Double-Blind Study of Dextroamphetamine Versus Caffeine Augmentation for Treatment-Resistant Obsessive-Compulsive Disorder

Lorrin M. Koran, MD; Elias Aboujaoude, MD; and Nona N. Gamel, MSW

Introduction: Two small, double-blind, placebo-controlled, single-dose, crossover studies found dextroamphetamine (*d*-amphetamine) 30 mg clearly superior to placebo in relieving symptoms of obsessive-compulsive disorder (OCD). We conducted a 5-week, double-blind, caffeine-controlled study to test the hypothesis that *d*-amphetamine, added after an adequate selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) trial, would be more effective than caffeine in reducing residual OCD symptoms of moderate or greater severity.

Method: Between August 2006 and February 2008, we enrolled adults with *DSM-IV* OCD and a Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score of ≥ 20 after ≥ 12 weeks of adequate treatment with an SSRI or SNRI. Subjects were randomly assigned to double-blind *d*-amphetamine 30 mg/d or caffeine 300 mg/d added to their SSRI/SNRI and other medications. Responders (first week mean Y-BOCS score decrease of ≥ 20%) entered the study's 4-week double-blind extension phase.

Results: We enrolled 24 subjects, 11 women and 13 men, with a mean (SD) age of 40 (13.2) years and mean baseline Y-BOCS scores of 26.5 (4.1) for the *d*-amphetamine group (n = 12) and 29.1 (4.0) for the caffeine group (n = 12). At the end of week 1, 6 of 12 *d*-amphetamine subjects (50%) and 7 of 12 caffeine subjects (58%) were responders. At week 5, the responders' mean Y-BOCS score decreases were, for the *d*-amphetamine group (last observation carried forward), 48% (range, 20%–80%); and, for the caffeine group, 55% (range, 27%–89%). Obsessive-compulsive disorder and depression improvement were independent. The double-blind remained intact. No subject discontinued the study due to side effects.

Conclusions: Larger, double-blind, placebo-controlled trials of both *d*-amphetamine and caffeine augmentation are needed in OCD subjects inadequately responsive to adequate doses of an SSRI or SNRI.

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Corresponding author: *Lorrin M. Koran, MD, OCD Clinic, Room 2363, 401 Quarry Road, Stanford, CA 94305 (lkoran@stanford.edu).*

Two small, double-blind, placebo-controlled, crossover studies conducted before the introduction of selective serotonin reuptake inhibitors (SSRIs) found a single dose of dextroamphetamine (*d*-amphetamine) 30 mg[1,2] clearly superior to placebo in immediately relieving symptoms of obsessive-compulsive disorder (OCD). In addition, a case report[3] regarding Adderall (*d*-amphetamine and amphetamine salts) 30 mg/d taken alone and a report of 4 cases of successful Adderall augmentation of SSRIs in patients with childhood-onset OCD[4] suggested that *d*-amphetamine is effective over longer periods. An open-label, single-dose study of methylphenidate 40 mg in 11 OCD patients found no significant effect on obsessive-compulsive ratings,[5] but van der Feltz-Cornelis[6] described 2 cases of marked OCD symptom relief with methylphenidate monotherapy in patients with comorbid attention-deficit/hyperactivity disorder (ADHD).

In view of these data, we conducted a 5-week, double-blind, caffeine-controlled study to test the hypothesis that *d*-amphetamine, added after an adequate SSRI or serotonin-norepinephrine reuptake inhibitor (SNRI) trial, is more effective than caffeine in reducing OCD symptoms in patients whose symptoms have been inadequately responsive.

METHOD

Between August 2006 and February 2008, we enrolled adults aged 18–55 years who had *DSM-IV* OCD and a Yale-Brown Obsessive Compulsive Scale (Y-BOCS)[7] score of ≥ 20 after ≥ 12 weeks of treatment with an established effective dose of an SSRI (citalopram, escitalopram, or fluoxetine, ≥ 20 mg/d; paroxetine, ≥ 40 mg/d; sertraline, ≥ 50 mg/d)[8] or with a clinically reasonable dose of an SNRI (venlafaxine, n = 2, 225 mg/d and 300 mg/d; duloxetine, n = 5, 60–120 mg/d). The investigators established all diagnoses utilizing a structured interview, the Mini-International Neuropsychiatric Interview (MINI).[9] Potential subjects with a history of alcohol or substance abuse, bipolar disorder, panic disorder, schizophrenia, or heart disease, seizures, glaucoma, or serious medical disease (including blood pressure greater than 140 mm Hg systolic or 90 mm Hg diastolic) were excluded. We also excluded those with hoarding as their only OCD symptom; those taking clomipramine, an MAO inhibitor, or

a drug (eg, fluvoxamine) inhibiting hepatic enzyme CYP1A2 (which is involved in caffeine metabolism); those weighing less than 100 lb; and women of childbearing potential not using a medically acceptable contraceptive method.

After being fully informed regarding the study and signing an informed consent approved by the Stanford Institutional Review Board, subjects were randomly assigned to receive 2 identical-appearing pills containing a total of either *d*-amphetamine 30 mg (bottles A and B pills, 15 mg each) or caffeine 300 mg (bottle A pills, 200 mg; bottle B pills, 100 mg), to be taken each morning during the study's first week in addition to their SSRI/SNRI and other medications. Subjects had refrained from drinking caffeine-containing beverages for a week before starting study medication. To help ensure that subjects and investigators would remain blind to treatment assignment, we used caffeine, with its ability to induce feelings of energy, positive mood, and drug "high" and its side effects of nervousness and jitteriness[10–12] as the placebo treatment, not expecting any therapeutic benefit from it. Subjects were informed that no benefit was expected from caffeine and it was being used simply as an active placebo to mask treatment-group assignment. They were also informed that if they were assigned to the caffeine group, they would be offered a 3-day trial of open-label *d*-amphetamine after they completed study participation.

Subjects were seen at a screening followed by a baseline visit, at which times inclusion/exclusion criteria, OCD symptoms, comorbid conditions, and vital signs were assessed. Each evening during the first week of study medication, a study psychiatrist called the subject to obtain a Y-BOCS rating. Subjects had to experience a mean Y-BOCS score decrease of ≥ 20% over the week to be continued into the study's 4-week double-blind extension phase. All subjects were seen at the end of week 1, and continuing subjects were then seen weekly to evaluate symptoms and adverse events. We administered the Y-BOCS, Montgomery-Asberg Depression Rating Scale (MADRS),[13] and the self-rated Spielberger State-Trait Anxiety Inventory (STAI)[14] at screening and baseline and repeated these assessments, along with the Clinical Global Impressions-Improvement (CGI-I) scale[15] and an unpublished Drug Effect Scale at the end of weeks 1–5. The Drug Effect Scale asked subjects to rate "Do you like the drug?" and "How high are you now?" on a scale of zero (not at all) to 10 ("the most I have liked any drug" or "the highest I have ever been"). We utilized criteria suggested by Mittman and colleagues[16] to classify subjects as having mild depression (MADRS scores 9–17) or at least moderate depression (MADRS scores ≥ 18).

Mean changes from baseline in rating scale scores were tested with Student paired 2-sample *t* test, using a significance level of $P \leq .05$, and these analyses were checked with nonparametric Wilcoxon signed ranks tests. Relationships among rated variables were tested with Pearson product moment correlation tests, using a significance level of $P \leq .05$ and checked with nonparametric Spearman rank order correlations. The nonparametric tests produced no different conclusions regarding statistical significance.

RESULTS

We enrolled a preplanned total of 24 subjects, all white, 11 women and 13 men, with a mean (SD) age of 40 (13.2) years (range, 19–62 years [the 62-year-old was a protocol exception]). An additional 60 individuals were not enrolled: 31 callers were not interested after hearing study details; 27 were ineligible (exclusionary comorbid condition, 9; inadequate OCD medication trial, 7; transportation issue, 6; insufficient OCD severity, 2; age, 2; taking clomipramine, 1); and 2 were excluded after screening (1 with obsessive-compulsive personality disorder rather than OCD and 1 with comorbid paranoid schizophrenia). Table 1 presents subjects' baseline clinical characteristics. Active comorbid conditions were major depressive disorder (n = 5), dysthymic disorder (n = 7, including 1 major depressive disorder subject), generalized anxiety disorder (n = 3), and social anxiety disorder (n = 1). No subject carried a diagnosis of comorbid attention-deficit disorder, nor did our clinical evaluations suggest this diagnosis in any subject.

Randomization resulted in assignment of 12 subjects to each treatment group. The 2 groups did not differ significantly in mean age at onset of OCD or mean baseline Y-BOCS, MADRS, or STAI scores (Table 1); 4 subjects in the *d*-amphetamine group were taking an SNRI, as were 3 subjects in the caffeine group. More subjects in the caffeine group were taking an augmenting atypical antipsychotic drug (5 versus 3), and fewer a benzodiazepine (1 versus 4). Approximately half the subjects in each group had had 1 or more atypical antipsychotic drug augmentation trials, and 10 in each group had had previous SSRI/SNRI trials of indeterminate adequacy and magnitude of effect (Table 1).

At the end of week 1, 6 of 12 subjects (50%) in the *d*-amphetamine group and 7 of 12 subjects (58%) in the caffeine group met the Y-BOCS response criterion (decrease of ≥ 20%), allowing continuation into the 4-week extension of double-blind treatment. Among subjects taking an atypical antipsychotic drug, 1 of 3 in the *d*-amphetamine group and 3 of 5 in the caffeine group met this criterion. Yale-Brown Obsessive Compulsive Scale scores decreased statistically significantly from baseline to the end of week 1 (Table 1), with a mean 21% decrease (range, 26% increase to 52% decrease) for the *d*-amphetamine group and a mean 33% decrease (range, 0%–74% decrease) for the caffeine group. Four subjects (33%) in the *d*-amphetamine group and 5 (42%) in the caffeine group met the recommended criterion for *full response*: a Y-BOCS score decrease of ≥ 35% and a CGI-I score of 1 or 2 (very much or much improved).[17] The mean scores for the Drug Effect Scale-liking subscale were 4.3 (range, 0–10) for *d*-amphetamine and 5.4 (range, 1–10) for caffeine; the mean scores for the Drug Effect Scale-"high" subscale were 1.8 (range, 0–6; with

Table 1. Baseline Clinical Characteristics and Subsequent Clinical Measures in Subjects With Obsessive-Compulsive Disorder (OCD) Receiving Dextroamphetamine or Caffeine

	Initial 1-Week Phase		End of Week 5	
Characteristic or Measure	Dextroamphetamine (n = 12)	Caffeine (n = 12)	Dextroamphetamine (n = 6)[a]	Caffeine (n = 7)
Gender				
Female	5	6	…	…
Male	7	6	…	…
Age, mean (SD), y	42.3 (12.8)	37.8 (13.7)	…	…
Prior medication trials, mean				
Atypical antipsychotic[b]	2.4	2.5	…	…
SSRI/SNRI[c]	3.0	3.7	…	…
Age at onset of OCD, mean (SD), y	11.6 (4.7)	16.0 (12.2)	…	…
Baseline score, mean (SD)				
Y-BOCS	26.5 (4.1)	29.1 (4.0)	25.2 (2.0)	27.9 (4.5)
MADRS	13.0 (10.2)	16.8 (9.0)	11.5 (8.3)	16.0 (8.1)
STAI	49.5 (13.6)	55.6 (6.0)	54.1 (5.1)	43.7 (10.5)
End of week 1				
Y-BOCS score, mean (SD)	21.3 (8.1)[d]	20.0 (8.7)[e]	…	…
MADRS score, mean (SD)	12.7 (12.5)	11.4 (8.2)	…	…
STAI score, mean (SD)	48.2 (18.2)[f]	49.0 (10.9)[g]	…	…
No. of subjects with CGI-I score = 1 or 2	6	7	…	…
End of week 5				
Y-BOCS score, mean (SD)	…	…	13.3 (6.9)	13.0 (8.4)
MADRS score, mean (SD)	…	…	10.2 (7.6)	9.7 (6.0)
STAI score, mean (SD)	…	…	37.5 (10.0)	41.3 (10.7)
No. of subjects with CGI-I score = 1 or 2	…	…	5	7

[a]Last-observation-carried-forward analysis.
[b]n = 7 in dextroamphetamine group; n = 6 in caffeine group.
[c]n = 10.
[d]$t = 2.45$, $P \leq .001$ for difference from baseline.
[e]$t = 2.57$, $P \leq .001$ for difference from baseline.
[f]Not significant.
[g]$t = 2.45$, $P \leq .05$.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, MADRS = Montgomery-Asberg Depression Rating Scale, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, STAI = State-Trait Anxiety Inventory, Y-BOCS = Yale-Brown Obsessive Compulsive Scale.
Symbol: … = not applicable.

7 rating 0) for *d*-amphetamine, and 2.6 (range, 0–9; with 6 rating 0) for caffeine.

Mean MADRS scores did not change significantly in either treatment group from baseline to the end of week 1. However, 1 of 4 subjects in the *d*-amphetamine group who had a baseline "moderate depression" MADRS score improved to the mild range, as did 3 of 6 analogous subjects in the caffeine group; and both subjects in the *d*-amphetamine group who had baseline "mild depression" MADRS scores recovered, along with 2 of 4 analogous subjects in the caffeine group. State-Trait Anxiety Inventory scores decreased significantly for the caffeine group, but not for the *d*-amphetamine group (Table 1). There was no significant correlation between percent change in Y-BOCS scores and percent change in either MADRS or STAI scores.

Using caffeine to establish the double-blind was successful: at week 1, the investigators correctly identified the drug group for only 11 of the 24 subjects (46%) and for only 54% of responders; both of these figures are no better than chance. Only one third of subjects correctly guessed their drug assignment (*d*-amphetamine, 42% correct; caffeine, 25% correct.)

Twelve of the 13 continuing subjects maintained or increased their OCD improvement during the next 4 weeks of continued double-blind study drug; 1 subject in the *d*-amphetamine group discontinued at the end of week 2 for inadequate improvement (Y-BOCS score decrease = 20%). At the week 5 rating, the mean Y-BOCS score decreases (last observation carried forward) were as follows: *d*-amphetamine, 48% (range, 20%–80%) and caffeine, 55% (range, 27%–89%) (Table 1). Four subjects (33%) in the *d*-amphetamine group and 6 (50%) in the caffeine group met the criterion for full response.

At endpoint, the mean MADRS score had decreased significantly from baseline in the caffeine group ($t = 2.45$, $P \leq .05$), but not in the *d*-amphetamine group. However, the 3 subjects in the caffeine group with baseline moderate MADRS depression remained moderately depressed, as did the 2 analogous subjects in the *d*-amphetamine group. One subject in the *d*-amphetamine group who had mild depression worsened to moderate depression. Percent changes in Y-BOCS and MADRS scores were not significantly correlated. State-Trait Anxiety Inventory scores decreased significantly from baseline in the *d*-amphetamine group ($t = 2.45$, $P \leq .05$), but not in the caffeine group (Table 1).

The double-blind remained intact. At the end of week 5, the investigators guessed that all subjects (being responders) were receiving *d*-amphetamine, and thus were correct for

5 of 12 (42%); only 1 subject guessed (correctly) that she was taking caffeine, while the rest guessed they were taking *d*-amphetamine, a correct guess rate of 6 of 12 (50%).

Of the 5 subjects who did not respond to caffeine during week 1, four did not respond subsequently to a 3-day, open-label trial of *d*-amphetamine 30 mg/d; one did.

Side effects were mild to moderate and included, in the *d*-amphetamine group, transient insomnia, dry mouth, and decreased appetite and, in the caffeine group, nausea and intermittent jitteriness. Mean (SD) pulse rate in the caffeine group rose from baseline by 2 beats per minute, and in the *d*-amphetamine group from 79 (4) bpm to 90 (14) bpm at week 1 and 101 (14) bpm at week 5. These means were strongly influenced by 1 subject whose pulse rate rose to 127 bpm. Mean (SD) blood pressure increased slightly in the caffeine responder group from 126/80 (9/8) mm Hg at baseline to 130/80 (12/6) mm Hg at week 5, and in the *d*-amphetamine responder group rose from 121/75 (12/7) mm Hg at baseline to 133/89 (18/9) mm Hg. No subject exhibited sustained diastolic hypertension. Study drug dose was reduced to 1 pill daily (caffeine 200 mg or *d*-amphetamine 15 mg) for 6 of 24 subjects (25%) because of adverse events: increased pulse/blood pressure (*d*-amphetamine, 3; caffeine, 1), irritability (caffeine, 1), and nausea and abdominal pain (caffeine, 1).

DISCUSSION

Although the sample size is modest, this is the largest and longest controlled trial of *d*-amphetamine augmentation treatment in patients with OCD. Despite the subjects having treatment-resistant OCD, half the subjects randomly assigned to *d*-amphetamine experienced an immediate, marked reduction in OCD symptom severity, as did somewhat more than half of those randomly assigned to caffeine. Change in OCD severity was independent of change in depression symptoms, and neither study drug was associated with a drug "high" or induced greater drug "liking." The OCD symptom improvement associated with both study drugs was maintained or increased over 5 weeks of double-blind administration, during which the blind was successfully maintained. No subject discontinued the study because of adverse events, but 1 in 4 required a dose reduction. Changes in vital signs in the *d*-amphetamine group suggest the advisability of careful monitoring in any future trials of this augmentation strategy.

Contrary to our hypothesis, augmentation with *d*-amphetamine was not more effective than caffeine augmentation in reducing subjects' OCD symptoms. Given that caffeine appeared to be slightly more effective, in terms of both the number of responders and the degree of response, one interpretation of the study results is that neither drug is pharmacologically effective in OCD, and the response in both treatment groups was due to the placebo effect. In retrospect, we believe that a number of considerations argue against this interpretation. First, as noted earlier, *d*-amphetamine 30 mg/d monotherapy has been reported effective in OCD subjects in 2 single-dose, double-blind crossover trials.[1,2] Second, *d*-amphetamine and caffeine share a neurotransmitter effect: both release dopamine in the brain (with regional variations).[18] Moreover, caffeine also increases cerebral concentration of tryptophan and serotonin and affects serotonin release, uptake, and turnover.[18,19]

Third, the immediate, marked response to both drugs is unlike the response to all other drugs used to treat OCD, and did not diminish with time, as would be expected of a placebo response. Moreover, most responders to both drugs continued to experience benefit during many months of subsequent clinical observation. Four of the 6 *d*-amphetamine responders continued to benefit for at least 6 months; 1 tried augmenting with caffeine instead and experienced a larger response. Of the 7 caffeine responders, 3 elected to try *d*-amphetamine, of whom 1 responded about equally and has continued it for more than 6 months, 1 had a smaller response and returned to caffeine, and 1 had no response. Only 1 of the 4 caffeine nonresponders opting for the open-label *d*-amphetamine trial responded. These poststudy results suggest that response to these 2 drugs, like response to other anti-OCD medications, is idiosyncratic and may reflect differences in underlying central nervous system pathophysiology. Interestingly, differing responses to amphetamine are related to differences in dopamine transporter alleles both in subjects with ADHD[20] and in healthy subjects.[21] Differing responses to caffeine are well established,[18] but the genetic contribution remains to be elucidated.

Finally, placebo response rates among OCD subjects in other double-blind, placebo-controlled augmentation trials, using a ≥35% decrease in Y-BOCS score as the response criterion, have consistently been quite low. In augmentation trials of atypical antipsychotic medications, the mean response rate is 11%.[22] Placebo response rates were 0% in 2 lithium[23] and 2 buspirone[24,25] augmentation trials. These rates are far lower than those we observed utilizing this Y-BOCS criterion (33% [*d*-amphetamine] and 50% [caffeine]). Like subjects in the earlier trials, our subjects had undergone previous drug trials without substantial benefit.

If *d*-amphetamine and caffeine are producing a pharmacologically induced therapeutic effect in OCD, what might be the mechanism? The increased release of dopamine induced by both drugs may increase D_1-receptor stimulation in the prefrontal cortex. This increase is associated with increased attention regulation and working memory in patients with attention-deficit/hyperactivity disorder.[26] These functional improvements could lead to fewer obsessional intrusions, increased ability to shift attention away from them, and, thus, decreased urges to perform compulsions. These changes were, in fact, the kinds of improvement many responders reported. In addition, some noted

increased mental energy, allowing them to pull away from obsessions, and improved mood and decreased anxiety, giving them greater motivation to resist OCD symptoms. Interestingly, some subjects in both groups responded despite also continuing atypical antipsychotic drugs, which preferentially block dopamine D_2 as compared to D_1 receptors. Alternatively, reduced OCD symptoms may reflect interactions between drug-induced changes in dopamine and serotonin activity in various brain regions.[18] Since our study was not aimed at elucidating a mechanism of action, these speculations are extremely tentative.

How could a ubiquitous drug like caffeine, if truly helpful in OCD, have not yet been observed to be beneficial despite being consumed by thousands of OCD patients? One explanation would be as follows. Assume that a plasma caffeine concentration threshold exists for producing a clinical effect in OCD. Then, the single, large dose (300 mg) we administered would produce a higher peak concentration than would smaller repeated doses delivered by caffeinated beverages consumed over a morning or a day. Furthermore, assuming zero-order elimination (elimination rate independent of drug concentration), the blood concentration produced by our single dose would remain above the required concentration threshold for a longer period.[27]

CONCLUSION

Since this study does not rule out a placebo response as the explanation for sustained reduction in subjects' OCD symptoms, neither study drug can be recommended for routine clinical use as an augmentation strategy. However, in view of the immediate, marked, sustained, and frequent response to both *d*-amphetamine and caffeine augmentation, larger, double-blind, placebo-controlled trials of both drugs are indicated. Short-term trials could quickly test whether our results reflect a placebo response or a pharmacologic effect. In a design again comparing *d*-amphetamine and caffeine, bupropion might be added as a placebo condition, since it appears to be ineffective in treating OCD,[28] has some stimulating properties, and is modestly effective in attention-deficit disorder.[29]

Drug names: bupropion (Aplenzin, Wellbutrin, and others), buspirone (BuSpar and others), citalopram (Celexa and others), clomipramine (Anafranil and others), dextroamphetamine (Dexedrine, Dextrostat, and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

Author affiliations: Department of Psychiatry and Behavioral Sciences, Stanford Medical Center, Stanford, California.

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