Psychopharmacology (2002) 161:213–221
DOI 10.1007/s00213-002-1050-1

ORIGINAL INVESTIGATION

Justin M. Nash · Kenneth A. Holroyd
Lori A. Rokicki · Steven Kvaal · Donald B. Penzien

The influence of placebo awareness on stimulant drug response in a double-blind trial

Received: 8 June 1999 / Accepted: 11 February 2002 / Published online: 6 April 2002

Abstract *Rationale:* Critics have called into question findings from double-blind placebo-controlled studies because subjects are given drug administration instructions informing them of a placebo condition. The assertion that these drug administration instructions bias estimates of effectiveness has undergone surprisingly little empirical investigation. *Objectives:* The primary objective of this study was to determine whether drug administration instructions informing subjects of a placebo condition affect the drug response and affect the saliva concentration of the stimulant. *Methods:* We assessed caffeine responses and levels of saliva concentration of caffeine in 52 subjects who were randomly assigned to receive one of two drug administration instructions: (a) placebo-informed instructions (i.e., individuals informed of the placebo) analogous to those used in double-blind studies and (b) placebo-uninformed instructions (i.e., individuals informed they are taking an active stimulant). *Results:* On most measures (systolic blood pressure, heart rate, hand steadiness, reaction time, fatigue, and tension), drug administration instructions did not significantly influence caffeine response. Instructions also had no significant effect on saliva concentration of caffeine. However, only individuals who were uninformed of the placebo condition showed significant diastolic blood pressure and vigor increases with 125 mg caffeine, and significant hand steadiness impairment and vigor increases with 325 mg caffeine compared to placebo. *Conclusions:* These overall findings suggest that a limited bias is introduced by drug administration instructions. The results do not support any suggestion that information about the existence of a placebo condition dramatically influences conclusions drawn about drug responses in placebo-controlled trials.

Keywords Placebo · Expectancy · Caffeine · Double-blind design · Informed consent

J.M. Nash (✉)
Centers for Behavioral and Preventive Medicine,
Department of Psychiatry and Human Behavior,
Brown Medical School, The Miriam Hospital, CORO Building,
One Hoppin Street, Providence, RI 02903, USA
e-mail: Justin_Nash@Brown.edu

K.A. Holroyd
Department of Psychology, Porter Hall, Ohio University,
Athens, OH 45701, USA

L.A. Rokicki
Illinois Institute of Technology, Institute of Psychology,
3101S. Dearborn, Chicago, Illinois, USA

S. Kvaal
Roosevelt University,
2911W. Cullom Ave. #2, Chicago, IL 60618, USA

D.B. Penzien
UMC Head Pain Center,
University of Mississippi Medical Center,
2500 North State Street, Jackson, MS 39216-4505, USA

Introduction

Before being approved by the Food and Drug Administration (FDA) and marketed by pharmaceutical companies, a new drug must undergo a lengthy and stringent process to prove its safety and effectiveness. The final step in this process is the double-blind placebo-controlled trial. The standard informed consent procedure in placebo-controlled trials includes making participants aware of the possibility of receiving a placebo. This informed consent implies an assumption that informing subjects does not affect drug responses in a way that would alter the conclusions drawn about the effectiveness of the drug.

Some contend (e.g., Kirsch and Weixel 1988; Kirsch and Rosadino 1993) that because subjects in placebo-controlled trials are routinely informed that they may receive a placebo, drug responses observed in research trials may differ from the responses that will be obtained in clinical practice. They believe that different expectancies are created by differences in the drug administration instructions employed in placebo-controlled trials and in clinical practice. Consequently, our ability to generalize results from clinical trials to clinical practice is limited

(Kirsch and Weixel 1988; Kirsch and Rosadino 1993). Any inappropriate generalization of results from drug trials to physician practice therefore can have significant clinical implications. For example, there is ongoing debate about whether the effects of antidepressant medication have been overestimated in clinical practice (Dawes 1998; Enserink 1999; Greenberg and Fisher 1994; Kirsch and Sapirstein 1998; Klein 1998; Rehm 1998).

The assertion that drug administration instructions used in double-blind trials bias estimates of drug response has received surprisingly little empirical attention. A handful of studies conducted largely by critics (e.g., Kirsch and Rosadino 1993; Skovlund 1991) has attempted to address this question and is often cited as calling into question the external validity of placebo-controlled trials. Kirsch and Rosadino (1993) have reported that after subjects have consumed caffeinated coffee, tension increased only in those who were not informed they could receive a placebo (decaffeinated beverage). Those who were informed they could receive placebo coffee did not have an increase in tension. In two studies (Skovlund 1991; Bergman et al. 1994), analgesia was lower for patients who were aware they could be receiving a placebo than for those who were expecting a pain reliever. These studies are among many others indicating that drug administration instructions influence both placebo and drug responses (e.g., Tetreault and Bordeleau 1971; Kirsch and Weixel 1988; Kleijnen et al 1994; Flaten 1998; Flaten et al. 1999). Indeed, even serum levels of a drug may be influenced by drug administration instructions. Flaten et al. (1999) have reported significantly higher carisoprodol serum concentration in those subjects who were told it would have a relaxing effect compared to those told it would have a stimulating effect. These findings have been used to challenge the external validity of typical double-blind placebo-controlled studies because current double-blind placebo-controlled methods may fail to detect some genuine drug effects.

In addition to findings from these studies that question the generalizability of the double-blind design, review studies suggest that drug effectiveness in clinical practice may be overestimated. Kirsch and Sapirstein (1998, 1999) used a meta-analytic approach to contend that 75% of the effectiveness of an antidepressant is accounted for by placebo effects. Although other studies using a similar methodology provide consistent findings (Joffe et al. 1996; Walach and Maidhof 1999), the contention has been met with much criticism (e.g., Dawes 1998; Hamburg 2000; Klein 1998; Rehm 1998). Several literature reviews have found that treatment effects are consistently smaller in double-blind placebo-controlled trials than in single- and non-blind drug trials (e.g., Smith et al. 1969; Shulzbacher 1973; Smith et al. 1980; Greenberg and Fisher 1989; Greenberg et al. 1992). For example, in two studies Greenberg et al. (Greenberg and Fisher 1989; Greenberg et al. 1992) documented that antidepressants were judged to be most effective in studies in which the antidepressant was compared to a placebo under standard double-blind conditions. Antidepressant effects were considerably more modest in studies when compared to an "active placebo" control (i.e., one that produces side effects similar to the active drug) or in studies where the antidepressant was used as a standard control (along with placebo controls) for newer antidepressant medications. They conclude that the apparent effectiveness of antidepressant medication in these studies results largely from the ability of patients to break the double-blind and not from the pharmacological effects of antidepressant medication.

In this study, we sought to determine whether drug responses are affected by drug administration instructions informing individuals that they may receive a placebo. We examined the effect of the subjects' knowledge that they might receive a placebo on stimulant drug response. We compared caffeine responses observed with two drug administration instructions: (1) placebo-informed instructions (i.e., individuals informed they may receive a placebo) analogous to those used in double-blind placebo-controlled drug evaluation studies and (2) placebo-uninformed instructions (i.e., individuals unaware of the placebo condition and informed that they would be taking an active stimulant). In the first set of hypotheses, we expected that with each set of drug administration instructions, the responses to 125 mg and 325 mg caffeine would be larger than the responses to placebo. On those measures where drug administration instructions influenced drug response, we hypothesized that at each of the three dose levels (i.e., placebo, 125 mg, 325 mg), placebo-uninformed instructions would yield responses of greater magnitude than placebo-informed instructions. If knowledge of a placebo condition does not influence drug response, then empirical support could be provided for the conclusions that are drawn about drug responses in double-blind placebo-controlled clinical trials. In contrast, if knowledge of a placebo condition does influence drug response, then questions could be raised about the conclusions that are drawn in double-blind placebo-controlled clinical trials.

Compared to previous studies (e.g., Kirsch and Rosadino 1993), this study examined this issue with a design that was more similar to that used in clinical trials. The drug was administered in capsule form and the subjects were informed that the drug under investigation was a stimulant. Being unaware that caffeine was the drug under investigation would eliminate conditioned effects that may occur when someone knowingly ingests caffeine. This study also tested the effect of drug administration instructions on saliva concentration of caffeine to determine whether differential absorption of caffeine occurred with placebo awareness. In this study, behavioral performance measures were included (reaction time and hand steadiness), along with physiological and self-report mood measures, allowing responses in three response domains (physiological, self-report mood, and behavioral performance) to be investigated. Also tested in this study was whether placebo awareness had a similar effect on drug response at different dose levels (125 mg and 325 mg caffeine).

Materials and methods

Subjects

Subjects were 52 (22 male, 30 female) introductory psychology students receiving course credit for participation. Subjects were low-dose caffeine consumers as defined as averaging no more than four caffeine consumption days per week or ingesting no more than 85 mg caffeine on a daily basis. Subjects averaged 46.4 mg caffeine intake daily, or about a cup of tea or can of soft drink per day. Individuals were excluded if they reported or were found to have consumed caffeine within 24 h of the experiment, were allergic to milk products, had any chronic disease or regularly took any medication for the treatment of a physical or mental disorder, or had blood pressure baseline readings above 140 mmHg systolic or 80 mmHg diastolic. We did not assess for smoking status, alcohol use, or past history of physical or mental disorder.

Two of the 52 subjects who participated in the experiment were not included in the statistical analysis. One dropped out because of side effects (at 125 mg caffeine); the other was excluded because a friend had already participated in the study. Thus, 50 subjects were included in the analysis. Each of the 50 subjects was randomly assigned to one of the two drug administration instruction protocols: placebo-uninformed or placebo-informed. Within each of these protocols, subjects were assigned to one of six possible dose orders (PL→125 mg→325 mg; PL→325 mg→125 mg; 125 mg→PL→325 mg; 125 mg→325 mg→PL; 325 mg→PL→125 mg; 325 mg→125 mg→PL) with the constraint of having an equal number of subjects and males in each order.

All subjects provided written informed consent. The consent form did not specify caffeine but described it as a mild stimulant that is a safe and widely used preparation with temporary effects that will not last for more than a few hours. The only adverse effect mentioned was the possibility of feeling somewhat jittery for a brief period. The study was approved by the institutional review board (IRB) and was performed in accordance with the clinical standards laid down in the 1964 Declaration of Helsinki. IRB members were aware of the deception used in the research methodology.

Caffeine capsules

The drug, caffeine anhydrous (USP), was prepared in identical gelatin capsules from combinations of caffeine and powdered mild lactose. Dosage levels were 0 mg (placebo), 125 mg caffeine, and 325 mg caffeine.

Design and experimental manipulation

The experiment was conducted in individual sessions in a one between-subjects, two within-subjects (2×3×4; drug administration instructions×dose level×trials) design, with the restriction of having groups largely equivalent in terms of number of subjects and sex distribution.

Administration instructions, the between-groups factor, were either placebo-informed or placebo-uninformed drug administration instructions. Those subjects receiving placebo-informed drug administration were told: "In order to investigate the effects of this stimulant, on each of the first three days that you participate in the experiment you will be given either a placebo, a low dose of the stimulant, or a moderate dose of the stimulant. On one day you will receive a placebo, on another day you will receive a low dose, and on another day you will receive the moderate dose. The dose you receive will be determined randomly." Subjects were also told what physiological, subjective, and motor effects to expect with the placebo, low dose, and moderate dose. Subjects receiving placebo-uninformed drug administration instructions were told: "In order to investigate the effects of this stimulant, you will receive a moderate dose of the stimulant. You will be given this dose of the stimulant on the first three days you participate in this experiment. Because the stimulant may not have the same effects each day it is taken, we are having you take the stimulant three separate days so we can more accurately evaluate its effects. Numerous factors such as the amount of sleep and the foods and beverages you consumed in the last 48 hours influence the responses you have to the stimulant, so we must assess its effects more than once." The additional information that these subjects received regarding the drug effects to expect was identical to the information placebo-informed subjects received for moderate dose effects.

Dose levels, a within-subjects factor, were 0 mg lactose placebo, 125 mg caffeine (low), and 325 mg caffeine (moderate). *Trials*, a within-subjects factor, were baseline assessment (T0), drug assessment 1 (T1; 20 min after drug intake), drug assessment 2 (T2; 40 min after drug intake), and drug assessment 3 (T3; 60 min after drug intake).

Study procedure

Subjects were first screened and those who did not meet specific exclusion criteria were recruited to participate. Those who agreed to participate had an appointment scheduled and were instructed to not consume any food or liquid, except water, from 2 h prior to their appointment on the test days. Consistent with caffeine studies, subjects were also instructed to not consume any coffee, tea, chocolate, or soft drinks from 6 h prior to their appointments (e.g., Roache and Griffiths 1987). We did not conduct urine toxicology screens for prescribed drugs or other substances of abuse. We also did not provide specific instructions regarding nicotine or alcohol use between test days.

On all participation days, upon arriving for their appointments at a university research laboratory building, subjects were greeted by the experimenter dressed in a white lab coat and escorted to the testing room. All task instructions were delivered via audiotape and all measures were administered remotely from an adjoining room.

On day 1 only, subjects were given a 17-min orientation to the experiment that included written informed consent, detailed instruction in the performance of motor tasks, and practice of all tasks. Following orientation on day 1, baseline recordings of mood, hand steadiness, and reaction time were taken. Baseline recordings of physiological measures were completed on day 4 because a true resting assessment of physiological measures is best achieved after the subject has become sufficiently acclimated to the environment. Days 2 and 3 began with baseline recordings of mood and behavioral performance measures.

Experimental manipulation/drug administration instructions

After baseline assessment on days 1, 2, and 3, the subject viewed a 5-min videotaped presentation containing the experimental manipulation of drug administration instructions. Both groups of subjects (placebo-informed and placebo-uninformed), after viewing the videotaped presentation on each day capsules were administered, completed two tasks that were designed to reinforce the drug administration manipulation presented on the videotape. In the first task, subjects read a summary of the experiment that was consistent with the particular drug administration instructions they received. In the second task, subjects completed a brief multiple choice questionnaire that included questions about the experimental procedure and stimulant effects.

Drug administration, assessment of drug responses, and collection of saliva samples

After viewing the videotape and completing the tasks to reinforce the drug administration manipulation, each subject was given the capsule containing the appropriate dose level (0 mg, 125 mg,

325 mg) for that day. The experimenter was blind to the dose level and drug administration condition. On all three drug administration days (days 1, 2, and 3) there were three assessment trials (T1, T2, T3) to test the effects of the drug. Assessment trials began 20 min, 40 min, and 60 min after drug intake.

During each assessment trial, subjects started with simultaneous physiological recordings (systolic blood pressure, diastolic blood pressure, and heart rate), then completed self-report ratings (mood, perceived drug strength), and finally performed behavioral tasks (hand steadiness, reaction time). Following each trial, 2–3 ml saliva were collected in a 5-ml cryovial. These samples were collected 30 min, 50 min, and 70 min after caffeine ingestion. Samples were frozen immediately and stored at –40°C to –70°C. During the 7-min intertrial interval, most subjects took the option of reading magazines that were provided.

At the end the sessions on days 1, 2, and 3, subjects were given exit instructions that reminded them that any effects of the mild stimulant were safe and self-limiting. Each subject was also given instructions regarding food and caffeine intake for the following day and a phone number to contact the investigator if any questions arose at a later time. The duration of the experiment on these days was approximately 90 min.

Physiological baseline and debriefing

Day 4 was an abbreviated session reserved for baseline recordings of physiological measures and debriefing. Day 4 was chosen to provide the closest approximation of true resting assessment when no drug was administered and when subjects were acclimated to the environment. Otherwise, subjects may have shown elevated blood pressure readings while anticipating the start of an experiment in a new environment. Subjects were told that all drug administration sessions had been completed and that a resting (non-drug administration) recording would be taken of blood pressure and heart rate. Subjects were allowed 4 min of listening to music to become acclimated. Blood pressure and simultaneous heart rate recordings were then taken. Subjects then rested for another 4 min, followed by a final recording of blood pressure and heart rate. After these readings were taken, the subjects were debriefed. At debriefing, subjects were asked if they had any prior knowledge of the experiment and were given the opportunity to ask questions. Questions that did not threaten the integrity of the experiment were answered.

Measures

The three *physiological responses*, heart rate, systolic blood pressure, and diastolic blood pressure, were assessed simultaneously using an automated blood pressure and pulse rate monitor (Model SD-700 A; Industrial & Biomedical Sensors Corporation, Waltham, Mass.). For each of the physiological responses, three measurements were taken over a 4-min period with a 15-s interval between measurements. At each assessment, the median of the three measures was used as the value.

There were two *behavioral performance* measures: hand steadiness and reaction time. Hand steadiness was measured by means of a stylus-in-hole hand steadiness tester (Lafayette Instruments, Lafayette, Ind.). The subject inserted the 1-mm metal stylus into a 4-mm diameter hole using the dominant hand. Any time the stylus made contact with the side of the hole, a count was registered on an electrical LED counter located remotely in the experimenter control room. During each assessment, three 15-s trials were conducted and recorded. An intertrial interval of 10 s was used. The score was the median of the three trials. Lower scores indicated greater steadiness.

Reaction time was assessed using a simple reaction time paradigm. The apparatus was a human response panel with a spatial array of ten white lights (9 mm diameter each) grouped into two vertical columns of five lights spaced 1.7 cm apart. The panel also included a rectangular response key measuring 6.4 cm horizontally by 3.8 cm vertically. A trial began with the presentation of a warning tone which indicated the onset of the lights (all ten simultaneously) in 2 to 5 s. Simultaneously with light onset, an LED timing device measuring milliseconds was triggered. The subject was seated with his or her dominant hand placed on a marked location on the table 33 cm below the response key. The subject pressing the response key terminated timing. The intertrial interval, that is, time between subject response and next warning tone was 5 s. The reaction time score, measured in milliseconds, was the median of the three trials.

Subjective mood was assessed using the brief 38-item version of the Profile of Mood States (POMS) questionnaire (McNair et al. 1971). Eight empirically derived scales are formed from the POMS: tension-anxiety, depression-dejection, anger-hostility, vigor, fatigue, confusion-bewilderment, and total mood disturbance. *Perceived drug strength* was assessed using a single question, "How strong of a drug effect have you been feeling?" (Chait and Griffiths 1983). The response was based on a five-point Likert-type scale: 1, no effect; 2, mild effect but not sure; 3, mild effect but sure it is a drug effect; 4, moderately strong; 5, very strong.

Statistical analysis

To assess whether placebo awareness influenced saliva concentration of caffeine, an ANOVA was performed with Drug Administration Instructions (placebo-informed, placebo-uninformed) and Sex as the between-subject factors and Dose Level (125 mg, 325 mg) and Trials (T1, T2, T3) as the within-subject factors.

To assess whether placebo awareness influenced stimulant drug response, two sets of analyses were conducted. In the first set of analyses, testing the first set of hypotheses, the intention was to address the question as to whether different conclusions regarding drug responses would be drawn if individuals were informed of the placebo condition as opposed to uninformed of the placebo condition. To address this question, the first set of analyses examined drug responses separately under each set of instructions. That is, the analyses assessed whether caffeine produced larger responses than placebo (a) when individuals were informed that they may be taking a placebo (i.e., placebo-informed instructions) and (b) when individuals were not informed that they may receive a placebo (i.e., placebo-uninformed instructions). A series of four planned comparisons were conducted under each set of drug administration instructions on all measures except ratings of drug strength. In each comparison, changes from T0 to T3 at the 125-mg and 325-mg caffeine dose levels were compared to changes from T0 to T3 with placebo. For ratings of perceived drug strength, ratings of drug strength at the 125-mg and 325-mg caffeine dose levels were compared to that with placebo only at T3. This is because subjects did not rate drug strength before taking the capsules.

A second set of analyses testing the second set of hypotheses was conducted to follow-up on the findings of the first analysis where drug administration instructions had a significant influence as assessed in the above-mentioned analyses. In these analyses, the intention was to determine whether the instructions influence occurred with the placebo doses or with one or both of the active stimulant doses. Only on measures where instructions influenced drug response were analyses conducted at each dose level to assess whether placebo and caffeine responses were greater in magnitude for individuals who were not informed they might receive a placebo compared to those who were informed they might receive a placebo. At each dose level, changes from T0 to T3 under placebo-uninformed instructions were compared to changes from T0 to T3 under placebo-informed instructions. For ratings of perceived drug strength, at each of the three dose levels at T3 only, ratings of drug strength under placebo-uninformed instructions were compared to ratings under placebo-informed instructions. To examine whether differences in the magnitude of drug response could be accounted for by perceived drug strength, the second set of analyses was conducted a second time with perceived drug strength serving as a covariate.

Table 1 ANOVA results (F values) for caffeine responses that were significantly greater than placebo responses with placebo-uninformed instructions and with placebo-informed instructions. Caffeine did not produce a significantly greater effect than placebo for heart rate and reaction time with either drug administration instructions

Measure	125 mg		325 mg	
	Placebo-uninformed	Placebo-informed	Placebo-uninformed	Placebo-informed
Systolic BP	–	–	11.18***	11.92***
Diastolic BP	5.79*	–	–	9.92***
Hand steadiness	–	–	11.48***	–
Vigor	9.51**	–	16.58***	–
Fatigue	11.89***	10.72***	11.52***	21.51***
Tension	–	–	10.63***	6.74*

***P<0.001, **P<0.005, *P<0.01

Table 2 Means and standard deviations with placebo-informed instructions (n=26) and with placebo-uninformed instructions (n=24)

Measure	Treatment	Placebo-informed						Placebo-uninformed					
		T0		T1		T3		T0		T1		T3	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Diastolic BP	Placebo	67.42	8.36			68.69	8.85	63.54	8.46			65.08	8.89
	125 mg	67.42	8.36			69.89	6.77	63.54	8.46			69.00	6.77
	325 mg	67.42	8.36			73.62	6.33	63.54	8.46			68.38	8.35
Hand steadiness	Placebo	31.27	16.15			28.77	16.00	37.87	13.81			36.83	13.61
	125 mg	31.15	16.98			32.96	17.33	38.87	11.24			39.22	16.15
	325 mg	34.31	16.00			32.54	15.82	38.00	15.17			45.61	15.59
Vigor	Placebo	12.16	4.04			9.16	3.13	13.13	4.60			11.04	5.03
	125 mg	13.28	5.21			11.32	4.39	12.88	4.95			13.54	6.44
	325 mg	13.40	4.78			12.04	4.23	12.71	5.12			14.25	5.46
Drug strength	Placebo			1.28	0.54	1.20	0.50			1.50	0.74	1.91	1.15
	125 mg			1.48	0.71	1.76	0.72			1.59	0.67	2.27	1.62
	325 mg			1.48	0.65	1.96	0.84			1.64	0.73	2.41	1.14
Saliva caffeine	125 mg			1956	1296	2034	1391			1635	1428	2162	775
	325 mg			4287	3808	5763	2366			4781	3072	6027	2355

In all analyses, F values were adjusted using the Huynd-Felt procedure in cases of violations of assumptions of sphericity. As further protection against making a type I error, the alpha level was adjusted for the number of contrasts tested using Dunn's multiple comparison procedure (also referred to as Bonferroni t procedure). This procedure has been noted to be highly conservative (Holland and Copenhaver 1988). Even with Bonferroni t corrections, all but a few of the significant hypotheses were significant beyond the P<0.001 alpha level.

Results

Saliva concentration of caffeine

A significant dose×time interaction [F(2,90)=3.29, P<0.05] showed that 325 mg caffeine produced a greater increase in saliva concentration of caffeine than 125 mg caffeine. Drug administration instructions did not have any significant effect on saliva concentration of caffeine.

Caffeine effects under each set of drug administration instructions

This first set of analyses assessed whether caffeine produced larger responses than placebo (a) when individuals were informed they may be taking a placebo (i.e., placebo-informed instructions) and (b) when individuals were not informed they may receive a placebo (i.e., placebo-uninformed instructions). Significant effects observed under each set of drug administration instructions are presented in Table 1. Figures and a table (Table 2) of means and standard deviations are provided only for those measures for which instructions influenced response.

Caffeine effects observed with placebo-informed instructions

At 125 mg, caffeine responses were larger than placebo responses on only one of eight measures. At 325 mg, caffeine responses were larger than placebo responses on four of eight measures.

At 125 mg caffeine. The 125 mg caffeine dose produced a greater decrease in fatigue than did placebo [F(1,163)=10.72, P<0.001]. The 125 mg caffeine and placebo responses did not differ for systolic blood pressure, diastolic blood pressure, heart rate, hand steadiness,

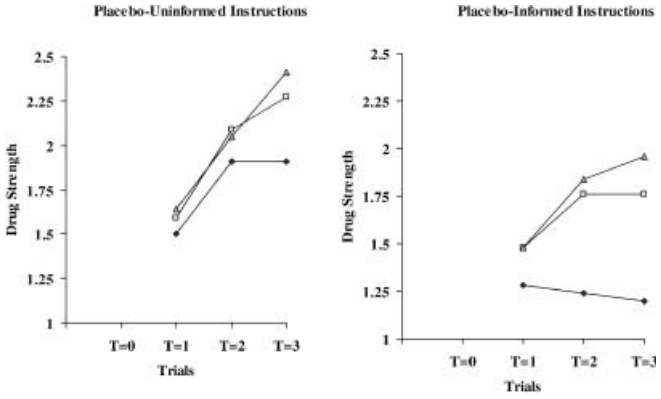

Fig. 1 Drug strength rating as a function of caffeine dose, trials, and drug administration instructions (*solid diamonds* placebo, *open squares* 125 mg, *solid squares* 325 mg)

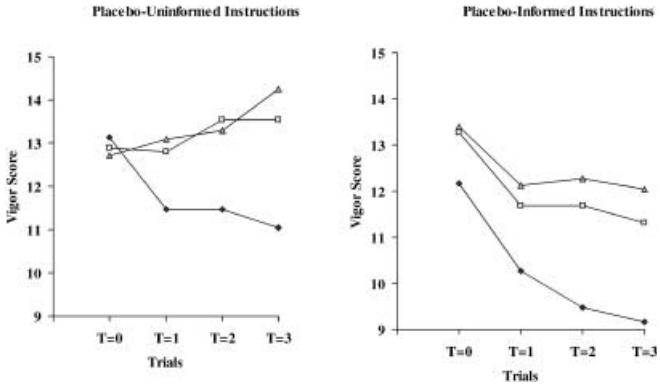

Fig. 3 Vigor as a function of caffeine dose, trials, and drug administration instructions (*solid diamonds* placebo, *open squares* 125 mg, *solid squares* 325 mg)

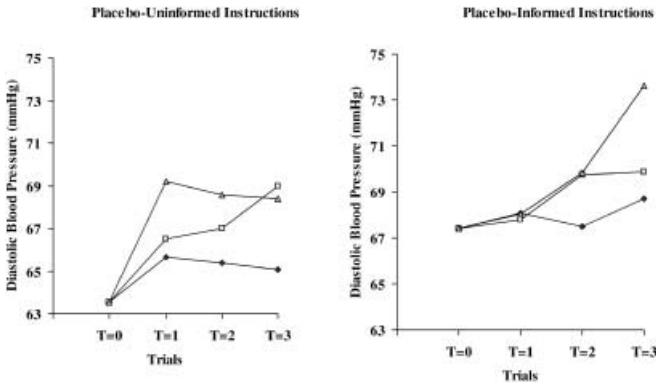

Fig. 2 Diastolic blood pressure as a function of caffeine dose, trials, and drug administration instructions (*solid diamonds* placebo, *open squares* 125 mg, *solid squares* 325 mg)

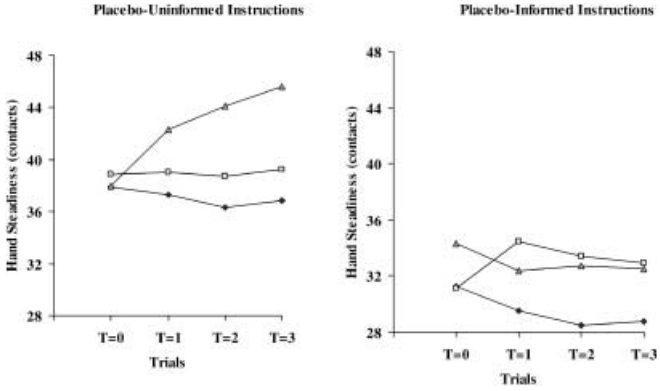

Fig. 4 Hand steadiness as a function of caffeine dose, trials, and drug administration instructions (*solid diamonds* placebo, *open squares* 125 mg, *solid squares* 325 mg)

reaction time, vigor, or tension. Regarding perceived drug strength, at T3 the 125-mg dose yielded a significantly stronger perceived drug effect than did placebo [F(1,270)=7.59, $P<0.005$]. This is shown in Fig. 1.

At 325 mg caffeine. The 325 mg caffeine dose produced a greater decrease in fatigue [F(1,163)=21.51, $P<0.001$] and greater increases in systolic blood pressure [F(1,276)= 11.92, $P<0.005$], diastolic blood pressure [F(1,272)=9.92, $P<0.001$], and tension [F(1,220)=6.74, $P<0.01$] than did placebo. The effect for diastolic blood pressure is displayed in Fig. 2. The 325 mg caffeine response and the placebo response did not differ for heart rate, hand steadiness, reaction time, or vigor. Regarding perceived drug strength, at T3 the 325-mg dose yielded a significantly stronger perceived drug effect than did placebo [F(1,270)=13.99, $P<0.001$]. This is shown in Fig. 1.

Caffeine effects observed with placebo-uninformed instructions

At 125 mg, caffeine responses were larger than placebo responses on three of eight measures. At 325 mg, caffeine responses were larger than placebo responses on five of eight measures. These significant effects are presented in Table 1.

At 125 mg caffeine. The 125 mg caffeine dose produced a greater decrease in fatigue [F(1,163)=11.89, $P<0.001$], and greater increases in diastolic blood pressure [F(1,272)=5.79, $P<0.05$] and vigor [F(1,250)=9.51, $P<0.001$] than did placebo. The effects for diastolic blood pressure and vigor are displayed in Figs. 2 and 3, respectively. The 125 mg caffeine and placebo responses did not differ for systolic blood pressure, heart rate, hand steadiness, reaction time, tension, or perceived drug effect.

At 325 mg caffeine. The 325 mg caffeine dose produced greater decreases in hand steadiness [F(1,270)=11.48, $P<0.001$] and fatigue [F(1,163)=11.52, $P<0.001$], and greater increases in systolic blood pressure [F(1,276)= 11.18, $P<0.001$], tension [F(1,220)=10.63, $P<0.001$] and vigor [F(1, 250)=16.58, $P<0.001$] than did placebo. The effects for vigor and hand steadiness are displayed in Figs. 3 and 4, respectively. Regarding perceived drug strength, at T3 the 325-mg dose (but not the 125-mg

Table 3 ANOVA results (F values) comparing magnitude of responses under placebo-uninformed instructions and placebo-informed instructions on measures where instructions influenced drug response (*n.s.* not significant)

Measure	Placebo	125 mg caffeine	325 mg caffeine
Diastolic BP	n.s.	n.s.	n.s.
Hand steadiness	n.s.	n.s.	13.24***
Vigor	n.s.	8.31**	10.18***
Drug strength	5.27*	n.s.	n.s.

***P<0.001, **P<0.005, *P<0.05

dose) yielded a significantly stronger perceived drug effect than did placebo [F(1,270)=5.33, P<0.025]. This is shown in Fig. 1.

Comparison of responses under each set of drug administration instructions

The second set of analyses was conducted only on those measures (i.e., diastolic blood pressure 125 mg, 325 mg; hand steadiness 325 mg; vigor 125 mg, 325 mg) in which drug administration instructions influenced drug response. This was to determine whether placebo and caffeine responses were greater in magnitude when individuals were not informed they might receive a placebo than when individuals were informed they might receive a placebo. The results are shown in Table 3. When the second set of analyses was conducted using perceived drug strength as a covariate, the results did not differ.

Placebo. Larger placebo responses were not observed with placebo-uninformed instructions than with placebo-informed instructions on diastolic blood pressure, hand steadiness, or vigor. Regarding perceived drug strength, at T3 a significantly stronger perceived drug effect was observed with placebo-uninformed than with placebo-informed instructions [F(1,235)=5.27, P<0.025]. This effect is shown in Table 3 and Fig. 1.

At 125 mg caffeine. At 125 mg, vigor increased more with placebo-uninformed instructions than with placebo-informed instructions [F(1,349)=8.31, P<0.005]. The same result occurred when perceived drug strength served as a covariate in the analysis [F(1,349)=7.63, P<0.005]. Responses to 125 mg caffeine did not differ under the two drug administration instructions for diastolic blood pressure or perceived drug effect. These effects are shown in Table 3 and the vigor effect in Fig. 3.

At 325 mg caffeine. Hand steadiness was impaired more and vigor increased more with placebo-uninformed instructions than with placebo-informed instructions [F(1,110)=13.24, P<0.001; F(1,349)=10.18, P<0.001, respectively]. These effects are shown in Table 3 and Figs. 3 (vigor) and 4 (hand steadiness). When these analyses were conducted with perceived drug strength as the covariate, the same result occurred for both hand steadiness [F(1,110)=12.92, P<0.005] and vigor [F(1,349)= 9.35, P<0.001]. Responses to 325 mg caffeine did not differ with the two drug administration instructions for diastolic blood pressure or perceived drug effect.

Discussion

This investigation sought to determine whether drug administration instructions that inform individuals of a placebo condition, as is standard practice in clinical trials, influence the conclusions that are drawn about the drug responses. The study also sought to determine whether drug administration instructions influenced saliva concentration of caffeine. In general, relative to placebo, similar caffeine responses were observed whether or not individuals were aware that they might be receiving a placebo. With both placebo-informed and placebo-uninformed drug administration instructions, relative to placebo, 125 mg caffeine produced significant fatigue decreases and 325 mg caffeine produced significant systolic blood pressure and tension increases and fatigue decreases. Regardless of drug administration instructions, relative to placebo, 125 mg caffeine did not produce significant changes in systolic blood pressure, heart rate, hand steadiness, reaction time, or tension. Likewise, the 325 mg caffeine did not produce significant changes in heart rate or reaction time with either instructional set. Inconsistent with the findings of Flaten et al. (1999), drug administration instructions in this study did not affect saliva concentration of caffeine.

Although similar caffeine responses were observed with the two drug administration instructions on most measures, drug administration instructions yielded different drug responses on one measure from each of the three response domains: diastolic blood pressure (physiological), hand steadiness (behavioral performance), and vigor (subjective mood). Only individuals who were uninformed of the placebo condition showed significant diastolic blood pressure and vigor increases with 125 mg caffeine relative to placebo. Similarly, only placebo-uninformed individuals showed significant hand steadiness impairment and vigor increase with 325 mg caffeine compared to placebo. When the magnitude of these responses was directly compared under each set of instructions, those unaware of the placebo had greater changes in vigor at 125 mg, and in vigor and hand steadiness at 325 mg than those aware of a placebo. These findings were not accounted for by the variance associated with perceptions of drug strength. In an analysis of the perceived strength of the drug effect, those unaware of the placebo reported a greater drug effect than those aware of the placebo only when taking the placebo dose (and not either caffeine dose). Any influence that drug administrations had did not occur differentially at the different dose levels.

These results do show some consistency with those indicating that to some extent placebo awareness influ-

ences drug response (Tetreault and Bordeleau 1971; Kirsch and Weixel 1988; Kirsch and Rosadino 1993). These other studies focused on only a few measures obtained under limited conditions. The findings also show consistency with literature reviews indicating that estimates of drug effects are larger when adequate control conditions are not employed. The meta-analysis of Greenberg et al. (1992) indicated that the methodology of antidepressant research (i.e., integrity of blindness) was more important than the drug being studied in predicting the outcome of a clinical trial. In contrast to the findings other studies (Kirsch and Weixel 1988; Fillmore and Vogel-Sprott 1992; Fillmore et al. 1994), we did not find greater responses to the placebo dose in those who were uninformed compared to those who were informed of the placebo condition. In this study, the lack of influence of instructions on placebo dose response occurred despite a greater perceived drug strength being reported on the placebo dose (and not on either caffeine dose) by those uninformed of the placebo. The different instructions thus appear to be sufficient to have an effect on placebo expectancies but not powerful enough to yield greater placebo responses.

Our findings do not support any conclusion that information about the existence of a placebo condition dramatically influences conclusions drawn about drug responses. The overall picture suggests limited bias introduced by instructions. When the bias exists, more conservative estimates of stimulant drug responses likely occur. To the extent that drug responses in clinical trials can be assumed to generalize to clinical practice, the double-blind placebo-controlled trial is not likely to yield drug responses that (a) would not be found in clinical practice or (b) would be larger than responses found in clinical practice. More conservative estimates might occur because some active drug responses, but not placebo responses, are larger in magnitude with placebo-uninformed instructions than with placebo-informed instructions. An assessment of expectancies created by drug administration instructions would have provided information on the mediating role of expectancies in placebo and drug response. The influence of perceived drug strength on response was assessed in a covariance analysis but was found to have little effect. It is acknowledged that the problem with using perceived drug strength as an approximation of expectancies is that it confounds expectancy and drug effect.

The findings of this study support the argument that informing participants of the placebo condition in double-blind placebo-controlled method is appropriately conservative and effectively guards against the overestimation of drug effects. The findings, however, are limited to the laboratory context and are not assumed to be generalizable to actual clinical trials. The subjects in this study were of a narrow age range and do not necessarily reflect the responses that could be expected from older adults. Moreover, it is difficult to know whether uneven randomization of potentially confounding characteristics (e.g., smoking, mental illness, etc.) contributed to any of the findings. Future investigations might continue to move in a more naturalistic and ecologically valid direction. An example would be using patients in a medical setting who would be given an agent designed for symptom reduction. It would be wise to assess the mediating role of expectancies on drug response in any future studies. By assessing expectancies, causal modeling could determine the extent to which drug response is accounted for by expectancies created by instructions or some other variable under study.

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