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LEADING ARTICLE

Pharmacologic Management of Cognitive Disengagement Syndrome (CDS) and Implications for Attention-Deficit/Hyperactivity Disorder (ADHD) Treatment: Emerging Treatments and Recommendations for Future Research

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Abstract
Although the study of cognitive disengagement syndrome (CDS; previously called sluggish cognitive tempo) first emerged in the 1980s, very little is known about treating CDS or its impact on evidence-based interventions for attention-deficit/hyperactivity disorder (ADHD) with which it frequently co-occurs. The objective of this leading article was to investigate the existing evidence on medication treatment and CDS, including studies that have examined CDS response to medication and CDS as a moderator of ADHD treatment response. A total of seven studies were identified. At present, the limited existing literature suggests that psychostimulants such as methylphenidate and lisdexamfetamine, as well as atomoxetine, may improve CDS symptoms, although replication and research on related medications is needed. However, there are indications that CDS symptoms may predict a reduced response to methylphenidate in children with ADHD. Although untested, research on the neurobiological, neuropsychological, and behavioral correlates of CDS point to a possible benefit of other ADHD medications (e.g., guanfacine), medications that treat narcolepsy (e.g., modafinil), and medications traditionally used to treat depression and anxiety (e.g., viloxazine, bupropion, fluvoxamine), some of which have also recently been used in ADHD management. The article concludes with recommendations for future research on pharmacologic treatment and CDS.

1 Introduction

Cognitive disengagement syndrome (CDS), previously called sluggish cognitive tempo [1], is a constellation of behaviors that includes daydreaming, staring off or spacing out, mental confusion, lethargy, and slowed behavior or thinking [1–3]. Cognitive disengagement syndrome was first written about in the 1980s, when factor analytic studies produced evidence of a separate "sluggish tempo" factor distinguished from many of the inattentive and disorganized symptoms that are the hallmark of the

Key Points

A limited number of studies have examined the pharmacologic management of cognitive disengagement syndrome (CDS; previously sluggish cognitive tempo), providing preliminary support of the use of methylphenidate, lisdexamfetamine, and atomoxetine in the treatment of CDS.

Evidence suggests elevated CDS symptoms may predict a smaller attention-deficit/hyperactivity disorder symptom response to methylphenidate treatment.

More research is needed to replicate prior study findings and examine additional medications in the treatment of CDS, including related attention-deficit/hyperactivity disorder stimulant medications with similar mechanisms of action (e.g., dexmethylphenidate, mixed amphetamine salts) and medications that may target correlates of CDS (e.g., modafinil, guanfacine, bupropion, viloxazine, and serotonergic antidepressants).

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attention-deficit/hyperactivity disorder (ADHD) inattentive symptom dimension [4, 5]. Historically, CDS has been studied and understood through its convergence with and divergence from ADHD [1, 3], and researchers largely continue to conduct CDS research using ADHD participants given the high comorbidity with ADHD (i.e., 25–40% of youth with ADHD have elevated CDS symptoms) [6–9]. Still, research has shown that CDS is unique from ADHD, as evidenced by many studies documenting different structures and phenomenology [2, 10, 11], neuropsychological profiles [10, 12–14], and correlates (e.g., CDS symptoms uniquely predict internalizing symptoms and social withdrawal over and beyond ADHD symptomology) [1, 2, 6, 10, 11, 15, 16]. Further, the occurrence of CDS has been observed across countries, languages, and cultures, including the USA [8], South Korea [17], Turkey [18], Spain [19], and Iran [20].

Cognitive disengagement syndrome is currently conceptualized as a distinct syndrome, though it is not yet established whether to best conceptualize CDS as a transdiagnostic construct, a domain to advance understanding of ADHD heterogeneity, or a distinct psychiatric disorder [1]. It is also unclear if CDS comprises a single dimension or multiple dimensions, including daydreaming, mental confusion, and hypoactivity [1]. This is in part because CDS-specific rating scales have existed for only little more than a decade and include somewhat different item sets that range from 8 to 15 items [21]. For recent reviews of the reliability/validity, measurement, and conceptualization of CDS, see [1, 12, 21].

Given the growing body of evidence that CDS is distinct from, yet overlapping with, ADHD, researchers have also begun investigating whether CDS symptoms are responsive to evidence-based treatments for ADHD [1, 3]. The purposes of the current leading article were to summarize neurobiological and neuropsychological correlates of CDS to shed light on medication candidates for treatment, review the current evidence regarding medication treatment for CDS or CDS as a moderator of treatment efficacy in individuals with ADHD, and discuss possible future directions in CDS' medication management.

2 Neurobiological Correlates of CDS

Research examining the neurobiological correlates of CDS is quite limited, though most of the current evidence points to irregularities in the dorsal attention network (DAN) and/or default mode network (DMN) [22–26]. The DAN is the network that is activated during goal-driven attention (i.e., selecting stimuli in the environment based on prior information, expectations, and goals, and linking said stimuli to the appropriate motor response) and re-orientation of attention (i.e., attention and adjustment of response to unexpected stimuli) [23], whereas the DMN is activated in instances lacking high attentional and cognitive demand [23]. A study of school-aged children found that CDS symptoms were associated with larger gray and white matter volume in DAN-related brain regions, while adjusting for ADHD-inattentive (ADHD-I) symptoms [22]. A study of adolescents documented CDS-specific hypoactivity of the left superior parietal lobule, a region that is part of the DAN, during a cued flanker task [24]. This contrasts with research showing more activation of the superior parietal lobule during a go-no go task in children with ADHD and elevated CDS symptoms, though this study did not examine whether findings were uniquely related to CDS symptomatology [25]. A study of the event-related potential correlates of ADHD and CDS found that children aged 7–12 years with elevated ADHD and CDS symptoms had similar difficulties on a continuous performance task, though the strongest ADHD-related EEG correlates of these difficulties were not linked to CDS symptoms [26]. However, authors noted that CDS symptoms were correlated with parietal and parietal-central regions (though the correlation was not statistically significant) [26], which is consistent with CDS-specific attentional difficulties being related to DAN disruptions. Overall, this research points toward a link between CDS and impairments in sustained goal-driven attention and re-orientation [22–26]. This may result from a lack of pruning (hence, larger volumes) that would improve the efficiency of goal-driven vigilance and response to unexpected stimuli [22–25]. Such anomalies may give rise to the slower processing speed and apathy observed in CDS [22].

In considering the DMN's role in CDS, studies in typically developing groups find the DMN and DAN to be tightly segregated and anti-correlated, with goal-directed tasks activating the DAN and deactivating the DMN [23]. However, in a study of school-aged children, greater CDS symptoms were associated with less segregation and specification of the DMN and DAN [22]. This aligns with research showing that the DAN may be more related to attention and goal-driven control when an individual is oriented toward stimuli in the environment, whereas the DMN is recruited when processing is internally focused (e.g., introspection, self-reflection, memory) [23]. This has clear implications for CDS, which is marked by internal, rather than external, distraction [27]. These findings are also consistent with less efficient processing in brain networks related to CDS, given the lower specification of networks [22, 23].

Finally, one study had found subcortical anomalies related to CDS symptoms. Ünsel-Bolat et al. [28] found higher white matter integrity in subcortical regions (anterior and posterior internal capsule, bilateral cerebral peduncle, and fornix) linked to CDS in children with and without ADHD [28]. Interestingly, the authors noted that the fornix has projections from the locus coeruleus [28], another subcortical region that is strongly connected to the ventral attention network [23]. The ventral attention network is the network that works in tandem with the DAN with respect to

the re-orienting response, allowing for goal-driven attention to break as necessary to re-orient and respond to relevant stimuli in the environment [23]. Although most of the current research points toward cortical, rather than subcortical, involvement in CDS, specifically the DAN and DMN it is clear more research is needed given the limited number of studies coupled with differing methodologies and discrepant findings.

3 Neuropsychological Correlates of CDS

Prior studies have examined neuropsychological and cognitive correlates of CDS [1, 6, 12]. As slowed thought and/or behavior are core CDS behavioral correlates [1–3], researchers have investigated whether slowed processing speed is part of CDS' neuropsychological profile [10, 12, 14, 29, 40]. However, when compared with both individuals with ADHD who do not exhibit CDS as well as typically developing populations, those with CDS have not consistently demonstrated a slower processing speed [1, 12, 13], though Tamm et al. [29] recently found consistent associations between CDS and slowed cognitive processing. Other evidence to support a link between CDS and a slowed processing speed comes from studies in early childhood [30, 31, 33] that generally showed weak associations, whereas studies of older children and adults have had mixed findings [10, 13, 14, 29, 32–40]. This lack of strong and consistent association was one impetus for changing the terminology from sluggish cognitive tempo to CDS, in addition to the derogatory connotation carried by the word "sluggish" [1, 41, 42].

Although only two studies have examined behavioral re-orienting to novel stimuli in CDS, results this far have been consistent with neurobiological findings implicating the DAN [24, 43]. In fact, one of these studies also observed superior parietal lobule hypoactivity during a cued flanker task [24]. This study, along with another, suggests that individuals exhibiting CDS have difficulty disengaging their attention to re-orient to novel stimuli [24, 43]. Further, unlike some other neuropsychological correlates (e.g., response time variability, working memory), difficulties in re-orienting may differentiate CDS from ADHD [12, 24, 43].

There is some evidence that individuals exhibiting elevated CDS symptoms make more omission errors on sustained attention tasks [2, 10, 14, 39, 44], though again, not all studies have found support for this association [29]. Findings observing more omission errors may suggest weaknesses in signal detection (and hence possible differences in the dorsal and ventral attention networks of the brain) [23] or orientation toward environmental stimuli (and thus possible differences in the DAN and the DMN) [23]. This is also consistent with emerging work showing that CDS is related to more self-reported mind-wandering [45, 46], which is defined by internally focused thoughts [47].

Finally, researchers have investigated whether CDS may be related to differences in reaction time, reaction time variability, working memory, inhibition, intelligence, and cognitive flexibility [12]. While increased reaction time variability and deficits in working memory have been clearly documented in ADHD [48, 49], research to date has been variable with respect to whether these deficits also apply to CDS [12]. Similarly, studies examining intelligence, inhibition, and cognitive flexibility in CDS have shown mixed or weak associations [12].

Taken together with studies examining CDS' neurobiological correlates, findings suggest that medications that target difficulties with sustained attention as a result of internal focus and difficulty re-orienting to novel stimuli (thus resulting in signal detection errors) [12, 22, 24–26, 28], rather than difficulties with executive function linked to subcortical brain regions [12], may be of particular benefit to individuals experiencing elevated CDS symptoms. Importantly, however, medications that target the hallmark symptoms, neuropsychological correlates, and neurobiological correlates of ADHD may still be beneficial given the high co-occurrence and some research indicating overlapping neuropsychological and neurobiological profiles [1, 12].

4 Pharmacotherapy Studies for the Treatment of CDS

There have been four prior investigations (using three unique study samples) evaluating pharmacotherapy for treating CDS symptoms. A summary of analytic details and findings of each study can be found in Table 1. These investigations exclusively focused on ADHD medications, including both psychostimulants and atomoxetine, primarily in individuals with ADHD.

A recent open-label trial of 185 children (ages 8–12 years) with ADHD examined parent and teacher ratings on the Barkley Sluggish Cognitive Tempo Scale-Children and Adolescents [50] before and after treatment [51]. The investigators found methylphenidate improved both parent- and teacher-rated CDS total and CDS daydreaming symptom scores, whereas CDS-hypoactive/sleepy symptom scores improved with treatment by the parent, but not teacher [51]. This study was limited to a 1-month follow-up and included participants who were largely (80% of $N = 185$) diagnosed with an ADHD combined presentation (ADHD-C) [51]. This is particularly important when evaluating and questioning the generalizability of these findings given that many individuals with ADHD who have higher rates of CDS symptoms have been diagnosed with ADHD-I [1].

A randomized controlled trial of 38 adults (mean age = 34.6 years) with ADHD and co-occurring elevated CDS symptoms found that, compared with placebo, lisdexamfetamine improved CDS symptoms with moderately large effect sizes (Cohen's d = 0.61–0.68) [52]. Of note, treatment-related change scores for ADHD and CDS ratings were only modestly correlated (shared variance of 24%), suggesting partial distinctiveness of these two constructs and their lisdexamfetamine response [52]. This study had more balance of individuals diagnosed with ADHD-C (66%) and ADHD-I (34%). The investigators did over-sample for individuals with executive functioning difficulty, which may have resulted in a more impaired population with ADHD and CDS [52]. However, this may make their findings even more promising given this context.

Evidence regarding the efficacy of atomoxetine in the treatment of CDS comes from two papers that used the same parallel-group placebo-controlled data of children between the ages of 10 and 16 years (50–54% with ADHD-I across treatment groups) [53, 54]. Children with dyslexia only and dyslexia plus ADHD (dyslexia+ADHD) were randomized to atomoxetine or placebo and compared following 16 weeks of treatment. Children with ADHD only were also included, though they all received atomoxetine treatment and thus were not included in medication versus placebo analyses. From weeks 16 to 32, there was no placebo control, and analyses were conducted for all included diagnostic groups to examine changes from baseline. After 16 weeks of treatment, children with dyslexia+ADHD had more atomoxetine-related parent- and teacher-reported improvements in CDS symptoms compared with children in the placebo group, and children with dyslexia only had more atomoxetine-related youth-rated improvements in CDS symptoms compared with the placebo group [53]. After 32 weeks of treatment, changes from baseline within the atomoxetine-treated group supported that children had atomoxetine-related improved parent- and teacher-rated CDS symptoms in all three groups: dyslexia+ADHD, dyslexia only, and ADHD only [53]. A subsequent study using the same participants updated the original analyses by adding the total change in ADHD symptoms from baseline as a covariate in the models. Findings suggested a negligible effect on a change in CDS scores, indicating that an atomoxetine-related improvement in CDS ratings was not dependent on a change in ADHD ratings [54]. Beneficial effects of atomoxetine on CDS symptoms (which include hypoactivity/sleepiness) are notable given the side-effect profile of atomoxetine in participants with ADHD, with 15–17% experiencing somnolence with atomoxetine (vs 2–4% with placebo) in controlled trials [55, 56].

Although initial findings suggest that methylphenidate, lisdexamfetamine, and atomoxetine may improve CDS symptoms, it is important to underscore that the current evidence is based on very few studies (i.e., one study sample for each medication has been examined) with both small and limited samples. Replication and the inclusion of populations with elevated CDS without ADHD, for instance, are needed before conclusions can be drawn. Further, there was no randomization in the study examining methylphenidate treatment for CDS [51], and the study of atomoxetine treatment used only partial randomization (i.e., no randomization for the ADHD-only group) and relied heavily on a change from baseline in its conclusions [53, 54]. In addition to addressing these gaps in the literature, research on ADHD stimulant medications with related mechanisms of action (e.g., dexmethylphenidate, mixed amphetamine salts, dextroamphetamine) is clearly warranted.

5 CDS as a Moderator of Treatment Response for ADHD

As summarized in Table 2, three studies have examined whether CDS moderates and impacts medication-treatment response for ADHD symptoms, all of which examined methylphenidate treatment response [51, 57, 58]. The first study examining this question was a naturalistic study by Ludwig et al. [58] that found no differences in treatment response based on either continuous or dichotomous measures of CDS in 88 children (aged 4–17 years) with ADHD [58]. However, a recent open-label trial by Fırat et al. [51] found that higher baseline teacher, but not parent, CDS total symptom scores were associated with a smaller improvement in total ADHD symptoms in 185 children (aged 6–12 years) with ADHD, and higher reported symptoms on the CDS daydreaming subscale were associated with a smaller improvement in inattentive symptoms specifically [51]. The discrepancy in findings by Ludwig et al. [58] and Fırat et al. [51] is further complicated by findings from a double-blind, randomized, placebo-controlled crossover trial by Froehlich et al. [57] which found only CDS-sleepy/hypoactive symptoms predicted diminished methylphenidate-treatment response rated by a clinician masked to treatment allocation (methylphenidate vs placebo) in 171 children (aged 7–11 years) with ADHD. Specifically, masked clinicians reviewed participants' ADHD symptom ratings during both their methylphenidate and placebo periods in comparison to their pre-study baseline scores, and children were considered to be non-responders if clinicians did not rate either allocation period as showing palpable improvement compared with baseline. Children were considered to be placebo responders when the masked clinician rated their response on placebo to be better than both baseline and their methylphenidate period. Froehlich et al. [57] found higher teacher-reported ratings of CDS-sleepy/hypoactive symptoms, but not CDS daydreaming symptoms, predicted masked clinician-rated non-response or placebo response, rather than methylphenidate beneficial response (parent ratings of CDS were not

Table 1 Studies examining medication treatment of CDS

Study	Medication	Sample	Design	Measure of CDS	Findings	Limitations/notes
Fırat et al. (2021) [51]	MPH Long-acting once/day or short-acting 2–3 times/day Minimum 0.3 mg/kg/day Titration period: 1 month	Children with ADHD aged 8–12 (mean = 9.4 years) *N* = 185, 80% ADHD-C, 81% male	Open-label trial comparing pre-treatment ratings to ratings 1-month post-stabilization of medication dose	Teacher- and parent-report on Barkley's Child SCT[a] Rating Scale [50] Subscales: (1) sluggish, (2) daydreaming	MPH related to improvements in: (1) both parent- and teacher-rated CDS daydreaming dimension symptoms, (2) teacher- but not parent-rated CDS sluggish dimension symptoms Older children had greater MPH-related reductions in CDS symptoms whether outcomes were rated by parent or teachers	Non-randomized treatment and dose assignment, no placebo control Limited follow-up Sample only included individuals with ADHD Most of the sample had ADHD-C CDS and ADHD symptoms measured by parent and teacher report
Adler et al. (2021) [52]	LDX 30 mg/day titrated up or down in 20-mg increments over initial 3 weeks (range: 30–70 mg)	Individuals with ADHD aged 18-60 years (mean = 34.6 years) *N* = 38, 66% ADHD-C, 34% male	Randomized placebo-controlled crossover trial (4 weeks on each condition)	Self-report on the CDS subscale of the Barkley Adult ADHD Rating Scale (≥26 on scale for inclusion)	LDX treatment improved CDS symptoms more than placebo, though effects were only significant during the first treatment block (indicating possible carry-over effect) CDS and ADHD change scores only shared 24% variance	Dosing schedules were not randomized Limited follow-up Small sample, only included individuals with ADHD Oversampled for individuals with executive functioning difficulties CDS and ADHD symptoms measured by self-report

Table 1 (continued)

Study	Medication	Sample	Design	Measure of CDS	Findings	Limitations/notes
Wietecha et al. (2013) [53] and McBurnett et al. (2017)[c] [54]	ATX 0.5 mg/kg/day for 3 days, then 1.0–1.4 mg/kg/day	Children and adolescents aged 10–16 years (mean = 12 years) with: Dyslexia+ADHD (N = 124) Dyslexia (N = 58) ADHD[b] only (N = 27) 62% male	Randomized placebo-controlled trial (16 weeks) with open-label extension phase for treatment group (16 additional weeks)	Parent-, teacher-, and self-report on the Kiddie-SCT[a] Multidimensional Self-Concept Scale	By week 16: higher mean changes from baseline for ATX group compared with placebo group for parent- and teacher-reported CDS in dyslexia+ADHD group and youth-rated CDS in dyslexia-only group; ADHD-only group not included in placebo-controlled analyses[b] Post-hoc analyses: adding ADHD total change scores to the models did not alter findings By week 32: children in all 3 groups had parent- and teacher-rated ATX-related changes in CDS scores (compared to their baselines); youth-reported ATX-related changes in CDS scores observed only in the dyslexia+ADHD and ADHD-only groups Post-hoc analyses: adding ADHD total change scores to the models did not alter findings	Did not adjust for ADHD symptoms Original aims did not include analysis of treatment for CDS Heavy reliance on parent ratings (low teacher participation) Non-randomized dose and ADHD-only group[b]

ADHD attention-deficit/hyperactivity disorder, *ADHD-C* ADHD combined presentation, *ATX* atomoxetine, *CDS* cognitive disengagement syndrome, *K-SADS* Kiddie Schedule of Affective Disorders and Schizophrenia, *LDX* lisdexamfetamine, *MPH* methylphenidate, *SCT* sluggish cognitive tempo

[a]Where the name of the scale incorporated "SCT" terminology, we did not update terms to "CDS"

[b]ADHD-only all received ATX treatment and were not randomized to a treatment arm/did not receive placebo

[c]Wietecha et al. [48] and McBurnett et al. [54] utilized the same sample and data

collected). Froehlich et al. [57] also found methylphenidate dose response on parent- and teacher-reported inattentive, hyperactive-impulsive, and total ADHD symptoms was diminished for children who had more CDS sleepy/hypoactive symptoms [57]. Of note, this finding was more striking in children who had ADHD-C compared with ADHD-I [57].

There are many possible reasons for discrepancies in the literature examining the moderating role of CDS in methylphenidate treatment for ADHD. The study by Ludwig et al. [58] observing no moderating effect of CDS on the efficacy of methylphenidate treatment for ADHD used a smaller sample than the other two studies [51, 57]; this smaller sample increases the likelihood of false negatives. Moreover, Ludwig et al. [58] used a brief unidimensional measure of CDS that includes only four CDS items (i.e., "being confused or lost," "daydreaming," "stares," and "drowsiness") [58], whereas the other two studies used more comprehensive rating scales [51, 57] (see Table 2 for more information). Thus, Ludwig et al. [58] may not have observed a moderating effect of CDS because of its limited and potentially less sensitive or comprehensive measure of CDS, particularly given that the two other studies both had measures that captured two possible CDS dimensions [51, 57]: cognitive symptoms involving daydreaming/mental confusion and motor symptoms involving hypoactivity [1]. Differences in study findings may also have been related to discrepancies in the sample composition. Ludwig et al. [58] exclusively examined whether CDS predicted the methylphenidate-ADHD treatment response among children with ADHD-I [58], whereas the two studies reported moderating effects (including children with both ADHD-C and ADHD-I) [51, 57]. Of note, Froehlich et al. [57] found a more marked link between a smaller methylphenidate treatment response in children with ADHD-C compared with children with ADHD-I. Hence, the overall pattern of findings across these three studies suggests that higher levels of CDS symptoms may confer a greater vulnerability to reduced methylphenidate ADHD treatment effects in those with ADHD-C versus ADHD-I.

In summary, given the inconsistency in the pattern of findings across all three prior studies, further examination of the moderating effects of CDS, and possible CDS subdimensions, on methylphenidate response is warranted. Additional avenues for future study include determining whether CDS symptoms moderate the responses to other (stimulant and non-stimulant) ADHD medications as well.

6 Additional Medications to be Examined in Future CDS Studies

As previously mentioned, replication and further examination of methylphenidate, amphetamines, and atomoxetine in the treatment of CDS are needed given the very limited research that has been conducted to date. Future investigation of additional medications targeting the behavioral aspects (e.g., daydreaming, mind wandering, and hypoactivity) and apparent neuropsychological deficits (e.g., signal detection/omission errors, orienting of attention) seen with CDS may also prove fruitful.

Modafinil, which is approved by the US Food and Drug Administration for the treatment of narcolepsy and its associated daytime sleepiness [59], is a logical candidate to address the hypoactive/sleepy aspects of CDS. Intriguingly, modafinil may target the brain-based mechanisms of dysfunction in CDS, given the documentation of CDS-associated abnormalities in the DAN [22–26] and prior evidence that modafinil produces increased activation of the DAN and frontal parietal control network [60].

The alpha-agonist guanfacine may also provide benefit, given previous evidence that individuals with CDS may have a propensity toward signal detection errors [2, 10, 14, 39, 44] and that guanfacine may ameliorate errors of omission in individuals with ADHD [61, 62]. However, evidence from animal studies calls into question the utility of guanfacine in the treatment of CDS, as animal models have suggested specific reductions to impulsivity symptoms and possible worsening of signal detection errors at high doses [63]. Additionally, because 38% of 513 patients receiving extended-release guanfacine in placebo-controlled trials experienced somnolence (compared with 1% of the 149 participants who received placebo) [64], guanfacine-associated sleepiness is a potential barrier to its use in CDS. The adverse effect of guanfacine of somnolence may explain the animal model findings, as somnolence could lead to more omission errors. Of note, although both clonidine and guanfacine share a common mechanism of action as alpha-agonists, clonidine may be theoretically less likely than guanfacine to provide benefit in individuals with CDS as it is generally more sedating [65]. In addition, prior studies suggest that clonidine may have adverse effects on both spatial and temporal orientation [66]. Given this evidence, clonidine may potentially exacerbate CDS-related deficits in both somnolence and orienting of attention.

Finally, medications with the potential to address CDS' core behavioral characteristics (such as daydreaming/mind wandering) along with prominent mental health comorbidities, such as depression, may also be important targets for future study, particularly as CDS is increasingly conceptualized as falling under the internalizing rather than externalizing umbrella of psychopathology [16, 67–69]. For example, bupropion and viloxazine may represent leading candidates to address both the daydreaming aspects of CDS and its mood-related comorbidity. Bupropion has shown utility for the off-label treatment of inattention [70]. This includes potentially addressing CDS-related deficits in signal detection by reducing errors of omission [2, 10, 14, 39, 44, 71].

Table 2 Studies examining the moderating role of CDS in the treatment of ADHD

Study	Medication	Sample	Design	Measure of CDS	Measure of ADHD	Findings	Limitations/notes
Fırat et al. (2021) [51]	MPH Long-acting once/day or short-acting 2–3 times/day Minimum 0.3 mg/kg/day, non-randomized dosing Titration period: 1 month	Children with ADHD aged 8–12 years (mean = 9.4 years) *N* = 185, 80% ADHD-C, 81% male	Open-label trial comparing pre-treatment ratings to ratings 1-month post-stabilization of medication dose	Teacher and parent report on Barkley's Child SCT[a] Rating Scale [50] Subscales: (1) sluggish, (2) daydreaming	Inclusion: K-SADS Lifetime version Outcome: parent and teacher report on SNAP-IV	Higher daydreaming and sluggishness scores at baseline predicted a smaller improvement of teacher-reported ADHD total symptom scores Higher daydreaming scores at baseline predicted a smaller improvement of teacher-reported inattentive symptom scores	Non-randomized treatment and dose assignment, no placebo control Limited follow-up Sample only included individuals with ADHD Most of the sample had ADHD-C CDS and ADHD symptoms measured by parent and teacher report
Froehlich et al. (2018) [57]	MPH Long-acting, osmotic release oral 6 randomized dosing schedules involving 3 dose conditions and placebo	Children with ADHD aged 7–11 years (mean = 8.6 years, ADHD-I; 7.9 years, ADHD-C) *N* = 171, 74% ADHD-I, 70% male	Randomized placebo-controlled crossover trial (4 weeks each)	Teacher report of CDS on 12 items rated on 4-point scale (0 = rarely/never, 1 = sometimes, 2 = often, 3 = very often) EFA produced daydreaming and sluggish/sleepy factors	Inclusion: parent and teacher report on Vanderbilt scales [68, 69] Outcome: Masked physician rating of MPH beneficial response vs non-response/placebo response Parent and teacher report on Vanderbilt scales	Higher ratings of sluggish/sleepy factor associated with non-response/placebo response and diminished MPH dose response on both parent- and teacher-rated ADHD symptoms Effect more marked for ADHD-C vs ADHD-I Daydreaming factor and ADHD subtype were not associated with response to MPH	Limited follow-up Sample only included individuals with ADHD Most of the sample had ADHD-I CDS symptoms measured by teacher report ADHD symptoms measured by parent and teacher report

Table 2 (continued)

Study	Medication	Sample	Design	Measure of CDS	Measure of ADHD	Findings	Limitations/notes
Ludwig et al. (2009) [58]	MPH Short-acting 2–3 times/day Minimum 0.3 mg/kg/day, non-randomized dosing	Children and adolescents with ADHD aged 4–17 (mean = 11.4 years) *N* = 88, 100% ADHD-I, 71% male	Observational design with 1-month follow-up	Parent report of CDS on 4 items included on CBCL [77], defined dichotomously (at least one vs no CDS items rated as "frequently") and dimensionally with total score	Inclusion: K-SADS Epidemiological version Outcome: parent report on SNAP-IV	No differences in response to MPH treatment found based on CDS symptoms modeled either dichotomously or dimensionally	Non-randomized dose assignment, no placebo control Limited follow-up Sample only included individuals with ADHD-I Relatively small sample Non-optimal measure of CDS CDS and ADHD symptoms measured by parent report

ADHD attention-deficit/hyperactivity disorder, *ADHD-C* ADHD combined presentation, *ADHD-I* ADHD inattentive, *ATX* atomoxetine, *CBCL* Child Behavior Checklist, *CDS* cognitive disengagement syndrome, *EFA* exploratory factor analysis, *K-SADS* Kiddie Schedule of Affective Disorders and Schizophrenia, *LDX* lisdexamfetamine, *MPH* methylphenidate, *SCT* sluggish cognitive tempo, *SNAP-IV* Swanson, Nolan, and Pelham version IV scale

[a]Where the name of the scale incorporated "SCT" terminology, we did not update terms to "CDS"

Bupropion also has Food and Drug Administration approval for the treatment of depression [72], which could be important for the treatment of the disengagement and lethargy associated with CDS, along with any co-occurring depressive symptoms. Importantly, however, some formulations of bupropion, such as Wellbutrin®, may increase the risk of suicidal thoughts and behaviors, including among children and young adults aged 24 years or younger [72]. As such, these formulations are not approved for use in people aged younger than 18 years [72]. Viloxazine, a norepinephrine reuptake inhibitor with additional effects on the serotonin system [73] has long been used in Europe to treat depression [74]. Recently, viloxazine was approved by the Food and Drug Administration for the treatment of ADHD in children and adolescents [75]. However, specific data regarding the effects of viloxazine on CDS-related neuropsychological processes and/or neural networks are currently lacking, and the side effects of viloxazine such as somnolence are a possible impediment to its utility in CDS treatment [76]. Some researchers have also called for research examining whether selective serotonin-reuptake inhibitors, such as fluvoxamine, fluoxetine, or sertraline, may be beneficial in the treatment of CDS given the higher prevalence of anxiety and depression in individuals experiencing CDS [1, 2, 6, 10, 11, 15, 16], as well as the overlapping symptoms (e.g., lethargy, difficulties with alertness) [1, 2, 6, 10–12, 15, 16].

7 Conclusions

Despite its emergence in the 1980s, there is still a dearth of knowledge regarding the efficacious treatment of CDS and its possible moderating role of treatment efficacy. There is at present a small amount of literature providing preliminary support of the use of methylphenidate, lisdexamfetamine, and atomoxetine in the treatment of CDS. However, there is also evidence to suggest that, at least pertaining to the management of ADHD symptoms, individuals with ADHD and co-occurring CDS symptoms may be less responsive to methylphenidate treatment. In closing, there is a critical need for: (1) replication of research examining methylphenidate, lisdexamfetamine, and atomoxetine in the treatment of CDS; (2) research examining related ADHD stimulant medications with similar mechanisms of action (e.g., dexmethylphenidate, mixed amphetamine salts) in the treatment of CDS; and (3) research examining medications that target behavioral, neurobiological, and neuropsychological correlates of CDS (e.g., modafinil, guanfacine, bupropion, viloxazine, and serotonergic antidepressants). Research should also strive to move away from studying CDS solely in the context of ADHD, as well as examine the mediators and moderators of medication treatment.

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Authors' Contributions Kelsey K. Wiggs searched for and read the literature and wrote and revised the current article. Tanya E. Froehlich searched for and read the literature and assisted in writing and revising the current article. Stephen P. Becker read the literature and assisted in writing and revising the current article. All authors have read and approved the final submitted manuscript, and agree to be accountable for the work.

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