

# Combined Stimulant and Guanfacine Administration in Attention-Deficit/Hyperactivity Disorder: A Controlled, Comparative Study

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**Objective:** Because models of attention-deficit/hyperactivity disorder (ADHD) therapeutics emphasize benefits of both enhanced dopaminergic and noradrenergic signaling, strategies to enhance D1 and  $\alpha_{2A}$  agonism may yield enhanced clinical and cognitive responses. This study tested the hypothesis that combined effects of a dopamine and noradrenergic agonist, d-methylphenidate extended-release (DMPH) with guanfacine (GUAN), an  $\alpha_{2A}$  receptor agonist, would be clinically superior to either monotherapy and would have equal tolerability.

**Method:** An 8-week, double-blind, 3-arm, comparative trial randomized 7- to 14-year-olds with DSM-IV ADHD to GUAN (1–3 mg/day), DMPH (5–20 mg/day), or a combination (COMB) with fixed-flexible dosing. Outcome measures were the ADHD Rating Scale IV (ADHD-RS-IV) and the Clinical Global Impression–Improvement (CGI-I) scale. Data on adverse events and safety measures were obtained.

**Results:** A total of 207 participants were randomized and received drug. Analyses showed significant treatment group main effects for ADHD-RS-IV ADHD total ( $p = .0001$ ) and inattentive symptoms ( $p = .0001$ ). COMB demonstrated small but consistently greater reductions in

ADHD-RS-IV Inattentive subscale scores versus monotherapies (DMPH:  $p = .05$ ;  $f^2 = .02$ ; and GUAN:  $p = .02$ ;  $f^2 = .02$ ), and was associated with a greater positive response rate by CGI-I ( $p = .01$ ). No serious cardiovascular events occurred. Sedation, somnolence, lethargy, and fatigue were greater in both guanfacine groups. All treatments were well tolerated.

**Conclusion:** COMB showed consistent evidence of clinical benefits over monotherapies, possibly reflecting advantages of greater combined dopaminergic and  $\alpha_{2A}$  agonism. Adverse events were generally mild to moderate, and COMB treatment showed no differences in safety or tolerability.

**Clinical trial registration information:** Single Versus Combination Medication Treatment for Children With Attention Deficit Hyperactivity Disorder (Project1); <http://clinicaltrials.gov/>; NCT00429273.

**Key words:** ADHD, children, guanfacine, methylphenidate,  $\alpha_{2A}$

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Attention-deficit/hyperactivity disorder (ADHD) is the most commonly diagnosed mental disorder in children, with a prevalence of 9%<sup>1</sup>; some 2.8 million children in the United States receive psychostimulant medication. ADHD shows diagnostic persistence (30%–70%) and morbidity into adulthood.<sup>2–4</sup> ADHD outcomes vary regardless of treatment: when persistent, ADHD affects nearly all domains of functioning.<sup>3–6</sup>

Current ADHD medications, including psychostimulants and guanfacine, robustly ameliorate ADHD symptoms in the short term, with “responder” rates of 65% to 75%<sup>7,8</sup> and 50% to 67.5%<sup>9–11</sup> for stimulants and guanfacine, respectively.<sup>12,13</sup> Despite symptom reduction with monotherapies,

there is little evidence to show that medications change long-term trajectories of either symptoms or academic, psychiatric, and social outcomes,<sup>14–19</sup> although some acute<sup>17,20</sup> and follow-up studies find modest academic gains.<sup>21,22</sup> The discordance between symptom reduction from standard treatments and continued impaired functioning long term highlights the importance of identifying treatments that better remediate proximal causes of negative outcomes.

Closer examination of ADHD monotherapy outcomes reveals likely explanations for lack of disorder-modifying effects. Besides the substantial number of nonresponders and those who experience intolerable side effects, too few patients experience “normalization” of ADHD with monotherapy.<sup>7,23</sup> Normalization rates vary by domain: symptomatic normalization with methylphenidate was observed in 58% of children with ADHD in one report, 50% of participants showed normalization of inattention, yet only 30% demonstrated normalized academic efficiency.<sup>20</sup> In the Multimodal Treatment of ADHD study (MTA), even with rigorous dose optimization, only 56% achieved symptomatic



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remission.<sup>24</sup> Such findings contrast with recommendations that remission of ADHD should be a goal.<sup>7</sup>

Recommendations for greater symptom reduction spring from observations that residual symptoms are associated with negative outcomes in school, social, and emotional domains.<sup>2,23</sup> A variety of clinical and contextual factors influence outcomes, but, relevant to medication treatment, cognitive functioning has also emerged as important.<sup>25-28</sup>

Medication effects on cognitive control, encompassing working memory (WM) and inhibitory control, are crucial to consider, given the robust association of their deficits with ADHD,<sup>29,30</sup> as well as influence on outcomes.<sup>25-28</sup> Effects of stimulants on cognition in ADHD are more variable than symptom reduction.<sup>31-33</sup> Data on cognitive effects of guanfacine monotherapy in pediatric ADHD<sup>34</sup> are sparse; no data are available on cognitive effects of combined stimulant plus  $\alpha$  agonists.

Neurochemical models of ADHD and its treatment emphasize catecholaminergic influences on prefrontal cortical functioning (PFC).<sup>35,36</sup> Stimulants are thought to improve PFC function via increasing endogenous dopamine (DA) stimulation, especially at D1 receptors,<sup>37</sup> and increasing norepinephrine (NE) at  $\alpha_2$ -adrenergic receptors.<sup>37</sup> Guanfacine appears to exert beneficial PFC effects through selective postsynaptic  $\alpha_{2A}$  agonism.<sup>38</sup> Agonists at both D1 and  $\alpha_{2A}$  receptors produce inverted U-shaped WM functions.<sup>38-40</sup> In some models, optimal DA stimulation of cortical D1 receptors paired with D2 inhibition of nigral-striatal activity are theorized to underlie stimulant benefits,<sup>41</sup> augmented by noradrenergic effects on reaction time and switching deficits.<sup>42</sup> Taken together, these models suggest that treatments with optimized D1 and  $\alpha_{2A}$  agonism may yield superior effects on clinical and cognitive targets.<sup>36</sup>

The purpose of this study was to test the hypothesis that clinical and cognitive responses in ADHD to combined treatment robustly enhancing both DA and NE would be superior to monotherapies.<sup>35,40</sup> Therefore, we assessed the relative efficacy of a psychostimulant (d-methylphenidate extended-release [DMPH]) versus an  $\alpha_{2A}$  agonist, guanfacine (GUAN), versus their combination (COMB) on ADHD symptoms, clinical response rates, and cognitive outcomes in an 8-week randomized, blinded, comparative trial, using a hybrid within-/between-subjects design with sequential addition of medications to maximize power. Effects on cognition and electroencephalography (EEG) correlates are presented in separate reports.<sup>43,44</sup>

## METHOD

### Participants

The sample consisted of children and adolescents 7 to 14 years of age who were diagnosed with ADHD. All participants were enrolled in the Translational Research to Enhance Cognitive Control (TRECC) ADHD study (ClinicalTrials.gov Identifier: NCT00429273). Participants were recruited from clinic referrals, radio and newspaper advertisements, community organizations (Children and Adults with ADHD [CHADD]; www.chadd.org), local schools, and primary care physicians. Parents and participants provided written

informed permission and assent, respectively. All study procedures were approved by the University of California, Los Angeles (UCLA) institutional review board and were overseen by a data safety and monitoring board.

Inclusion criteria were as follows: male or female individuals 7 to 14 years of age; *DSM-IV* ADHD (any subtype) diagnosed by semistructured diagnostic interview (Kiddie-Schedule for Affective Disorders and Schizophrenia—PL [K-SADS-PL])<sup>45</sup> and clinical interview; and Clinical Global Impression—Severity (CGI-S) score  $\geq 4$  for ADHD.

Exclusion criteria were as follows: autistic disorder, chronic tic disorder, psychosis, bipolar disorder, or structural heart defects; current major depression or panic disorder; systolic or diastolic blood pressure  $>95$ th or  $<5$ th percentile for age and body mass index (BMI); medical condition contraindicating stimulants or  $\alpha$  agonists; and need for chronic use of other central nervous system (CNS) medications.

### Study Design

The study was an 8-week double-blind, randomized, controlled trial with 4 treatment conditions: placebo only, DMPH: d-methylphenidate extended-release (5–20 mg/day) + placebo; GUAN: guanfacine (1–3 mg/day) + placebo; and COMB: treated combination of guanfacine and DMPH. We used a hybrid within-between subject experimental design in which each participant was assessed sequentially in at least 2 different treatment conditions, and maximally to 3 of the 4 treatment conditions. Because of ethical and practical considerations, the order of the treatment conditions was not counterbalanced; instead, participants were randomized in a 1:1:1 ratio to 3 different treatment sequences covering the periods baseline, weeks 1 to 4, and weeks 5 to 8 as follows:

sequence 1: Placebo—Placebo + DMPH

sequence 2: Guan—Guan + Placebo

sequence 3: Guan—Guan + DMPH

Thus, during the first 4 weeks, two-thirds of the participants received guanfacine (sequences 2 and 3) whereas one-third of the participants were given a placebo (sequence 1); beginning in week 5, participants initially given guanfacine added either DMPH (sequence 3) or a placebo (sequence 2) to their regimen, whereas those who started on placebo added DMPH (sequence 1).

Guanfacine (immediate-release form, as guanfacine extended release was not available at beginning of study) and placebo dosing mirrored titration schedules in prior trials.<sup>9,10</sup> Dosing clinicians were blinded to group assignment. Initial dosing was 1 capsule (0.5 mg or placebo) twice daily for week 1; week 2, the dose increased to 1 mg twice daily as tolerated; and week 3, doses increased to 1.5 mg twice daily as tolerated. If Clinical Global Impression—Improvement (CGI-I) ratings were either 1 or 2 (much improved or very much improved), no dose increase was made; no dose increases were allowed after week 3. Optimal guanfacine dose was determined by CGI-I ratings, ADHD Rating Scale—Version IV (ADHD-RS-IV)<sup>46</sup> and side effects at end of week 3, by consensus agreement of 2 independent study clinicians, and was defined as the lowest dose providing maximal improvement while minimizing adverse events. A minimum total daily dose of 1.0 mg was required for continuation.

DMPH (dual-beaded, extended-release formulation) dosing followed published experience.<sup>47</sup> Two dose schedules were based upon baseline weight. Participants  $<25$  kg received 1 capsule (5 mg or placebo) of DMPH once daily for week 5; week 6 the dose was increased to 10 mg DMPH daily; and week 7 the dose was increased to 15 mg daily. For participants  $\geq 25$  kg, DMPH began with 10 mg DMPH once daily; week 6 it increased to 15 mg daily; and week 7 it increased to 20 mg daily. No dose increases were allowed after week 7. Low, medium, and high stimulant doses were assessed weekly for

behavioral response and tolerability to determine the “optimal” DMPH according to the identical process described above.

We note that this differs by degree from a traditional 3-arm longitudinal design with each arm receiving a specific treatment over the entire study period, but this is a hybrid sequential within-/between-subjects design. This design arose from the clinical and ethical need to keep trial length and placebo-only exposure to a minimum. However, the within-subject component also increases statistical power. Moreover, because prior reports show maximal benefit from both treatments within 3 to 4 weeks, this design allows us to compare the medication conditions (placebo, GUAN, DMPH, and COMB) by combining all participants and time points for which that condition occurred, after adjusting for overall drift.

### Outcome Measures

We used ADHD behavioral ratings from independent evaluators and parents, vital signs, electrocardiograms, adverse event

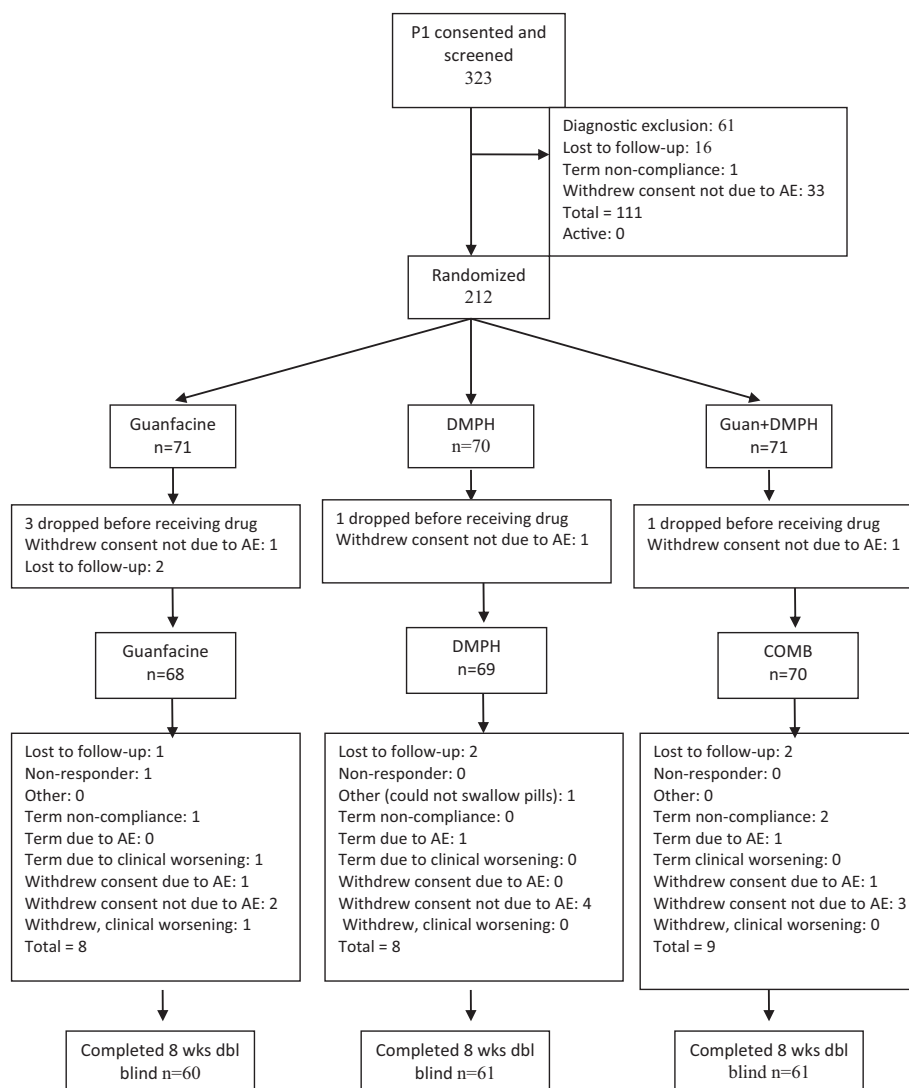
recordings, a cognitive battery,<sup>43</sup> and other secondary measures, including repeat electroencephalograms.<sup>44</sup>

**Symptom Assessments.** A blinded clinician without knowledge of adverse events completed the CGI-S and ADHD-RS-IV at baseline and at the end of each within-subject condition or last visit based on parent, participant, and other available data. A treating clinician completed the CGI-I at baseline and each week.

**Side Effect Assessments.** Side effects were measured via a structured instrument, using a modification of the Physical Symptoms Checklist<sup>48</sup> and open-ended clinician inquiry.

**Clinical Endpoints.** The primary clinical efficacy variables for treatment were the 3 scores from the ADHD-RS-IV (Inattentive and Hyperactive-Impulsive subscales, and total score) and the CGI-I. Our primary definition of treatment response was CGI-I 1 or 2 (“very much improved” or “much improved”) versus nonresponder. We also examined a second response criterion, adding a reduction in ADHD-RS-IV total scores of  $\geq 30\%$  from baseline to week 8 to the initial CGI-I criterion.<sup>24</sup>

**FIGURE 1** Disposition (Consolidated Standards of Reporting Trials [CONSORT]) for all enrolled study participants. Note: AE = adverse event; COMB = combination; DMPH = d-methylphenidate extended-release; GUAN = guanfacine.



## Statistical Analyses

All analyses were conducted in SAS 9.2. For the longitudinal models, we used Proc Mixed, with a compound symmetric covariance structure to account for repeated measurements within participants. The data were modeled with treatment condition (DMPH, GUAN, COMB, or untreated/placebo [UN/PBO]) and time as within-subject effects, and age as a participant-level covariate. Note that in this model, the placebo effect is confounded with the time effect and cannot be estimated separately, as the change from baseline to week 4 for participants in sequence 1 (the group with multiple measurements in the untreated/placebo condition) could be equally explained by effects of retesting or placebo effects. The pairwise comparisons between the different treatment conditions are 1 degree of freedom contrasts of the condition effect in this model. All tests used a 2-sided significance level of  $\alpha = .05$ . For the pairwise comparisons of the treatment conditions, we report Cohen's  $f^2$  effect size difference, which is recommended for analyses involving  $F$  tests or analysis of variance models.<sup>49</sup> Small, medium, and large  $f^2$  values are traditionally defined as 0.02, 0.15, and 0.35, respectively.

For the analyses of treatment response, we used Pearson  $\chi^2$  tests, comparing the rates in the 3 treatment sequences (ending with GUAN alone, DMPH alone, or COMB), along with number needed to treat (NNT)<sup>50</sup> as the effect size. For NNT, small, medium, and large effects are defined as 9, 4, and 2, respectively.<sup>50</sup>

## RESULTS

### Demographics and Disposition

A total of 212 participants were deemed eligible and randomized (Figure 1). Of those, 207 received at least one dose

of study drug and form the safety and intent-to-treat samples (Table 1). Mean age was 10.0 (SD  $\pm$  2.1 years), and 142 (68%) were male. No significant group differences were found for age, IQ, sex, ADHD subtype, height, weight, percentage of oppositional defiant disorder (ODD) comorbidity, or baseline ADHD-RS-IV scores. Mean final (week 8) daily doses of DMPH were 16.0 ( $\pm$  3.9) mg for DMPH-only and 15.1 ( $\pm$  4.8) mg for COMB. Mean final daily doses of guanfacine were 2.2 ( $\pm$  0.7) mg for GUAN-only and 2.4 ( $\pm$  0.6) mg for COMB. Mean mg/kg daily doses of guanfacine were 0.06 ( $\pm$  0.03) mg/kg/d for both guanfacine groups. Exposures to the 2 treatments were comparable to prior studies.<sup>9-11,20,32,51,52</sup> In all, 87.8% of the randomized sample completed the 8-week trial.

### Efficacy Measures

Results of the mixed model analyses are presented in Figure 2A to 2C and Table 2 (additional symptom data in Table S1, available online). There was strong agreement between the raw means and model estimates, suggesting excellent model fit. The corresponding figures show the changes in estimated means by treatment condition from baseline and over time. All participants showed improvement in their ADHD-RS-IV total score over time, independent of treatment condition as demonstrated by the significant effect for visit ( $F = 18.90$ ,  $df = 1$ ,  $p < .0001$ ), and significant effects of treatment condition ( $F = 10.14$ ,  $df = 3$ ,  $p < .0001$ ). Examination of the ADHD-RS-IV Inattentive subscale scores also showed improvements with significant

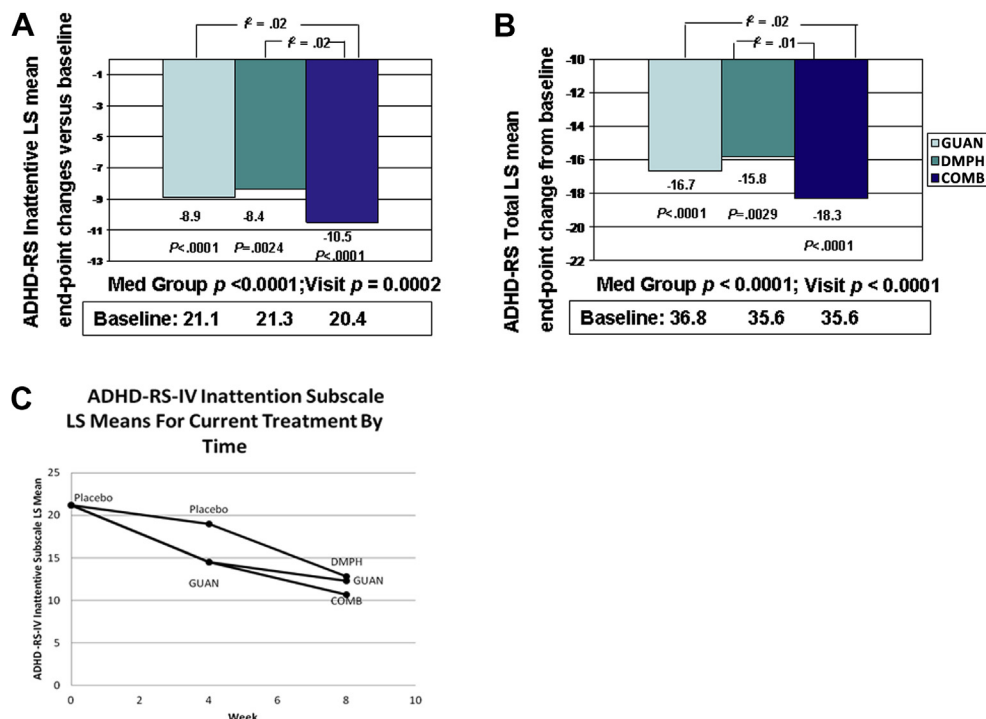
**TABLE 1** Participant Demographics by Assigned Treatment Group<sup>a</sup>

	GUAN (n = 68)	DMPH (n = 69)	COMB (n = 70)	Total (n = 207)
Age, y, mean (SD)	10.1 (2.1)	10.1 (2.0)	9.9 (2.2)	10.0 (2.1)
Sex, n (%)				
Male	45 (66.2)	46 (66.7)	51 (72.9)	142 (68)
Race/ethnicity, n (%)				
White	51 (75.0)	51 (73.9)	41 (58.6)	143 (69)
African American	7 (10.3)	10 (14.5)	19 (27.1)	36 (17)
Asian, Pacific Islander	7 (10.3)	4 (5.8)	5 (7.1)	16 (8)
Other	3 (4.4)	4 (5.8)	5 (7.1)	12 (6)
Hispanic	16 (23.5)	10 (14.5)	18 (25.6)	44 (21.3)
Weight, kg, mean (SD)	39.8 (17.5)	41.6 (16.2)	40.0 (16.7)	40.5 (16.7)
Height, cm, mean (SD)	140.6 (14.4)	142.9 (13.6)	141.2 (14.4)	141.6 (14.1)
Full Scale IQ	102.6 (14.2)	101.5 (13.3)	102.9 (13.0)	102.4 (13.5)
ADHD subtype, n (%)				
Inattentive	28 (41)	33 (48)	31 (44)	92 (44)
Hyperactive/Impulsive	1 (2)	2 (3)	2 (3)	5 (2)
Combined	38 (56)	32 (46)	35 (50)	105 (51)
ADHD-RS-IV baseline, mean (SD)				
Inattentive	21.3 (0.7)	21.2 (0.7)	20.3 (0.7)	
Hyperactive/Impulsive	15.9 (0.8)	17.2 (0.8)	14.7 (0.8)	
Combined	37.1 (1.2)	35.3 (1.2)	35.1 (1.2)	
Comorbidity, n (%)				
ODD	27 (40)	24 (35)	17 (24)	68 (33)

Note: ADHD = attention-deficit/hyperactivity disorder; ADHD-RS-IV = ADHD Rating Scale IV; COMB = combination; DMPH = d-methylphenidate extended-release; GUAN = guanfacine; ODD = oppositional defiant disorder.

<sup>a</sup>Forms efficacy and safety samples. No significant differences between groups (all  $p > .05$ ).

**FIGURE 2** (A) Changes in least-squares (LS) means for Attention-Deficit/Hyperactivity Disorder (ADHD) Rating Scale IV (ADHD-RS-IV) Inattentive subscale scores from baseline to week 8 for the 3 randomized treatment groups. (B) Changes in least-squares means for ADHD-RS-IV Total scores from baseline to week 8 for the 3 randomized treatment groups. (C) Least-squares mean ADHD-RS-IV Inattention subscale scores by current treatment condition from baseline to week 8. Note: COMB = combination; DMPH = d-methylphenidate extended-release; GUAN = guanfacine.



effects for visit ( $F = 14.20$ ,  $df = 1$ ,  $p = .0002$ ) and differences by treatment condition ( $F = 11.28$ ,  $df = 3$ ,  $p < .0001$ ). Similar effects were seen in ADHD-RS-IV Hyperactive-Impulsive subscale scores for visit ( $F = 12.42$ ,  $df = 1$ ,  $p = .0005$ ) and for treatment condition ( $F = 4.09$ ,  $df = 3$ ,  $p = .0069$ ).

To examine the specific nature of the treatment effects, 1 degree of freedom contrasts were used to compare each pair of medication conditions (Table 2). COMB showed superiority for total ADHD-RS-IV total score versus GUAN ( $t = -1.99$ ,  $p = .049$ , 2-tailed;  $f^2 = 0.02$ ), but did not differ statistically from DMPH ( $t = -1.84$ ,  $p = .066$ ;  $f^2 = 0.01$ ). For ADHD-RS-IV Inattentive subscale scores, COMB again showed superiority over GUAN ( $t = -2.28$ ,  $p = .02$ , 2-tailed;  $f^2 = 0.02$ ) as well as a trend of greater improvement than DMPH ( $t = -1.94$ ,  $p = .05$ ;  $f^2 = 0.02$ ); both differences yielded small but consistent effect size estimates. Examination of estimated marginal means shows that compared to the initial placebo-only condition and controlling for time, ADHD-RS-IV Total scores are substantially lower in the GUAN ( $-46\%$ ), DMPH ( $-44\%$ ), and COMB ( $-51\%$ ) conditions.

There were significant differences in treatment response (CGI-I "very much improved" or "much improved") for the 3 treatment sequences, with rates of 81% for sequence 1 (ending with DMPH alone), 69% for sequence 2 (ending with GUAN alone), and 91% for sequence 3 (COMB) ( $\chi^2 = 8.55$ ,  $df = 2$ ,  $p = .01$ ) (NNT 4.6: COMB versus GUAN; NNT 10:

COMB versus DMPH). Using the combined definition of treatment response based on CGI-I and end-of-trial ADHD-RS-IV total scores gave rates of 62%, 63%, and 75%, respectively (NNT 8.5: COMB versus GUAN; NNT 7.5: COMB versus DMPH).

### Safety Assessments

Treatment-emergent adverse events (TEAEs) with a frequency of  $\geq 10\%$  occurring at any time are shown in Table 3. Overall rates for any TEAE (mild, moderate, and severe) were high but did not differ among groups. No serious AEs occurred during the trial. Most TEAEs were mild to moderate in severity. Discontinuation at any time due to TEAEs was low and equivalent across groups: 1.5% (1/68) in GUAN, 1.5% (1/69) in DMPH, and 2.9% (2/70) in COMB. Discontinuation at any time because of lack of efficacy or clinical worsening was uncommon, with 2.9% (2/68) in GUAN, none in DMPH, and 1.4% (1/70) in COMB discontinuing because of these outcomes.

Cardiovascular indices at week 8 showed small changes from baseline. Mean sitting pulse rate declined by  $-4.1$  (12.6) beats/min for GUAN, increased by  $3.6$  (15.7) beats/min for DMPH, and increased by  $4.6$  (16.7) beats/min for COMB. Mean systolic blood pressure declined by  $-2.2$  (13.8) mm Hg for GUAN, increased by  $7.3$  (11.5) mm Hg for DMPH, and increased by  $3.5$  (14.1) mm Hg for COMB. Mean diastolic blood pressure declined by  $-3.8$  (11.4) mm Hg for GUAN,



**TABLE 2** Pairwise Comparisons of Least-Squares Mean Attention-Deficit/Hyperactivity Disorder Rating Scale IV (ADHD-RS-IV) Scores by Assigned Treatment Conditions

ADHD-RS Total Score	Estimated Difference	F	p Value	Effect Size $\eta^2$
COMB vs. Placebo	-10.66 ± 1.99	28.68	<.0001	0.12
COMB vs. GUAN	-2.67 ± 1.35	3.93	.049	0.02
COMB vs. DMPH	-2.89 ± 1.56	3.44	.065	0.01
GUAN vs. DMPH	-0.21 ± 1.31	0.03	.87	0.0001
GUAN vs. Placebo	-7.99 ± 1.22	42.43	<.0001	0.18
DMPH vs. Placebo	-7.77 ± 1.70	20.98	<.0001	0.01
Inattention Subscale	Estimated Difference	F	p Value	Effect Size $\eta^2$
COMB vs. Placebo	-5.89 ± 1.15	26.08	<.0001	0.11
COMB vs. GUAN	-1.79 ± 0.79	5.21	.023	0.02
COMB vs. DMPH	-1.74 ± 0.90	3.75	.054	0.02
GUAN vs. DMPH	0.049 ± 0.76	0	.95	0
GUAN vs. Placebo	-4.10 ± 0.71	33.26	<.0001	0.14
DMPH vs. Placebo	-4.14 ± 0.99	17.41	<.0001	0.01
Hyperactive-Impulsive Subscale	Estimated Difference	F	p Value	Effect Size $\eta^2$
COMB vs. Placebo	-5.10 ± 1.12	20.75	<.0001	0.09
COMB vs. GUAN	-1.10 ± 0.75	2.15	.14	0.01
COMB vs. DMPH	-1.37 ± 0.87	2.45	.12	0.01
GUAN vs. DMPH	-0.27 ± 0.72	0.14	.71	0.01
GUAN vs. Placebo	-4.0 ± 0.69	33.59	<.0001	0.14
DMPH vs. Placebo	-3.73 ± 0.92	16.32	<.0001	0.01

Note: COMB = combination; DMPH = d-methylphenidate extended-release; GUAN = guanfacine.

increased by 5.8 (10.4) mm Hg for DMPH, and increased by 3.7 (9.9) mm Hg for COMB. Changes in the QTcB were minor, with a decrease of -2.7 (16.4) milliseconds for GUAN, an increase of 9.9 (22.5) milliseconds in the DMPH group, and a decrease of -4.4 (20.8) milliseconds for COMB. No participant demonstrated a QTcB interval of  $\geq 500$  milliseconds or an increase of  $>60$  milliseconds during the trial. No clinically significant laboratory findings were observed.

## DISCUSSION

This study represents a novel test of a theory-driven combination of 2 drugs with distinct mechanisms of action for ADHD versus standard monotherapies. It is the first report, to our knowledge, to directly test the benefits of the combination to monotherapies in a sample not ascertained to be partially stimulant responsive.<sup>51,52</sup> Results from this comparative trial provide modest but cogent evidence for the clinical superiority of the combination treatment of a stimulant and an  $\alpha_{2A}$  agonist for the treatment of ADHD. On clinical global measures of response and ADHD symptoms (especially inattentive symptoms), combination treatment in most comparisons showed additional benefits without any evidence of diminished tolerability, safety concerns, or increased side effect burden. The symptomatic benefits of

combination treatment could yield improvements in longer-term outcomes, given the role of residual ADHD symptoms on functioning.<sup>2,23</sup> Results with this combination, based on neurochemical models of ADHD, add support for the “dual” model of the importance of optimized dopaminergic and noradrenergic effects in ADHD therapy.<sup>35</sup>

However, a deeper discussion of the effects of combination treatment is needed to support a determination of “superiority” over monotherapies. These comparisons focus solely on acute clinical effects; our initial interest in combination was its hypothesized superiority for both clinical and cognitive outcomes. A more comprehensive comparison admittedly requires joint consideration of broader effects, and at an individual level. The EEG effects suggest COMB exhibited greater normalizing effects than the monotherapies, by decreasing theta and increasing beta frequency band power.<sup>44</sup> That said, on clinical outcomes alone, in keeping with our hypotheses, COMB showed small but consistently greater reductions in ADHD-RS-IV Inattentive subscale scores to both monotherapies, and surpassed GUAN on ADHD-RS-IV total score comparison, again showing consistent, albeit small, effect size differences on these dimensional endpoints. Despite the small separation on symptom scores in comparison to GUAN, COMB emerged robustly superior by a 22% difference to GUAN on responder comparisons (NNT = 4.6), a moderate effect, with DMPH intermediate (NNT = 10). Importantly, tolerability did not differ by condition.

Can these small effect size differences be clinically significant? As pointed out by Kraemer and Kupfer,<sup>50</sup> treatments with equivalent risk and burden may be deemed clinically superior even with effect size differences far less than the small to medium effects that we have documented for COMB versus both monotherapies. For comparison, our approximate 3-point least-squares mean difference between COMB and the monotherapies is equivalent to the 3-point difference reported in the MTA between medication management versus behavior treatment groups on teacher Swanson, Nolan, and Pelham (SNAP) total scores.

Supporting a role for  $\alpha_{2A}$  modulation in ADHD treatment, our findings add to extant data on the efficacy of an  $\alpha_{2A}$  agonist, guanfacine. Guanfacine has emerged as approved ADHD monotherapy for children and adolescents with ADHD with moderate efficacy.<sup>9-11</sup> Another less selective  $\alpha_2$  agonist, clonidine, has benefits on ADHD symptoms from controlled trials in children with ADHD with<sup>53</sup> and without<sup>54</sup> tic disorders, and as an adjunctive treatment in children with ADHD partially responsive to stimulants.<sup>55,56</sup> Not surprisingly, guanfacine alone showed efficacy in reducing total ADHD symptoms (ADHD-RS total -46% from baseline) in our trial, with a very good clinical response rate (69% improved by CGI-I), nearly identical to a flexibly dosed monotherapy trial in adolescents (68%).<sup>11</sup>

The 2 pivotal trials of guanfacine extended release for ADHD using a randomized, fixed-dose design also showed remarkably comparable reductions in total ADHD symptom reduction by ADHD-RS (45% and 49%), with global responder rates of 54% to 56% and 50% to 56%.<sup>9,10</sup> Overall, our efficacy data with guanfacine appear to be on par with

**TABLE 3** All Treatment-Emergent Adverse Events Occurring During the Double-Blind Phase by Randomized Treatment Groups

Adverse Event, n (%)	COMB (n = 70)	DMPH (n = 69)	GUAN (n = 68)	p Value
Any adverse event	69 (98.6)	66 (95.7)	66 (97.1)	.93
Neuropsychiatric disorders				
Headache	23 (32.9)	23 (33.3)	34 (50.0)	.10
Irritability	18 (25.7)	12 (17.4)	15 (22.1)	.49
Sedation	16 (22.9)	4 (5.8)	12 (17.6)	.02
Somnolence	15 (21.4)	3 (4.3)	16 (23.5)	.01
Affect lability	8 (11.4)	14 (20.3)	7 (10.3)	.16
Gastrointestinal disorders				
Abdominal pain	16 (22.9)	18 (26.1)	19 (27.9)	.83
Abdominal pain upper	10 (14.3)	10 (14.5)	11 (16.2)	.97
Sleep disturbance				
Insomnia	24 (34.3)	20 (29.0)	18 (26.5)	.53
Metabolism and nutrition disorders				
Decreased appetite	25 (35.7)	31 (44.9)	15 (22.1)	.01
General disorders				
Lethargy	16 (22.9)	9 (13.0)	23 (33.8)	.02
Fatigue	12 (17.1)	5 (7.2)	22 (32.4)	.001
Vascular disorders				
Dizziness	7 (10.0)	6 (8.7)	8 (11.8)	.87

Note: COMB = combination; DMPH = d-methylphenidate extended-release; GUAN = guanfacine.

the monotherapy guanfacine extended release trials, with our greater global response rates likely reflecting our younger sample and our use of a fixed-flexible titration scheme, optimizing on clinical response. Notably, the one pivotal trial of guanfacine extended release that reported analyses by ADHD subtype found that those participants with ADHD Inattentive subtype (26% of all participants) in their sample showed no statistically significant benefit of guanfacine.<sup>10</sup> Such a finding suggests that guanfacine addition in our sample, with its higher proportion (44%) of participants with inattentive ADHD, would be predicted to yield less additive benefit. In that light, our observed COMB effects could represent an underestimate of the beneficial effects of COMB in individuals with combined ADHD, and could also support our focus on change in ADHD-RS-IV Inattentive symptoms where COMB showed greater separation from both monotherapies.

DMPH monotherapy showed expected clinical benefits with moderate reductions in ADHD symptoms and an intermediate clinical global response rate of 81% between the 2 comparison arms. Our observed responder rate is comparable to similar trials,<sup>12</sup> including the 79% responder rate in a comparative stimulant trial.<sup>57</sup> Yet the addition of a selective  $\alpha_{2A}$  to DMPH boosted comparative efficacy versus DMPH on most measures. Pairwise comparisons of DMPH to the COMB condition found COMB to be statistically superior to DMPH on ADHD-RS-IV inattentive symptoms and global response rates with small to moderate effect size differences.

Although overall response rates by CGI-I in our trial were high, examination of the other commonly applied combined categorical + dimensional response rate (CGI-I 1 or 2, "very much" or "much" improved, and >30% reduction in ADHD-RS-IV from baseline) is informative. Both

monotherapies yielded expected improvement rates of 62% and 63%, with COMB boosting response to 75% (NNT 7.5 and 8.5, versus DMPH and GUAN, respectively). The impact of these differences in "excellent" responses, although admittedly small to moderate effects, need to be examined over time to discern their clinical significance. However, at the very least, they underscore the continued challenge in ADHD therapeutics to achieve more robust, trajectory-changing outcomes.

The clinical implications of our results suggest that combination of DMPH and GUAN over 8 weeks is associated with substantial clinical benefits on ADHD symptoms in the short term, and is more successful at approaching contemporary goals for ADHD treatment. Our data, taken together with data from positive combined trials showing beneficial effects of guanfacine and clonidine addition to stimulants in ADHD partial responders,<sup>51,52</sup> and combined treatment in children with ADHD and chronic tic disorders,<sup>53</sup> provide solid evidence for the clinical benefits of combined stimulant and  $\alpha$ -adrenergic agonist treatment.

Our results also support the acceptable safety profile of COMB treatment. Adverse events observed were consistent with the literature for both monotherapies.<sup>47,58,59</sup> Guanfacine, as a monotherapy and as COMB, was associated with a greater frequency of sedation, fatigue, and somnolence. Most such adverse events were mild or moderate in severity, and very few participants discontinued due to any adverse events. There was no signal that COMB was associated with a greater adverse event burden or with any unique, serious adverse events.

The cardiovascular effects of the treatments were also consistent with the literature. Taken together with the largest extant studies of stimulants plus an  $\alpha_{2A}$  agonist, available data do not show evidence for added risk of this

combination in the treatment of healthy children and adolescents, although expected effects of bradycardia and hypotension have been observed,<sup>51-53,58,59</sup> and clinical recommendations should include mention of risk of syncope with  $\alpha_{2A}$  agonists. Therefore, the acute safety database for combination stimulant plus an  $\alpha_2$  agonist and initial longer-term data<sup>58,59</sup> argues for acceptable safety and very good tolerability.

Our study findings have several implications for ADHD biology. The primary hypothesis behind the COMB strategy rested on the consistent observations that cognitive control functions, especially WM and inhibitory control, are modulated by dopamine and noradrenaline.<sup>35-37</sup> Theories of ADHD continue to emphasize deficient or “imbalanced” dopamine systems,<sup>36,60</sup> and possibly noradrenergic dysregulation.<sup>35</sup> Although the core pathophysiology of ADHD is unknown, such catecholamine abnormalities are thought to underlie ADHD differences in PFC function, reward processing, and motivation. Arnsten and Pliszka have advanced the notion that DA and NE postsynaptic effects, at optimal levels, exert differing and complementary positive influences on information processing in the PFC.<sup>35</sup> Our data on the effects of COMB treatment on clinical outcomes, especially on inattentive ADHD symptoms, appear to support the above models of ADHD and WM biology and the effects of catecholamine agonists. However, these data do not confirm a dopamine or noradrenergic ADHD “deficit,” and we acknowledge that stimulants also have noradrenergic effects, complicating interpretation. Furthermore, the absence of pro-cognitive effects of guanfacine<sup>43</sup> raises the possibility

that this drug may also be acting presynaptically, or insufficiently engaging the target of prefrontal  $\alpha_{2A}$  receptors.

Although there are many strengths of the study, including blinded comparison of 3 treatments, an ADHD sample not selected for stimulant refractoriness, and flexible dosing to optimize benefit, our findings have several limitations. Larger group sizes would have enabled more conclusive tests of treatment differences. Our study design began with guanfacine first, with the addition of a stimulant second, which may yield differences in comparison to those study designs adding guanfacine to ongoing stimulants, and, like any sequential design, may blur the timing of individual treatment effects when combined. Furthermore, drug dosage was optimized by clinical response rather than cognitive response or biomarker, which might have better separated the treatments. Finally, we note that CGI-I ratings were made by treating clinicians, who were privy to side effect information.

In summary, results from our study suggest modest but consistent additional benefit from a carefully applied combination of a psychostimulant with a selective  $\alpha_{2A}$  agonist, guanfacine, on ADHD symptoms and global clinical responses. Our findings should also serve to encourage further research to identify a range of treatment strategies using other possible approaches to successfully improve the long-term trajectory of ADHD.  $\otimes$



### Clinical Guidance

- A comparison of combination treatment with guanfacine and dexamethylphenidate versus monotherapy with guanfacine or dexamethylphenidate in children and adolescents with ADHD showed that combination treatment was associated with greater improvement, particularly by categorical ratings, during the 8-week trial.
- Benefits of combined treatment may extend beyond children with ADHD who are partially responsive to stimulant monotherapy, based on this study.
- Combined treatment with an  $\alpha$  agonist + stimulant is one approach that may be more likely to achieve the goal of “remission” in ADHD therapy.
- Regular monitoring of cardiovascular parameters and warning parents about risks of syncope and dehydration is recommended when treating with both a stimulant and an  $\alpha$  agonist, but available data suggest no significant changes in overall safety.
- Combination treatment is generally well tolerated by most children and adolescents.

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**TABLE S1** Attention-Deficit/Hyperactivity Disorder (ADHD) Rating Scale IV (ADHD-RS-IV) Estimated and Actual Mean Scores at Baseline, Week 4, and Week 8

Total Estimated and Actual Mean Scores							
Assigned Group	Estimated/Observed	Current Med	Baseline Mean $\pm$ SE	Current Med	Wk 4 Mean $\pm$ SE	Current Med	Wk 8 Mean $\pm$ SE
COMB	Est means	Placebo	36.2 $\pm$ 0.6	Guanfacine	24.0 $\pm$ 0.8	Comb	17.9 $\pm$ 1.3
	Obs means	Placebo	35.6 $\pm$ 1.2	Guanfacine	25.3 $\pm$ 1.3	Comb	17.9 $\pm$ 1.3
GUAN	Est means	Placebo	36.2 $\pm$ 0.6	Guanfacine	24.0 $\pm$ 0.8	Guanfacine	19.5 $\pm$ 1.0
	Obs means	Placebo	36.8 $\pm$ 1.1	Guanfacine	23.5 $\pm$ 1.4	Guanfacine	18.7 $\pm$ 1.5
DMPH	Est means	Placebo	36.2 $\pm$ 0.6	Placebo	31.7 $\pm$ 1.0	DMPH	20.4 $\pm$ 1.3
	Obs means	Placebo	35.6 $\pm$ 1.0	Placebo	31.7 $\pm$ 1.0	DMPH	20.4 $\pm$ 1.0
Inattentive Subscale Estimated and Actual Mean Scores							
Assigned Group	Estimated/Observed	Current Med	Baseline Mean $\pm$ SE	Current Med	Wk 4 Mean $\pm$ SE	Current Med	Wk 8 Mean $\pm$ SE
COMB	Est means	Placebo	21.2 $\pm$ 0.4	Guanfacine	14.5 $\pm$ 0.4	Comb	10.7 $\pm$ 0.7
	Obs means	Placebo	20.4 $\pm$ 0.6	Guanfacine	15.2 $\pm$ 0.8	Comb	10.7 $\pm$ 0.7
GUAN	Est means	Placebo	21.2 $\pm$ 0.4	Guanfacine	14.5 $\pm$ 0.4	Guanfacine	12.3 $\pm$ 0.6
	Obs means	Placebo	21.1 $\pm$ 0.6	Guanfacine	14.5 $\pm$ 0.8	Guanfacine	11.6 $\pm$ 0.9
DMPH	Est means	Placebo	21.2 $\pm$ 0.4	Placebo	19.0 $\pm$ 0.6	DMPH	12.8 $\pm$ 0.7
	Obs means	Placebo	21.3 $\pm$ 0.5	Placebo	19.6 $\pm$ 0.7	DMPH	12.8 $\pm$ 0.7
Hyperactive-Impulsive Subscale Estimated and Actual Mean Scores							
Assigned Group	Estimated/Observed	Current Med	Baseline Mean $\pm$ SE	Current Med	Wk 4 Mean $\pm$ SE	Current Med	Wk 8 Mean $\pm$ SE
COMB	Est means	Placebo	15.0 $\pm$ 0.4	Guanfacine	9.6 $\pm$ 0.5	Comb	7.2 $\pm$ 0.8
	Obs means	Placebo	15.1 $\pm$ 0.9	Guanfacine	10.3 $\pm$ 0.8	Comb	7.3 $\pm$ 0.7
GUAN	Est means	Placebo	15.0 $\pm$ 0.4	Guanfacine	9.6 $\pm$ 0.5	Guanfacine	7.5 $\pm$ 0.8
	Obs means	Placebo	15.6 $\pm$ 0.8	Guanfacine	9.0 $\pm$ 0.8	Guanfacine	7.2 $\pm$ 0.6
DMPH	Est means	Placebo	15.0 $\pm$ 0.4	Placebo	12.7 $\pm$ 0.6	DMPH	7.6 $\pm$ 0.8
	Obs means	Placebo	14.3 $\pm$ 0.8	Placebo	12.8 $\pm$ 0.8	DMPH	7.6 $\pm$ 0.6
<i>Note: Assigned groups are final groups designated as COMB (guanfacine + dexamethylphenidate), GUAN (guanfacine + placebo), DMPH (placebo + dexamethylphenidate). Estimated means are values estimated from the mixed model for each arm at each time point based on the current medication status and accounting for drift over time. Observed means are the raw values for each arm at each time point. Comb = combination; Est = estimated; Med = medication; Obs = observed; SE = standard error.</i>							