Effect of Delayed-Release and Extended-Release Methylphenidate on Caregiver Strain and Validation of Psychometric Properties of the Caregiver Strain Questionnaire: Results from a Phase 3 Trial in Children with Attention-Deficit/Hyperactivity Disorder

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Abstract

Objectives: Inadequately controlled symptoms and associated impaired functioning have a significant negative impact on caregivers of children with attention-deficit/hyperactivity disorder (ADHD). This study aimed to assess the impact of evening-dosed, delayed-release and extended-release methylphenidate (DR/ER-MPH) treatment on caregiver strain, measured by the Caregiver Strain Questionnaire (CGSQ), and present post hoc psychometric analyses assessing the reliability and validity of the CGSQ, its ability to detect change (responsiveness), and to derive responder definitions.

Methods: The CGSQ was an exploratory efficacy endpoint in a phase 3, 3-week, randomized, double-blind, multicenter, placebo-controlled, forced-dose titration trial of DR/ER-MPH in children aged 6–12 years with ADHD (NCT02520388). Psychometric properties of the CGSQ evaluated post hoc included internal consistency using Cronbach’s alpha; test/retest reliability using intraclass correlation coefficients (ICCs); construct validity (known groups and convergent/divergent validity); responsiveness to changes in assessments of ADHD severity (ADHD Rating Scale-IV [ADHD-RS-IV], Conners’ Global Index–Parent [CGI-P], and Clinical Global Impression—Severity [CGI-S]/CGI—Improvement [CGI-I]); and meaningful change threshold (MCT) using receiver operating characteristic curves, which were used to compare response between DR/ER-MPH and placebo groups.

Results: Randomized DR/ER-MPH (54.5) and placebo (54.9) groups had similar mean CGSQ scores at screening. Caregivers of children on DR/ER-MPH reported significant reductions in CGSQ scores after 3 weeks of DR/ER-MPH treatment versus placebo (least-squares mean: 41.2 vs. 49.1; p < 0.001). The CGSQ demonstrated strong internal consistency (Cronbach’s alpha = 0.93). The CGSQ showed strong test/retest reliability (ICC = 0.95). Construct validity was supported by significant associations between the CGSQ and CGI-P (r = 0.74), CGI-S (r = 0.71), and CGI-I (r = 0.72). Responsiveness was demonstrated by the ability of the CGSQ to detect statistically significant changes in ADHD severity scores across treatment groups. The MCT for the CGSQ was estimated at a mean difference of 4.4 points on the CGSQ scale, with a 90% confidence interval ranging from 3.5 to 5.3 points.

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a chronic neurodevelopmental disorder characterized by symptoms of inattention and/or hyperactivity/impulsivity and impaired functioning (American Psychiatric Association 2013; Sallee 2015). Individuals with ADHD experience symptoms and associated impairments from the time of awakening until bedtime. Long-acting stimulants, including methylphenidate (MPH), are recommended as first-line treatment for children and adolescents with ADHD (Pliszka et al. 2017). Although commonly prescribed extended-release stimulants are effective, there remains an unmet need for control of ADHD symptoms and functional impairment that lasts throughout the entire waking day (Whalen et al. 2006; Sallee 2015; Childress 2016; Faraone et al. 2017).

Inadequate control of ADHD symptoms throughout the entire waking day not only impacts the affected individual but also leads to adverse outcomes for families and caregivers. For working parents, most interactions with their children typically occur in the mornings and evenings. Several studies have described that inadequate control of symptoms and related impairment during these bookends of the day is a source of strain for families and caregivers of children with ADHD that persists despite treatment with ADHD medications (Coghill et al. 2008; Sallee 2015; Faraone et al. 2017). In this article, and as previously described (Brannan et al. 1997), caregiver strain refers to the demands, difficulties, and negative consequences experienced by caregivers of children with mental, emotional, and behavioral problems.

In many studies, parents of children with ADHD have identified their children’s behavior as their primary source of stress and these burdens persist despite the use of medications (Brown and Pacini 1989; Coghill et al. 2008; Fridman et al. 2017; Leitch et al. 2019). Caregiver strain increases with increasing ADHD symptom severity, and the effect of symptom severity on treatment seeking is often mediated by caregiver burden (Angold et al. 1998; Theule et al. 2013; Bussing et al. 2015; Babinski et al. 2019). Very few studies, however, have investigated the effect of ADHD medication on caregiver strain. Studies have reported the positive impact of medication on caregivers and/or family using instruments such as the Family Strain Index or quality-of-life measurements (Svanborg et al. 2009; Kim et al. 2014; Silva et al. 2015), but they have not specifically measured the strain that caregivers attribute to caring for a child with ADHD.

Child/parent interactions have been identified as a key contributing factor to strain in caregivers of children with mental health conditions (Frank et al. 2017). Studies have reported improvements in child/parent interactions or child/parent conflicts with ADHD medication (Wilens et al. 2006); however, whether the duration of medication effect into the evening improves child/parent interactions remains equivocal. Stein et al. (1996) reported a reduction in parent/child conflicts with both twice-daily (BID) and thrice-daily (TID) stimulant treatment versus placebo; however, there was no significant difference between BID and TID conditions despite improved evening behavior with TID administration. On the contrary, Chronis et al. (2003) reported that parents reported improved pleasantness in interactions with their children receiving an afternoon stimulant dose versus placebo.

An instrument that focuses specifically on the added strain of caring for a child with an emotional or behavioral disorder is the Caregiver Strain Questionnaire (CGSQ), which covers several areas of caregiver strain. It was originally developed to measure the strain experienced by caregivers of children with serious emotional and behavioral problems over a previous 6-month period. It was validated initially in a sample of caregivers of children with parents in the military who needed mental health services, with a reported internal consistency (Cronbach’s alpha) of 0.93 (Brannan et al. 1997). The CGSQ has since been reported as a valid and reliable instrument across a variety of caregiver samples, including caregivers of children with autism (Stuart and McGrew 2009; Khanna et al. 2012), and Medicaid-enrolled children with emotional and behavioral disorders (Taylor-Richardson et al. 2006). For caregivers of children with ADHD, only the reliability of the CGSQ has been reported (Cronbach’s alpha = 0.92; Vander Stoep et al. 2017).

There is a lack of psychometric data concerning the validity of the CGSQ in caregivers of children with ADHD who are receiving pharmacotherapy. The work described in this article provides psychometric data for the CGSQ in a sample of caregivers of children with ADHD treated with delayed-release and extended-release MPH (DR/ER-MPH; trade name: JORNAY PM®). DR/ER-MPH (formerly HLD200) is an evening-dosed ADHD medication designed to delay the initial release of MPH by ~8 to 10 hours to provide onset of treatment effect upon awakening, lasting into the evening (Childress et al. 2018). Furthermore, without an immediate-release component, DR/ER-MPH has a monophasic pharmacokinetic profile without multiple peaks or troughs during the day (Childress et al. 2018). Two pivotal phase 3 trials of children with ADHD uniquely demonstrated significant improvements in ADHD symptoms and reduced functional impairment from awakening to evening with DR/ER-MPH treatment compared with placebo (Pliszka et al. 2017; Childress et al. 2020).

Herein, we present a prespecified exploratory efficacy endpoint from one of the phase 3 trials (ClinicalTrials.gov identifier: NCT02520388) that assessed the effects of DR/ER-MPH on caregiver strain, as measured by the CGSQ (Brannan et al. 1997), after 3 weeks of treatment with DR/ER-MPH. Post hoc psychometric analyses of the CGSQ are also presented here to confirm the choice of the scale as an adequate measure of strain and to support the validity of treatment effects seen in the phase 3 trial.

Methods

Study participants

Male and female children aged 6–12 years with ADHD were enrolled if they met the predefined study inclusion and exclusion
DR/ER-MPH REDUCES CAREGIVER STRAIN

Difficulties performing a morning routine of

Dosing was initiated at 40 mg/day each evening at 8:00 PM (DR/ER-MPH or placebo once daily each evening for 3 weeks. In the washout phase, participants were randomized in a 1:1 ratio to receive either DR/ER-MPH or placebo once daily each evening for up to 2 weeks (washout of prior medication if necessary, not a purely untreated baseline). Total possible scores ranging from 0 to 54 (DuPaul et al. 1998). Psychometric analyses used ADHD-RS-IV data from screening and week 3. Ratings on the ADHD-RS-IV were also obtained specifically from 6:00 AM to 9:00 AM (ADHD-AM-RS). Psychometric analyses used ADHD-AM-RS data rated over the previous week from baseline (randomization) and week 3. Higher scores indicate greater symptom severity.

Finally, the CGI-S and CGI-I are clinician-rated global scales that provide assessment of severity (CGI-S) and its change from baseline (CGI-I). For the psychometric analyses, the CGI-S scores from screening were used. It is rated on a 7-point scale from 1 (“not at all”) to 7 (“extremely ill”). The CGI-I was administered at week 3 and is also rated on a 7-point scale from 1 denoting “very much improved” to 7 denoting “very much worse” (Guy 1976). Scores below the midpoint indicate improvement and scores above the midpoint indicate worsening.

**Statistical and psychometric analyses**

All analyses were performed on the intention-to-treat (ITT) population, defined as all randomized participants who received at least one dose of study drug and had at least one postbaseline evaluation on the ADHD-RS-IV. The effect of DR/ER-MPH treatment on the CGSQ compared with placebo was assessed at week 3 using a prespecified analysis of covariance model with treatment as the main effect, and study center and baseline score as the covariates.

The *post hoc* psychometric analyses were conducted as part of the validation process for the CGSQ as a measurement of caregiver strain. Internal consistency for caregivers of children with ADHD was evaluated at screening using Spearman correlations and Cronbach’s alpha. Spearman correlations of each item with the total score, omitting the item, were calculated. A threshold of 0.30 (Stevens 1951) was used to evaluate the Spearman correlations. Cronbach’s alpha values were calculated for all items and after each item was deleted.

Test/retest reliability was evaluated using intraclass correlation coefficients (ICCs) between CGSQ total scores at screening and week 3. Test/retest reliability is the degree to which scores on a
scale are consistent when an individual is evaluated under the same conditions, but on different occasions. Ideally, every variable needs to be kept the same, so that the scale can only reflect the construct it is designed to measure (Aldridge et al. 2017). As the evaluation of test/retest reliability of the CGSQ requires assessment of participants under identical treatment conditions, which the study protocol did not account for, assessments were done in participants considered stable, (i.e., those having minimal ADHD-RS-IV score changes of −3 to +3 from screening to week 3). A two-way mixed ICC for absolute agreement was used to assess test/retest reliability (Shrout and Fleiss 1979). While there are no widely agreed upon benchmarks that can be used in the interpretation of the ICC, scale-level ICCs of ≥0.80 (Nunnally and Bernstein 1994) have been proposed as acceptable. For the purposes of this study, the following scheme was used: ICC <0.60 = poor; 0.60 to 0.69 = moderate; 0.70 to 0.79 = good; and 0.80 to 1.0 = very good.

Known-groups validity of the CGSQ was assessed by comparing CGSQ total scores at screening between subgroups defined by measures of ADHD severity (i.e., scores on the ADHD-RS-IV, CGI-S, and CGI-P grouped by tertiles). Convergent and divergent validity refers to the extent to which a measure relates to other measures or variables based on theoretical content, or the expected relationship with the variable(s) chosen. The CGSQ was expected to be correlated with both the ADHD-RS-IV and ADHD-AM-RS because the strain on the caregiver is presumed to be related to the severity of the ADHD symptoms (Angold et al. 1998).

Convergent and divergent validity analyses were based on the hypothesis that CGSQ total scores would be more strongly related to ADHD-RS-IV than ADHD-AM-RS, given that the former assesses outcomes throughout the day, as does the CGSQ. The ADHD-AM-RS assesses morning symptoms only and thus was expected to be less strongly associated with the CGSQ.

The ability of the CGSQ to detect change was evaluated by computing Spearman rank correlations between changes in CGSQ total scores and changes in the CGI-P, ADHD-RS-IV, ADHD-AM-RS, and CGI-I scores. Mean change in CGSQ scores were also compared between participants categorized into tertiles (based on direction and response on CGI-P, ADHD-RS-IV, ADHD-AM-RS, and CGI-I) and among participants categorized into predefined ADHD-RS-IV change categories (worse, stable, minimal improvement, and much improvement in ADHD-RS-IV scores from screening to week 3). Statistical significance was determined using ANOVAs with tests for linear trend to determine if mean changes in scores were different between groups.

Anchor-based estimates of meaningful change (meaningful change threshold [MCT]) for the CGSQ were identified to help interpret CGSQ total scores by providing responder definitions. Receiver operating characteristic curves were used to estimate MCTs by identifying the CGSQ score changes that best discriminated those simultaneously reaching two well-accepted response criteria (≥30% decrease in ADHD-RS-IV and patients categorized into CGI-I of 1 or 2) from those who do not (<30% decrease and CGI-I >2). A mean MCT, based on the responder definitions anchored to ADHD-RS-IV and CGI-I, was calculated and used as a responder definition to compare response (the proportion of patients reaching the responder definition) between DR/ER-MPH and placebo treatment groups using chi-square statistics.

Results

Baseline characteristics

Of the 163 children enrolled across 22 sites, a total of 161 children were included in the ITT population (DR/ER-MPH, n = 81; placebo, n = 80). Demographics and baseline characteristics of the study population have been described in detail elsewhere and were comparable between treatment groups (Pliszka et al. 2017). The mean final dose of DR/ER-MPH was 68.1 mg and ranged from 40 to 80 mg, and the most commonly prescribed final dosing time was 8:00 PM (83.8%) and ranged from 7:00 PM to 9:00 PM (Pliszka et al. 2017). When the baseline characteristics of randomized participants were evaluated, there were no significant differences in mean CGSQ total scores at screening between treatment groups (54.5 vs. 54.9; Fig. 1). At screening, 60.2% of participants were taking at least one medication for ADHD, with 58.4% of participants taking a stimulant medication and 9.3% taking a nonstimulant medication. The proportion of participants using each of these classes of prior medications was similar in the DR/ER-MPH and placebo groups.

Effect of DR/ER-MPH on caregiver strain

After 3 weeks of treatment, caregivers of children treated with DR/ER-MPH reported significantly lower strain compared with caregivers of children who received placebo, as measured by CGSQ total scores (least-squares means: 41.2 vs. 49.1; p = 0.001; Fig. 1). Mean CGSQ score decreased 12 points (20.6%) from screening to week 3 in the DR/ER-MPH group compared with a 4-point decrease (4.4%) in the placebo group (p < 0.001). When evaluated by randomized groups, mean CGSQ scores at screening were comparable between DR/ER-MPH and placebo.

Psychometric properties of the CGSQ

Reliability. Internal consistency of the CGSQ at screening was strong (Cronbach’s α = 0.93). Cronbach’s α remained the same when each item was deleted, and each item-total correlation was above the threshold of 0.30 (Stevens 1951), suggesting that all items contribute equally to the measure (Table 1). The CGSQ also demonstrated good test/retest reliability (ICC = 0.72; Table 2) among caregivers of stable participants (i.e., those with ADHD-RS-IV score changes between −3 and +3 from screening to week 3). Participants who were characterized as stable (n = 31) had no statistically significant change in mean (standard deviation) ADHD-RS-IV scores from screening (30.1 [10.4]) to week 3 (38.9 [11.4]).

Construct validity

Known groups validity was demonstrated for the CGSQ across all groups of increasing ADHD severity. CGSQ total scores increased linearly with CGI-S categories (p < 0.05) as well as ADHD-RS-IV (p < 0.0001) and CGI-P (p < 0.0001) scores. Mean CGSQ total scores were also progressively higher (worse) as ADHD severity worsened (as measured by CGI-S, CGI-P, and ADHD-RS-IV tertiles), with significant linear trends (p < 0.0001; Supplementary Table S1).

Convergent and divergent validity of CGSQ total scores was assessed using correlations with both ADHD-RS-IV and ADHD-AM-RS at screening and baseline, respectively. As hypothesized, the correlation was stronger between CGSQ total scores and ADHD-RS-IV (Spearman correlation: 0.457, p < 0.0001) than with ADHD-AM-RS (0.265, p = 0.0006) confirming convergent and divergent validity of the CGSQ (Table 2).

Ability to detect change

Mean changes in CGSQ total scores were found to have significant linear trends (p = 0.004) across ADHD-RS-IV change categories, suggesting that improvements in ADHD-RS-IV scores are reliably related to improvements in CGSQ total scores (Supplementary Table S2). There were also significant positive
correlations (Spearman correlations: 0.54–0.65, all \( p < 0.0001 \))
between changes in CGSQ total scores with changes in ADHD-RS-IV, ADHD-AM-RS, and CGI-P scores from screening to week 3 (baseline to week 3 for ADHD-AM-RS) as well as with CGI-I absolute scores at week 3 (Table 2). When changes in CGSQ total

scores were examined within the tertiles of ADHD severity, greater changes in ADHD-RS-IV, ADHD-AM-RS, and CGI-P change scores were associated with significantly greater changes in CGSQ total scores (all \( p < 0.0001 \)). Greater improvement reported in CGI-I ratings was also associated with greater improvements (reductions) in CGSQ total scores (all \( p < 0.0001 \); Supplementary Table S2).

**Interpretation of CGSQ scores**

The mean anchor-based MCT for CGSQ total score was estimated as \(-9.0\), computed as an average of the MCTs for \(-6\) decrease in ADHD-RS-IV, 1 or 2 (\(-12\)) for CGI-I of 1 or 2 (\(-12\)). On using this MCT estimate as a responder definition, the proportion of participants with a meaningful change was significantly greater among the DR/ER-MPH treatment group versus placebo (53.2%)

**Table 1. Reliability of the Caregiver Strain Questionnaire**

| CGSQ item                          | Cronbach’s \( \alpha \) | Item-total correlations\(^a\) |
|-----------------------------------|--------------------------|-------------------------------|
| 1. Interruption of personal time  | 0.93                     | 0.72                          |
| 2. Missing work                   | 0.93                     | 0.71                          |
| 3. Family routine disruption      | 0.93                     | 0.72                          |
| 4. Having to do without things    | 0.93                     | 0.71                          |
| 5. Negative mental/physical health effects | 0.93 | 0.68                        |
| 6. Child getting into trouble     | 0.93                     | 0.57                          |
| 7. Financial strain               | 0.93                     | 0.58                          |
| 8. Less attention to other family members | 0.93 | 0.72                        |
| 9. Disruption of family relationships | 0.93 | 0.78                       |
| 10. Disruption of family social activities | 0.93 | 0.73                      |
| 11. Feeling isolated              | 0.93                     | 0.73                          |
| 12. Sad or unhappy                | 0.93                     | 0.72                          |
| 13. Embarrassed                   | 0.93                     | 0.66                          |
| 14. Relating to child (reversed score) | 0.94 | 0.32                        |
| 15. Feeling angry toward child    | 0.93                     | 0.46                          |
| 16. Worried about child’s future  | 0.93                     | 0.51                          |
| 17. Worried about family’s future | 0.93                     | 0.58                          |
| 18. Guilty about child’s illness  | 0.93                     | 0.58                          |
| 19. Resentful                     | 0.93                     | 0.51                          |
| 20. Tired or strained             | 0.93                     | 0.70                          |
| 21. Toll taken on family          | 0.93                     | 0.79                          |

\(^a\)Item-total correlations calculated using Spearman’s rank correlation coefficient.

**Table 2. Reliability, Validity, and Responsiveness of the Caregiver Strain Questionnaire**

| Psychometric property            | CGSQ total |
|----------------------------------|------------|
| Reliability                      | 0.93       |
| Cronbach’s \( z \)              |            |
| ICC (95% CI)                     | 0.72 (0.50–0.86) |
| Validity\(^a\)                   |            |
| ADHD-RS-IV                       | 0.457 (\( p < 0.0001 \)) |
| ADHD-AM-RS\(^b\)                | 0.265 (\( p = 0.0006 \)) |
| Sensitivity to change\(^a\)      |            |
| ADHD-RS-IV                       | 0.62 (\( p < 0.0001 \)) |
| ADHD-AM-RS\(^b\)                | 0.54 (\( p < 0.0001 \)) |
| CGI-P                            | 0.65 (\( p < 0.0001 \)) |
| CGI-I                            | 0.61 (\( p < 0.0001 \)) |

\(^a\)Spearman’s rank correlations.
\(^b\)ADHD-AM-RS at baseline.
Dr/ER-MPH; MCT, meaningful change threshold; CGI-I, Clinician Global Impression—Improvement; DR/ER-MPH, delayed-release and extended-release methylphenidate; ADHS-RS-IV, attention-deficit/hyperactivity disorder rating scale-IV; CGSQ, Caregiver Global Strain Questionnaire; p-Value from chi-square test.

| Responder definition | DR/ER-MPH, n (%) | Placebo, n (%) | Difference (%) | 95% confidence interval | p-Valueb |
|----------------------|------------------|----------------|----------------|-------------------------|----------|
| Responder definition was estimated as the mean MCT for the following anchors: ≥30% decrease in ADHD-RS-IV (–6) and CGI-I ≤2 (–12). | 42 (53.2) | 23 (29.9) | 23.3 | 8.0–38.5 | 0.003 |

b-Value from chi-square test.

ADHD-RS-IV, attention-deficit/hyperactivity disorder rating scale-IV; CGI-I, Clinician Global Impression—Improvement; DR/ER-MPH, delayed-release and extended-release methylphenidate; MCT, meaningful change threshold.

The results should also be considered in light of limitations of the study design discussed previously (Pliszka et al. 2017). The study included children aged 6–12 years, without significant comorbidities, and with at least a partial response to MPH; therefore, the applicability of these findings to parents of children in other age groups, ADHD profiles, and MPH-naive patients, respectively, is unknown. Lastly, the short duration of the study limits extrapolation of findings over the long term.

Conclusions

Caregivers of children with ADHD reported significant reductions in caregiver strain after 3 weeks of treatment with DR/ER-MPH versus placebo, as measured by the CGSQ. Post hoc psychometric analyses found the CGSQ to have strong internal consistency, good test/retest reliability, known groups validity, convergent and divergent validity, and sensitivity to change among caregivers of children aged 6 to 12 years with ADHD. An MCT of –9.0 was estimated for the CGSQ. The proportion of participants receiving DR/ER-MPH who achieved this MCT for the CGSQ was significantly greater than participants receiving placebo.

Clinical Significance

Several studies have described the considerable burden associated with caring for children with ADHD, even when they are receiving pharmacological treatment. Improvements in caregiver strain with 3 weeks of DR/ER-MPH treatment is likely related to the extended duration of effect of DR/ER-MPH, which provides...
control of ADHD symptoms from the early morning through to the evening, typically the times when the majority of family interactions occur. The CGSQ was shown to be a valid and reliable instrument for assessing caregiver strain, and may be helpful in clinical practice to optimize treatment outcomes that may affect the whole family.

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Supplementary Material

Supplementary Table S1
Supplementary Table S2

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