each block. The test took 20–25 min to administer.

Emotion perception

The Ekman faces test is a computer task assessing recognition of facial emotional expressions. A series of 36 stimuli featuring faces displaying 6 basic emotions such as anger, disgust, fear, happiness, sadness, and surprise (six emotions, six faces each) were presented. The number of correct identifications for each of the six emotions and the total correct identifications were the main dependent variables from this task.^[33] There was no time limit for the test, but all individuals completed the test within 40 min.

Cognitive flexibility

The Wisconsin card sorting test (WCST) was used to assess cognitive flexibility, presenting the task graphically on a computer screen. This task is thought to measure the ability to switch one's attentional set as task demands change. The WCST entails matching stimulus cards with one of the four category cards, in which the stimuli are multidimensional according to color (C), shape (S), and number (N), each dimension defining a sorting rule. By trial and error, the participant has to settle a preordained sorting rule given just the feedback ("right" or "wrong") on the screen after each sort. Two types of errors are possible, perseverative errors, in which the participants make a response in which they persist with a wrong sorting rule and nonperseverative errors.^[34] In this study, perseverative errors were used as dependent variables. The test took between 30 and 40 min to administer.

Working memory

A blocked WM task based on the classical "n-back" WM paradigm was used.^[35] Subjects viewed a sequence of single digits that were presented in random order at a rate of 1/s. They were instructed to determine if the current

digit was the same as the one displayed two (2-back target) steps before in the sequence. There were 120 trials. 5457872393161 is an example of the sequence of digits for 2-back trial highlighting the four 2-back targets. Button press events were used to record WM accuracy (the relative difference between hits and false alarms) and reaction times.^[35-37] The test took 25–30 min to administer.

Response inhibition

The GO/NOGO task was used to determine response inhibition in participants. The traditional, simple format of this task allows for examination of response inhibition under conditions in which other cognitive/behavioral processes are minimized. The traditional GO/NOGO task design involves only two stimuli: A Go stimulus and a No-go stimulus. Participants are instructed to respond rapidly, generally with a button press, to the presentation of GO stimuli only, and response inhibition is measured by the ability to appropriately withhold responding to NOGO stimuli. Typically, the task is weighted toward GO stimuli, to build up a prepotent tendency to respond, thereby increasing the inhibitory effort necessary to successfully withhold responding to NOGO stimuli.^[38,39] In this study, a blue square was used as a “GO” clue and a red square as the “NOGO” clue. Reaction time on GO trials, commission errors, and inability to refrain from pressing the button when seeing NOGO clue, which show impulsivity, were used as dependent variables. Administration of the test took 20–25 min.

Results

Table 1 represents demographic information and descriptive statistics. Participants were 34 pure opioid-dependent individuals aged between 22 and 45 (m = 33.6, standard deviation [SD] = 4.5) with an average of 9.3 years (SD = 2.9) of education. Mean years of opioid abuse was 6.94 (SD = 5.23). Of the 34 participants, 33 participants (97%) smoked. Mean duration of MMT was 23.18 (SD = 13.80) months, and the average dosage of methadone administration was 12.62 mg (SD = 6.91). The total amount of methadone administered was 1316.05 mg (SD = 1096.65).

Table 2 presents the scores of the participants on the various tests of executive functions. Correlations among methadone dose, MMT duration, total amount of methadone consumed, and the time (in hours) elapsed between last methadone administration and test procedure with participants’ scores on cold executive function tasks including WCST, 2-back, and GO/NOGO tasks are presented in Table 3.

As Table 3 shows the number of perseverative errors which shows cognitive flexibility deficits correlate significantly with methadone dosage, the total amount of methadone

Table 1: The demographic and methadone use characteristics of the participants

	Minimum	Maximum	Mean	SD
Age (years)	22.00	45.00	33.61	4.57
Education (years)	3.00	16.00	9.29	2.89
Opioid use (years)	00	18.00	6.94	5.22
Methadone dose (mg)	10.00	175.00	60.10	34.55
MMT duration (months)	3.00	72.00	22.17	13.80
Total amount of methadone administered (mg)	105.00	5250.00	1316.05	1096.65
Last administration of methadone (hours)	0.50	24.00	8.16	6.12

MMT=Methadone maintenance treatment; SD=Standard deviation

Table 2: Mean scores of the participants on the various measures

Tests	Minimum	Maximum	Mean	SD
Wisconsin				
Perseveration errors	1.00	20.00	7.29	4.30
2-back	16.00	34.00	26.50	4.21
GO/NOGO				
Reaction time	297.00	543.00	373.88	50.88
Commission errors	00	21.00	2.61	3.58
IGT cards				
A	15.00	34.00	25.32	4.61
B	20.00	38.00	26.76	4.72
C	15.00	33.00	23.26	4.51
D	13.00	37.00	24.67	5.10
Net score	-32.00	21.00	-2.26	12.28
Emotion perception				
Sad	1.00	5.00	3.82	1.05
Surprise	1.00	6.00	4.76	1.20
Happy	4.00	6.00	5.32	0.72
Fear	00	6.00	2.85	1.63
Angry	00	5.00	2.32	1.19
Disgust	1.00	6.00	3.26	1.42
Total emotion perception	14.00	30.00	22.23	3.5

SD=Standard deviation; IGT=Iowa gambling task; GO/NOGO=???

Table 3: Correlation coefficients showing the association of cold executive function scores with methadone dose, treatment duration, total methadone consumed, and time elapsed between last methadone dose and testing

	Methadone dosage	MMT duration	Total amount of methadone consumed	Time between last methadone dose and testing
WCST	0.534**	0.049	0.501**	0.384*
2-back	-0.370*	-0.398*	-0.569**	-0.052
GO/NOGO reaction time	0.244	0.419*	0.434*	0.041
GO/NOGO commission errors	-0.009	-0.218	-0.072	-0.050

MMT=Methadone maintenance treatment; WCST=Wisconsin card sorting test

that had been consumed, and the time between last methadone administration and test performance which is directly related to methadone concentration level in plasma. However, deficits in cognitive flexibility failed to correlate with MMT duration. The number of correct answers in 2-back task which represents WM capacity was significantly and negatively associated with both methadone dosage and MMT duration and the total amount of methadone consumed. There is no correlation between WM capacity and the time between last methadone dosing and test performance. Participants' reaction time in GO/NOGO positively correlated with MMT duration and total amount of methadone used. However, there was no correlation between reaction time with methadone dosage and last time of methadone administration. The number of commission errors in GO/NOGO task did not correlate with methadone usage.

Table 4 represents correlation coefficients among hot executive functions and methadone dosage, MMT duration, total methadone consumption, and time since dosing.

As shown in Table 4, IGT net score did not correlate significantly with methadone dosage, MMT duration, or total amount of methadone consumed. However, a point biserial correlation between methadone-maintained patients who made good and bad decisions and time between last methadone dosing and testing were highly significant. This indicates that the greater the time between dosing and testing, the better the decisions made. In other words, it can be assumed that as methadone concentration level in plasma

decreases, participants chose more advantageous cards and made more safe decisions. Methadone dosage correlated negatively with an accuracy of anger perception and total emotion perception scores. MMT duration positively correlated with interpretations of sadness and happiness and total scores of emotion perception. Total methadone consumption correlated significantly with the accuracy of fear perception. Time since dosing failed to correlate with emotion perception.

Finally, regression analyses were run to predict each of the indices of executive function using methadone dose, total amount of methadone consumed, duration of MMT, and time since dosing as predictors. Results demonstrated that methadone dose ($\beta = 0.534, t = 3.58, P < 0.01$) and time between dosing and testing ($\beta = 0.319, t = 2.307, P < 0.05$) accounted for 28.6% and 10% of the variance in cognitive flexibility deficits indicated by perseveration errors, respectively; total amount of methadone consumed accounted for 32.3% of the variance in WM deficits; duration of MMT ($\beta = 0.569, t = -3.911, P < 0.01$) explained 18.8% of the variance in psychomotor speed; time since dosing and testing ($\beta = 0.384, t = 2.353, P < 0.05$) accounted for 14.8% of the variance in decision-making ability; and methadone dose ($\beta = -0.433, t = -2.718, P < 0.05$) accounted for 18.8% of the variance in emotion perception.

Discussion

The present study used a single sample design to investigate the association of methadone dose, duration of MMT, total amount of methadone consumed, and time elapsed since last dose with hot and cold executive functions in methadone maintenance patients.

Analysis of the effects of methadone dose revealed that among the cold executive functions, deficits in cognitive flexibility correlated positively with methadone dose indicating that individuals who were receiving a higher dose of the drug revealed greater deficits. WM scores correlated negatively with methadone dose implying that higher doses of the drug are associated with greater deficits in WM. Indices of response inhibition (reaction time and commission errors) did not correlate significantly with methadone dose suggesting that neither psychomotor speed nor impulsivity is affected by the strength of the dosage of the drug. As regards hot executive functions, methadone dose was associated with deficits in emotion perception, especially the perception of anger, but not with decision-making.

Such mixed effects of methadone dose on cognitive performance are consistent with the literature. Studies exploring the association of methadone dose and cognitive

Table 4: Correlation coefficients showing the association of hot executive function scores with methadone dose, treatment duration, total methadone consumed, and time elapsed between last methadone dose and testing

	Methadone dosage	MMT duration	Total amount of methadone consumed	Time between last methadone dose and testing
IGT net score	-0.049	-0.212	-0.098	0.384*
Emotion perception: Sadness	-0.299	0.452**	0.090	0.059
Emotion perception: Surprise	0.025	0.137	0.121	0.074
Emotion perception: Happiness	-0.192	0.384*	0.169	-0.045
Emotion perception: Fear	-0.122	-0.286	-0.344*	-0.078
Emotion perception: Anger	-0.416*	0.324	-0.155	-0.048
Emotion perception: Disgust	-0.291	0.263	-0.058	0.294
Emotion perception: Total score	-0.433*	0.360*	-0.118	0.104

MMT=Methadone maintenance treatment

performance have produced controversial results. For example, Kelly found higher doses of methadone therapeutically more effective whereas Loeber found higher doses of methadone associated with worse cognitive performance and Darke found no association between methadone dose and cognitive performance.^[27,28,40] Impaired performance of methadone-maintained patients in WM is consistent with the results of previous studies.^[14,41] However, the fact that methadone dose did not correlate with psychomotor speed and decision-making is inconsistent with these studies. Evidence for deficits in attention, WM, memory, and executive function in chronic opioid abusers have been reported.^[22] It is difficult to differentiate whether the cognitive dysfunctions seen in the present sample are a consequence of acute methadone dosing or reflective of the effect of previous opioid use.

Duration of MMT correlated significantly with deficits in WM and psychomotor speed (longer reaction time), but not with deficits in cognitive flexibility. Exposure to MMT was also associated with better emotion perception, especially with the perception of sadness and happiness. That is, the longer a person is exposed to MMT, the greater the deficits in WM and the slower his cognitive performance, but the better his ability to perceive emotions.

Furthermore, total amount of methadone consumed by the patient undergoing MMT was significantly associated with deficits in cognitive flexibility, WM, psychomotor speed, and deficits in the perception of fear.

Multiple regression analyses imply that while the strength of methadone dose may affect cognitive flexibility, as time since dosing increases, decision-making improves. Furthermore, the total amount of methadone consumed impacts WM adversely, and duration of MMT tends to slow down mental processing.

Taken together, these findings imply that while MMT may be beneficial in reducing opiate dependence, suppressing withdrawal symptoms, and blocking euphoric effects of opioids, methadone dose level used should be maintained at an optimal level so as to prevent the occurrence of deficits in cognitive flexibility, and WM and the duration of MMT should be tailored so that cognitive functioning does not worsen. When exposure to MMT gets longer, WM gets even more deficient, and cognitive performance is slowed although emotion perception may improve. While the length of exposure to MMT may have to be controlled, it is the total amount of methadone consumed by the individual during therapy that worsens executive functions. Findings indicate that methadone dose affects cognitive performance. Rapeli suggested that cognitive deficit during early opioid abstinence may be associated with neural dysregulations in the prefrontal cortex induced by withdrawal and that rapid recovery of cognitive function

during opioid abstinence seems possible.^[22] In fact, some studies have shown that cognitive performance improves with stabilization of methadone dose.^[12,42] However, in the present study, longer MMT was associated with worse cognitive performance. This inconsistency of the findings from this study with previous studies may be attributable to differences in sample characteristics. In the current study, only pure opiate users were recruited whereas the previous studies reported findings for poly substance users. Curran suggested that the acute effects of methadone on the cognitive functioning of patients in MMT with a long history of opiate abuse can be avoided by administering divided doses of methadone.^[24] Longitudinal studies are needed to confirm these suggestions.

Time since dosing correlated positively only with deficits in cognitive flexibility and decision-making, but not with deficits in WM or response inhibition. That is, as time since dosing increased, individuals showed worse performance when they have to simultaneously attend to multiple sources of information and make decisions. In other words, it can be inferred that methadone does affect cognitive flexibility and decision-making positively so that cognitive performance during peak sessions may be facilitated by methadone. Cognitive performance differences as a function of session (peak vs. trough) have been reported in previous research. Baewert found that methadone-maintained patients made more perseverative errors on the WCST when time since dosing was 24 h (trough session) than when it was 90 min (peak session).^[43] Findings of the current study appear to confirm these previous findings as the performance of the individuals in this study tended to worsen as time since dosing increased. Performance on the IGT showed that subjects tended to make more advantageous decisions as time since dosing increased. These findings confirm those of previous studies that cognitive performance in methadone patients may be a function of time elapsed since last dosing.^[16,25,43] Using a within-subjects design and comparing the performance of MMT patients in peak and trough sessions, Rass reported worse performance during the peak session.^[16] The findings of the present study that MMT patients performance changed as a function of time relative to dosing is consistent with these previous results. That is, it appears that decision-making is a function of the concentration of methadone in blood plasma.

In sum, it appears that regardless of dosage, methadone administration is associated with impairment in the decision-making ability of individuals, but as time since dosing increases, decision-making appears to improve. The strength of methadone dose is directly associated with deficits in WM and cognitive flexibility, whereas it is not associated with psychomotor speed or impulsiveness. However, as treatment continues, deficits in WM and psychomotor speed continue to worsen whereas treatment

duration does not worsen cognitive flexibility. The total amount of methadone consumed is directly associated with deficits in WM, cognitive flexibility, psychomotor speed, and emotion perception. These results underscore the importance of manipulating methadone dose and treatment duration on an individual basis so that while therapy is effective in eliminating opiate dependence, the likelihood of cognitive impairments is minimized. Future studies in which the time relative to methadone dosing is systematically manipulated across different doses of methadone and for patients with varying history of opiate dependence will be able to shed more light on this issue.

The strength of the present study is that pure opiate users were studied and much longer MMT duration (as long as 6 years). Studies that reported normalization of cognitive performance had reported findings relevant to a few weeks and few months of MMT. The present study suggests that with longer durations of MMT, while psychomotor speed and WM may normalize, deficits in cognitive flexibility may continue and be a function of time relative to last dosing. With respect to methadone maintenance dose level, in contrast with a recent study, this study indicates that higher doses of methadone do increase the risk of impairment in executive functions.^[16] This study also implies that to keep cognitive impairment at a minimum, methadone dose and treatment duration will have to be customized considering the history of opiate abuse so that impairment attributable to long-term opiate use may be differentiated from acute methadone dosing. Longitudinal within-subject studies are needed to provide detailed information regarding the effects of methadone dose and amount as well as length of MMT and their interactions with time relative to dosing on executive functions.

It should be noted that the implications of the findings may be tempered by the fact that the possible contribution of patient characteristics such as level of education and history of psychopathology was not considered. Further investigation with larger samples controlling these factors may provide more useful data.

The current study indicates the distinct effects of short- and long-term methadone administration and underscores the importance of a customized treatment for opiate users.

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Conflicts of interest

There are no conflicts of interest.

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