Variable Patterns of Remission From ADHD in the Multimodal Treatment Study of ADHD

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Objective: It is estimated that childhood attention deficit hyperactivity disorder (ADHD) remits by adulthood in approximately 50% of cases; however, this conclusion is typically based on single endpoints, failing to consider longitudinal patterns of ADHD expression. The authors investigated the extent to which children with ADHD experience recovery and variable patterns of remission by adulthood.

Methods: Children with ADHD (N=558) in the Multimodal Treatment Study of ADHD (MTA) underwent eight assessments over follow-ups ranging from 2 years (mean age, 10.44 years) to 16 years (mean age, 25.12 years) after baseline. The authors identified participants with fully remitted, partially remitted, and persistent ADHD at each time point on the basis of parent, teacher, and self-reports of ADHD symptoms and impairment, treatment utilization, and substance use and mental disorders. Longitudinal patterns of remission and persistence were identified that considered context and timing.

Results: Approximately 30% of children with ADHD experienced full remission at some point during the follow-up period; however, a majority of them (60%) experienced recurrence of ADHD after the initial period of remission. Only 9.1% of the sample demonstrated recovery (sustained remission) by study endpoint, and only 10.8% demonstrated stable ADHD persistence across study time points. Most participants with ADHD (63.8%) had fluctuating periods of remission and recurrence over time.

Conclusions: The MTA findings challenge the notion that approximately 50% of children with ADHD outgrow the disorder by adulthood. Most cases demonstrated fluctuating symptoms between childhood and young adulthood. Although intermittent periods of remission can be expected in most cases, 90% of children with ADHD in MTA continued to experience residual symptoms into young adulthood.

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Decades of research characterize attention deficit hyperactivity disorder (ADHD) as a neurobiological disorder typically first detected in childhood that persists into adulthood in approximately 50% of cases (1–3). Substantial scientific work has examined ADHD persistence—the extent to which children with ADHD continue to meet DSM criteria for the disorder in adolescence and adulthood. However, less research has investigated remission (loss of symptoms and impairment), recurrence, and recovery (sustained remission over time). Most longitudinal ADHD studies simply define remission as "failing to meet DSM criteria," with few attempts to identify or define distinct subtypes and patterns of remission (4–6). Understanding common trajectories of ADHD remission, recurrence, and recovery is critical to informing provider, patient, and family treatment decisions.

In the most detailed past efforts to characterize the trajectory of ADHD, Biederman et al. (7, 8) demonstrated that 65%−67% young adults (mean age, 22 years) with childhood ADHD no longer met full DSM criteria. On the other hand, the vast majority (77%−78%) had clinically elevated ADHD symptoms, impairment, and/or continuation of ADHD treatments. Thus, most participants who were classified as having remitted ADHD on the basis of traditional DSM guidelines still experienced impairing subthreshold ADHD symptoms or experienced "remission" only when receiving ADHD treatment (e.g., stimulant medication). Biederman et al. detected a subgroup of children whose ADHD appeared fully remitted in young adulthood (~22%−23%), signifying possible recovery from ADHD. However, the longitudinal course and optimal definition of full remission remains understudied.

Most longitudinal work on ADHD remission and persistence reports only a single-time snapshot of functioning, even though ADHD is considered a life-course disorder (2, 4–6, 9, 10). There is virtually no scientific information on the extent to which individuals sustain remission long-term (i.e., recover from ADHD symptoms and impairments), experience recurrence of ADHD after remission (i.e., remission was temporary), or fluctuate between full remission, partial remission, and ADHD persistence, that is, whether ADHD might be a waxing and waning disorder. If remission is typically temporary, practice guidelines should emphasize the need for continued ADHD screening or monitoring after remission and for rapid response to symptom reemergence. If ADHD tends to wax and wane, factors modulating phenotypic expression must be identified and person-environment fit emphasized as a crucial framework for evaluation and treatment over time.

In this study, we investigated longitudinal patterns of remission from ADHD in the Multimodal Treatment Study of ADHD (MTA) follow-up (3, 10, 11), which utilized multi-informant assessment to measure ADHD symptoms, impairments, treatment utilization, and comorbidities across 16 years, spanning childhood through young adulthood. Using a thorough stepwise procedure, we 1) validated age-appropriate full remission symptom thresholds in childhood, adolescence, and young adulthood; 2) examined detailed symptom, impairment, comorbidity, and treatment utilization information to classify participants' ADHD as fully remitted, partially remitted, or persistent at each of eight MTA follow-up assessments; and 3) outlined longitudinal patterns of ADHD remission, recurrence, and recovery with attention to onset, duration, type (full or partial), and course of remission.

METHODS

The MTA (12) originally compared 14 months of pharmacological and psychosocial treatments for 579 children (7.0 to 9.9 years old) with DSM-IV ADHD, combined type. Baseline characteristics are summarized in Table S1 in the online supplement. Two years after baseline, 289 classmates were recruited as a local normative comparison group. The MTA continued 14 years of prospective follow-up assessments approximately biennially (eight assessments) until 16 years after baseline (13–16).

Participants

The subsample analyzed here (N=558; 95.3% of the original sample) includes participants with at least one follow-up assessment (beginning 2 years after baseline). Retention in adulthood (among participants who completed a 12-, 14-, or 16-year assessment) was 82% for the ADHD group (N=476) and 94% for the normative comparison group (N=272). On average, participants completed 6.2 of eight possible follow-ups (SD=2.25). Average age was 10.44 years (SD=0.87) at 2 years and 25.12 years (SD=1.07) at the 16-year follow-up.

The subsample did not differ from the full sample on any baseline variable.

Procedures

Follow-up assessments were administered to participants and parents at 2, 3, 6, 8, 10, 12, 14, and 16 years after baseline by bachelor's-level staff who were closely supervised and trained to be objective. Teacher ratings were obtained at childhood and adolescent assessments. For 2.3% of adult assessments, a parent was unavailable and ratings were collected from a nonparental informant (e.g., partner, sibling).

Measures

ADHD symptoms. Child and adolescent symptoms were measured using the Swanson, Nolan, and Pelham rating scale, completed by parents, teachers, and adolescents (17, 18). Symptoms in adulthood were measured using the Conners' Adult ADHD Rating Scale, completed by participants and parents (19). Both instruments measure DSM-IV-TR ADHD symptoms. Respondents rated symptoms over the previous 4 weeks on a scale from 0 (not at all) to 3 (very much). Scores of 2–3 indicated symptom presence, as is standard practice (20).

Impairment. In childhood and adolescence, impairment was measured using the parent-report Columbia Impairment Scale, which assesses 13 impairment domains on a severity scale ranging from 0 to 4 (21, 22). In adulthood, the parent- and self-report Impairment Rating Scale was used to rate impairment globally and in 11 domains on a scale from 0 (no problem) to 6 (extreme problem) (23). For the present study, we validated Columbia Impairment Scale and Impairment Rating Scale thresholds for "absence of impairment" (see section S2 in the online supplement) using normative data from the comparison group. These analyses indicated that for the Columbia Impairment Scale, absence of impairment was optimally defined as a rating ≤1 on all items. For the Impairment Rating Scale, absence of impairment was optimally defined as a rating ≤2 on all items (combining parent- and self-reports using an OR rule) (24).

Psychiatric diagnoses. The Diagnostic Interview Schedule for Children (DISC) (25) was administered using parent- and self-reports. Self-report began at the 6-year follow-up; the DISC was not administered at the 10-year follow-up. The DISC is a structured interview that queries the presence of DSM criteria using screening questions and supplemental probes. All disorders assessed by the DISC were documented. For a list of included disorders, see section S5 in the online supplement.

Service utilization. The Services for Children and Adolescents–Parent Interview (SCAPI) (26) was administered through the 10-year assessment. It collected between-assessment estimates of daily dose and number of days treated for ADHD

medications, as well as psychosocial and educational intervention utilization (including frequency, duration, and type of services). Similar information was collected at ages 12 through 16 using the Health Questionnaire, which queried therapy and medication, including dosages, duration, and type of services (11).

Analytic Plan

Defining full remission. Our first task was to empirically validate a "full remission" symptom count threshold that 1) represents normative symptom count levels based on normative comparison group percentiles (normativity) and 2) maximizes sensitivity and specificity in detecting childhood ADHD cases without residual impairments at follow-up (correct classification). We separately analyzed data from child (age <12 years), adolescent (ages 12–17.99 years), and young adult (age ≥18 years) follow-ups to consider developmentally specific thresholds. After reviewing normativity and correct classification data for each developmental group, selection of final thresholds considered parsimony, theoretical clarity, and ease of use by clinicians.

We began with four face-valid candidate definitions for full remission using equivalent thresholds for inattention and hyperactivity/impulsivity symptom counts (i.e., three, two, one, or none of both inattention and hyperactivity/impulsivity symptoms). We did not test four-, five-, and six-symptom remission thresholds given that five- and six-symptom thresholds indicate the *presence* of elevated symptoms in the DSM-5 A criteria for ADHD, and that the four-symptom threshold has repeatedly demonstrated validity as a norm-based threshold for adolescent and adult ADHD symptom elevations (1, 2, 27).

Each candidate definition used reports from all available informants, which were integrated using an OR rule: if any informant endorsed a symptom, it was counted as present (24). To prevent false negative symptom and impairment reports due to underreporting by participants with ADHD (3, 27), we required those meeting the "remitted" definition (and the "unimpaired" criterion) to have at least one other informant report to corroborate the lack of difficulties. Thus, to be categorized as being in full remission, one must be below the symptom threshold according to combined information from all informants, including at least one besides self.

With respect to normativity, we calculated normative comparison group percentiles for each symptom count threshold and developmental group. In this analysis, we excluded 31 normative comparison group participants with a baseline diagnosis of ADHD. Empirical percentiles were calculated as $m + 0.5k$, where m is the percentage of the comparison group scoring below threshold, and k is the percentage of the comparison group with scores that were at threshold. Based on standard norming procedures for mental health symptom measures, scores below the normative comparison group 84th percentile were considered in the normal range (28).

With respect to correct classification, receiver operating curve (ROC) analyses provide an index of diagnostic accuracy (area under the curve, AUC) for each candidate symptom count threshold (true positives plus true negatives divided by total sample) that optimizes both sensitivity and specificity (29). Absence of impairment (see section S2 in the online supplement) was the ROC criterion (i.e., indicating that symptoms were no longer clinically significant). Within each developmental period, when participants possessed multiple data points, we randomly selected one per participant for the ROC analyses.

Detecting cases with full remission of ADHD. We evaluated all cases for full remission of ADHD at each of eight follow-up assessments. We used a stepped procedure based on an AND rule that first required symptoms to fall below the full remission threshold according to all informants, then required absence of clinically significant impairment, and, finally, required discontinuation of all ADHD intervention for at least 1 month prior to the assessment (see section S3 in the online supplement). Exclusion of currently treated cases from the full remission category does not imply confidence that treatment is in every case dampening symptom expression; rather, it conservatively assures that symptom remission is not due to active treatment. Services for non-ADHD difficulties were allowed. For each assessment, we classified remaining cases as "persistent" or "partially remitted." We utilized a previously validated definition of persistence (3, 10), which applied the DSM-5 symptom threshold (five or six symptoms of either inattention or hyperactivity/impulsivity, depending on age) using the Conners' Adult ADHD Rating Scale (or the Swanson, Nolan, and Pelham rating scale) and an impairment threshold of 3 or higher on the Impairment Rating Scale (or the Columbia Impairment Scale). Partially remitted cases met criteria for neither persistence nor full remission.

Consideration of impairment due to other disorders. Following the stepped review procedure, we reexamined cases below the symptom threshold with continued impairment to estimate whether this impairment was due to residual ADHD symptoms (leading to a classification of partial remission) or to other psychiatric diagnoses, including substance use disorders (leading to a classification of full remission). Because the DISC does not address differential diagnosis, we assembled an expert clinical panel to review cases with clinically significant impairment that might be due to a problem other than ADHD. For each case, three board-certified child and adolescent psychiatrists and four licensed clinical psychologists reviewed psychiatric diagnoses, domains of impairment, ADHD symptom endorsements, and treatment utilization. They judged whether reported impairments were best explained by residual ADHD symptoms or a concurrent substance use or mental disorder. Most decisions (80.9%) were unanimous; no split vote had more than two dissenters. For further details, see section S5 in the online supplement.

Longitudinal patterns of remission, recurrence, and recovery from ADHD. Recurrence was defined as meeting criteria for "persistence" (full recurrence) or "partial remission" (partial

TABLE 1. Comparison of symptom remission thresholds in childhood, adolescence, and adulthood in the Multimodal Treatment Study of ADHD

Symptom Count Threshold	Symptom Remission (%)	Normative Percentile[a]	AUC[b]	SE	95% CI	p	Sensitivity (%)	Specificity (%)	False Positive (%)	False Negative (%)
Childhood										
≤3	18.5	72.5	0.675	0.041	0.595, 0.755	<0.001	49.2	85.8	14.2	50.8
≤2	13.2	66.1	0.658	0.042	0.576, 0.741	<0.001	41.0	90.7	9.3	59.0
≤1	10.0	54.4	0.640	0.043	0.556, 0.723	<0.001	34.4	93.5	6.5	65.6
0	5.3	23.1	0.582	0.043	0.499, 0.666	0.038	19.7	96.7	3.3	80.3
Adolescence										
≤3	17.7	60.3	0.681	0.044	0.595, 0.767	<0.001	50.0	86.2	13.8	50.0
≤2	12.7	51.3	0.687	0.045	0.599, 0.776	<0.001	46.2	91.3	8.7	53.8
≤1	8.1	37.7	0.670	0.046	0.529, 0.761	<0.001	38.5	95.6	4.4	61.5
0	5.0	15.0	0.623	0.047	0.531, 0.714	0.004	26.9	97.7	2.3	73.1
Adulthood										
≤3	40.3	81.0	0.732	0.027	0.679, 0.786	<0.001	71.8	74.7	25.2	28.2
≤2	31.2	71.2	0.721	0.029	0.665, 0.777	<0.001	61.0	83.2	16.8	38.9
≤1	20.3	49.0	0.660	0.031	0.600, 0.721	<0.001	42.0	90.1	9.9	58.0
0	7.4	16.8	0.552	0.031	0.491, 0.614	0.088	14.5	96.0	4.0	85.5

[a] The normative percentile is based on age-matched data from the Multimodal Treatment Study of ADHD's local normative comparison group.
[b] AUC=area under the curve

recurrence) after a period of full remission. We defined recovery as full remission of ADHD sustained for at least two consecutive assessments without a subsequent recurrence (full remission until study endpoint). On four occasions, a data point was missing but was bookended with two episodes of full remission. Here, continuity of recovery was assumed but the missing data point was not counted when the duration of full remission was calculated. In addition to the recovery pattern, three additional longitudinal patterns were defined. Stable persistence was persistent ADHD over the entire follow-up. A fluctuating pattern was defined by at least two changes in classification since baseline diagnosis of ADHD, in the absence of the recovery pattern. Stable partial remission was defined as displaying one classification change from persistent ADHD to partial remission that continued until study endpoint.

RESULTS

Defining the Symptom Threshold for Full Remission of ADHD

Normative comparison group percentile ranks indicated that across developmental periods, all candidate definitions for full remission of ADHD represented symptom counts within the comparison group's normative range of functioning (<84th percentile). AUC confidence intervals (Table 1) indicated that across developmental periods, all four candidate definitions detected absence of impairment at a level greater than chance (AUC>0.5). A stepwise series of curves indicated an increasing ratio of sensitivity to specificity when moving from the zero- to the three-symptom threshold.

For childhood and adulthood, the three-symptom threshold demonstrated optimal diagnostic accuracy (i.e., AUC value) and normativity (i.e., most normative comparison group participants had three or fewer ADHD symptoms in childhood [72.5%] and adulthood [81.0%]). Although the two-symptom threshold demonstrated optimal diagnostic

accuracy in adolescence, the three-symptom threshold was ultimately preferred because normativity was stronger for this threshold (60.3% of normative comparison group participants had three or fewer symptoms in adolescence, compared with 51.3% for the two-symptom threshold) and the two- and three-symptom thresholds did not significantly differ in AUC values (0.681 compared with 0.687; z=0.54, p=0.652). Adopting the three-symptom threshold for all developmental periods allowed parsimony and ease of use.

Detecting Cases With Full Remission of ADHD

Table 2 outlines the stepped classification process and lists the proportion of fully remitted cases by assessment at each step. Across assessments, the percentage of fully remitted cases ranged from 1.4% (at the 2-year assessment) to 18.5% (at the 10-year assessment). The percentage of partially remitted cases ranged from 37.2% (at the 10-year assessment) to 51.4% (at the 2-year assessment). The percentage of persistent cases (i.e., participants who met DSM-5 criteria for ADHD) ranged from 39.7% (at the 14- and 16-year assessments) to 55.9% (at the 6-year assessment).

Longitudinal Patterns of Remission, Recurrence, and Recovery From ADHD

Table 3 displays longitudinal patterns of remission, recurrence, and recovery as percentages of the whole sample (ADHD group) and selected subgroups (e.g., those with at least one full remission period). In total, 31.4% (N=175) of the sample met criteria for full remission for at least one time point. Among 175 fully remitting cases, 59.4% (N=104) demonstrated full (29.1%) or partial (30.3%) recurrence of ADHD after the initial episode of full remission. Recovery from ADHD was detected for 9.1% (N=51) of the sample. Additionally, 10.8% (N=60) of the sample were in the persistent category at all time points, 15.6% (N=87) experienced partial remission that was maintained through study

TABLE 2. Case classification at each assessment point in the Multimodal Treatment Study of ADHD[a]

Years After Baseline	N	Age (years)		Step 1: Below Symptom Threshold		Step 2: Below Symptom Threshold + Absence of Impairment[b]		Step 3 (Full Remission): Below Symptom Threshold + Absence of Impairment + Absence of Treatment[c]		Partial Remission		Persistent ADHD	
		Mean	SD	N	%	N	%	N	%	N	%	N	%
2	531	10.43	0.86	85	16.0	29	5.5	8	1.4	273	51.4	250	47.1
3	485	11.73	0.92	95	19.6	27	5.6	10	2.1	229	47.2	246	50.7
6	449	14.94	0.96	65	14.5	20	4.5	15	3.3	183	40.8	251	55.9
8	429	16.79	0.96	93	21.7	36	8.4	26	6.1	202	47.1	201	46.9
10	422	18.69	0.93	157	37.2	82	20.1	78	18.5	157	37.2	187	44.3
12	420	21.05	1.09	193	46.0	80	19.0	77	18.3	159	37.9	184	43.8
14	438	23.17	1.09	208	47.5	86	19.6	80	18.3	184	42.0	174	39.7
16	418	25.12	1.07	196	46.9	64	15.3	61	14.6	191	45.7	166	39.7

[a] To define persistence, we applied the DSM-5 symptom threshold using the Conners' Adult ADHD Rating Scale (or the Swanson, Nolan, and Pelham rating scale) and impairment threshold of "3 or higher" based on the Impairment Rating Scale (or the Columbia Impairment Scale). Partially remitted cases were those who met criteria neither for persistence nor for full remission.
[b] Includes 18 cases that were reintroduced after determining that impairment was fully explained by another mental disorder or substance use disorder.
[c] Absence of ADHD treatment was defined as absence in the past 30 days of medication, behavior therapy, and school services for ADHD.

endpoint, and 63.8% (N=356) demonstrated a pattern of fluctuating ADHD (Figure 1). Four cases had insufficient information for longitudinal classification. Supplemental analyses (see Figure S10 in the online supplement) illustrate longitudinal classifications when full and partial remission statuses were collapsed into one "remission" category. When the data were structured in this way, 48.5% met criteria for the fluctuating status by study endpoint.

Among the 9.1% who demonstrated recovery by the final MTA assessment (mean age, 25.12 years [SD=1.07]), the median duration of the recovery period was 4 years. Of the 51 participants classified as recovered, onset of recovery came in adulthood for 76.5% (N=39), in adolescence for 21.5% (N=11), and in childhood for 2.0% (N=1). Figure 2 depicts sample cases for the fluctuating and recovery patterns.

TABLE 3. Patterns of full remission, recurrence, and recovery from ADHD in the Multimodal Treatment Study of ADHD (N=558)

Subsample and Measure	N	%	Percent of Total sample
Full remission subsample	175		31.4
Remission at one assessment	85	48.6	15.2
Remission at multiple assessments	90	51.4	16.1
No recurrence	42	24.0	7.5
Partial recurrence[a,b]	53	30.3	9.5
Full recurrence[a,c]	51	29.1	9.1
Unable to judge recurrence[d]	29	16.6	5.2
Recovery subsample[e]	51		9.1
Duration of recovery period (N=51)			
2 years	18	35.3	3.2
4 years	17	33.3	3.0
6 years	7	13.7	1.3
8 years	6	11.8	1.1
≥10 years	3	5.9	0.5
Onset of recovery (N=51)			
Childhood (under age 12)	1	2.0	0.2
Adolescence (ages 12 to 17.99)	11	21.5	2.0
Adulthood (age 18 or over)	39	76.5	7.0

[a] The mean time from remission detection to recurrence detection was 2.60 years (SD=1.22).
[b] Met criteria for partial remission after an initial episode of full remission.
[c] Met full criteria for ADHD after an initial episode of full remission.
[d] Recurrence could not be judged when remission solely occurred at final time point.
[e] Recovery was defined as full remission that persisted for at least two consecutive assessments without being followed by a recurrence (includes first episodes of remission or recurrent episodes that meet this criteria). Eight cases that were classified as recovered experienced full remission followed by partial or full recurrence, and finally a second period of full remission that led to recovery, whereas 43 experienced no recurrence after the initial episode of full remission.

DISCUSSION

Our goal in this study was to understand the longitudinal course of ADHD remission from childhood to young adulthood. The results indicate that approximately one-third of children with ADHD experienced full remission at some point during 14 years of prospective longitudinal study. A majority of these fully remitting youths (∼60%) experienced full or partial recurrence of ADHD after the initial period of full remission. Only 9.1% of the children with ADHD demonstrated recovery from ADHD (i.e., sustained remission to study endpoint; mean age, 25 years) and only 10.8% demonstrated stable ADHD persistence across all time points. For most of the sample (63.8%), the follow-up period was characterized by fluctuating persistence and remission (full or partial) in the absence of recovery.

The results are consistent with previous findings that, at a single time point, most individuals who no longer meet DSM criteria for ADHD still experience elevated symptoms or impairments or are actively treated with medication (see Table 2) (7, 8). In the present study, full remission at a single assessment ranged from 1.4% to 18.5%. Young adult assessments corresponding temporally with Biederman and colleagues' estimates (i.e., 12- and 14-year assessments) demonstrated comparable full remission rates (18% compared with 22%−23%) (7, 8). Expanding on previously reported MTA findings (10), the present study indicates that 40%−50% of the ADHD group met DSM criteria for ADHD at any given follow-up. However, remission was typically partial, rather than full. The high prevalence of partial remission is consistent with the finding of Hechtman et al. (10) that many MTA ADHD group participants who did not meet ADHD symptom criteria in adulthood still suffered significant impairments. We also confirmed that most recoveries from ADHD begin in adulthood (see Table 3), although this finding could be partially an artifact of having fewer later assessments to detect recurrences.

The MTA's longitudinal perspective highlights that full remission at a single time point should not be conflated with recovery from ADHD. Only 9.1% of the MTA sample experienced recovery (i.e., sustained remission for multiple time points until study endpoint). After a period of full remission, recurrent ADHD symptoms were the rule, rather than the exception. Overall, the results suggest that over 90% of individuals with childhood ADHD will continue to struggle with residual, although sometimes fluctuating, symptoms and impairments through at least young adulthood. Our more nuanced longitudinal estimate of remission challenges claims that approximately half of children with ADHD outgrow their difficulties by adulthood.

On the other hand, few participants (10.8%) were characterized by a stable pattern of ADHD persistence across the follow-up period. Among those who did not recover, most experienced either stable partial remission (15.6%) or fluctuating, waxing and waning ADHD symptoms (63.8%) from childhood to young adulthood. This finding echoes Lahey et al. (30), who detected longitudinal symptom fluctuations in childhood ADHD that produced temporal instability in ADHD subtypes. Because our study was observational, we cannot draw definite conclusions about the causes of remission. However, we speculate about several possible sources of the waxing and waning symptom pattern. First, considering trait-state-error models of longitudinal data (31), these fluctuations may reflect a combination of individuals' genetic risks (i.e., traits), environmental factors (i.e., states), and measurement error. The high heritability of ADHD is well established (32), and we speculate that genetic risks for ADHD may reflect a propensity for symptom expression that is dependent on environmental factors (e.g., changes in teachers, living arrangements, academic setting or level, type of employment, and relationships with employment supervisors, roommates, and significant others). For example, the MTA data set

FIGURE 1. Longitudinal and cross-sectional patterns of remission, recovery, and persistence in the Multimodal Treatment Study of ADHD[a]
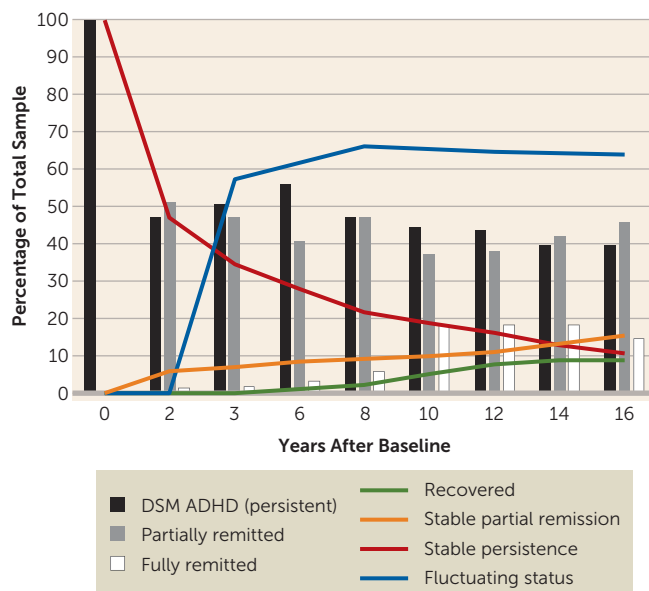

[a] Bar graphs indicate cross-sectional estimates for persistence, partial remission, and full remission of ADHD; line graphs display longitudinal patterns by time point. We defined recovery as untreated full remission of ADHD that persisted for at least two consecutive assessments without being followed by an episode of recurrence (that is, full remission continued until study endpoint). The green line in the graph thus represents the percentage of participants who had experienced onset of recovery by the corresponding time point. Individuals were classified as displaying stable persistence if they demonstrated persistent ADHD for all assessments to date in the follow-up period. The red line represents the percentage of participants who continued to demonstrate stable persistence at a given time point. Stable partial remission was defined as displaying one classification change from persistent ADHD to partial remission that was maintained until study endpoint. The orange line represents the percentage of participants who had experienced onset of stable partial remission by the corresponding time point. A fluctuating pattern indicated at least two changes to cross-sectional classification since baseline diagnosis of ADHD, in the absence of the recovery pattern. The blue line represents the percentage of participants who met criteria for fluctuating status at a given time point (which precludes also meeting criteria for recovery at any future time point within the study period).

previously revealed that adolescents with ADHD display temporary ADHD symptom spikes at the middle school transition (33). Measurement error, regression to the mean, and informant biases could contribute to apparent changes in symptoms and impairment. Nevertheless, the fluctuating patterns detected here reveal ADHD to be a dynamic rather than a static disorder. The extent to which environmental influences modulate symptom expression through neurobiological, basic cognitive, psychological, and behavioral mechanisms should be a future direction for research.

Our greatest limitation is that MTA follow-up was discontinued when participants were approximately 25 years of age. Therefore, it is not clear how longitudinal trends will continue into middle and older adulthood. Similarly, it is unclear whether the recovery pattern reflects permanent remission.

FIGURE 2. Sample cases with fluctuating and recovery patterns of remission of ADHD[a]

Case A: Fluctuating Pattern of Remission

Case B: Recovery Pattern
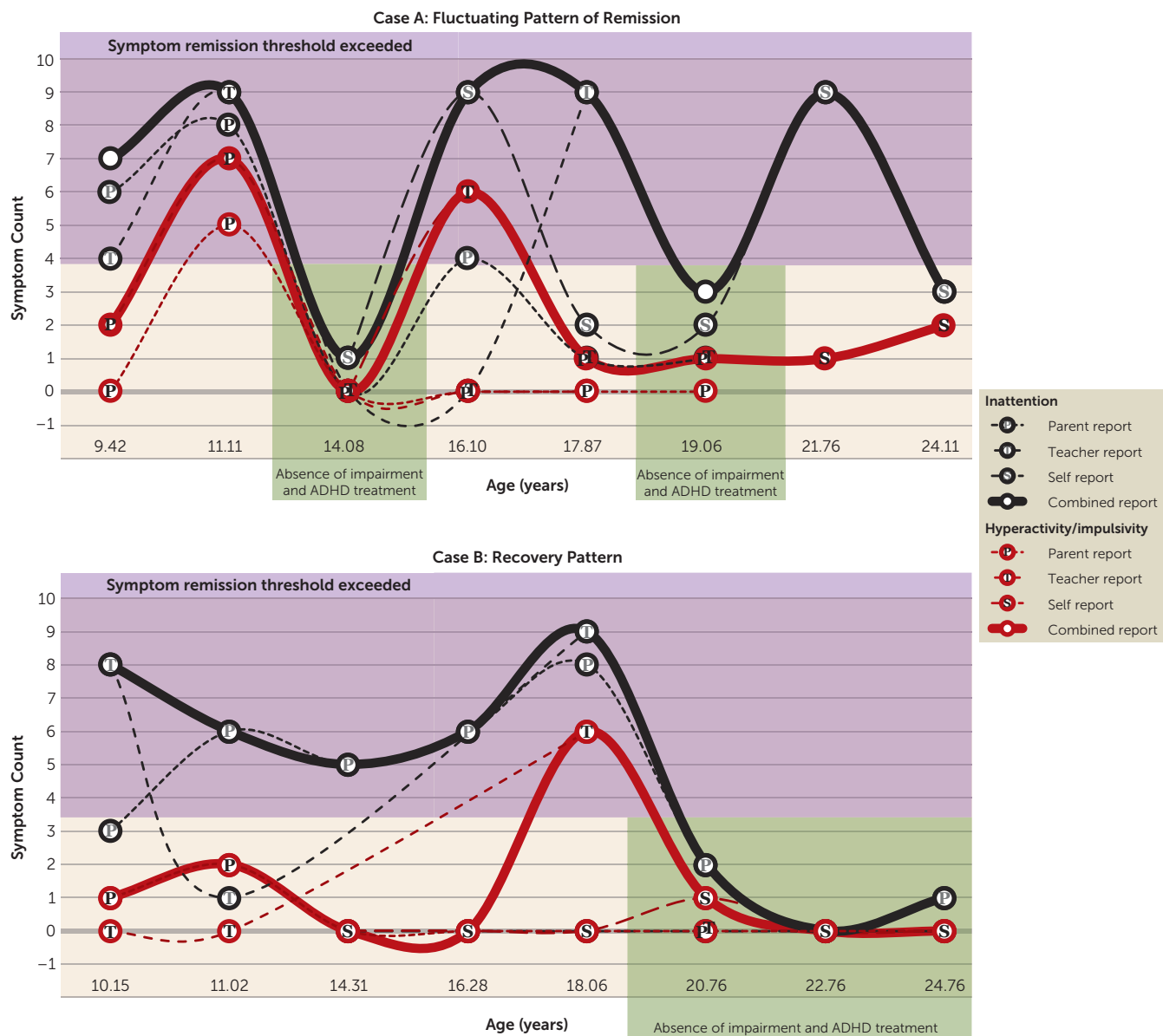
[a] Case A demonstrated clinically significant impairment during the 2-year (age 9.42), 3-year (age 11.11), 8-year (age 16.10), 10-year (age 17.87), and 16-year (age 24.11) assessments and was treated with methylphenidate during the 8-year assessment and with atomoxetine during the 14-year assessment (age 21.76). Case B demonstrated clinically significant impairment during the 2-year (age 10.15) through 10-year (age 18.06) assessments and was treated with methylphenidate during the 2-year, 3-year, and 6-year assessments (ages 10.15 through 14.31), received a classroom behavioral intervention for ADHD at the 3-year assessment (age 11.02), and attended a special school for ADHD at the 8-year assessment (age 16.28).

The MTA sample only recruited participants with combined type ADHD, and the results may not generalize to other ADHD subtypes or presentations. The literature lacked any empirical precedent for the boundary between full and partial remission. In our effort to define these categories, we attempted to balance false positive and false negative classifications while considering known methodological pitfalls and symptom and impairment norms in the MTA sample; however, alternative definitions that were considered (see section S6 in the online supplement) might have led to different estimates. Additionally, sensitivity analyses (see section S8 in the

online supplement) suggested that missing data may have produced an underestimate of the fluctuating pattern (by up to 10%) and that source switching may have had a very slight impact on diagnostic fluctuations. During childhood and adolescence, impairment ratings were available only from parents. Some adolescents may have met impairment criteria if teacher or self-ratings were available. Similarly, teacher ratings were of necessity discontinued in adulthood; some symptoms that were present in postsecondary academic settings may have gone undetected. The DISC was not administered at the 10-year assessment; thus, we could not review

comorbidities in impaired but asymptomatic cases for this time point. Decisions made by the expert clinical panel were likely imperfect because panel members were unable to query differential diagnosis during real-time clinical assessment.

We used empirically validated, absolute cut-points for symptom and impairment thresholds. Although reflective of diagnostic nosology, using cut-points to categorize continuous data can lead to statistical error. Furthermore, we did not test relative remission thresholds (i.e., within-subject reductions in symptom count), thresholds that defined remission as the absence of symptoms according to any available informant, or combination rules that require all informants to substantiate the presence of an ADHD symptom (34). Analyses to validate the definition of full remission should be replicated in larger, more diverse samples prior to clinical application. Requiring an informant to substantiate self-reports of remitted ADHD may have produced some false negative full remission classifications. Whereas we required absence of ADHD treatment as a criterion for full remission, some treated cases may have experienced remission that was independent of therapeutic intervention. Some impairments may have reflected residual effects of eliminated symptoms. Furthermore, some remission periods may have represented residual benefits of discontinued medication or behavioral treatments; the full relation between treatment and remission will be explored in a future MTA investigation. Future work should replicate our findings, characterize individuals who recover from ADHD, follow trajectories through older adulthood, and identify contributors to symptom fluctuations.

CONCLUSIONS

The study findings emphasize that childhood-onset ADHD is a chronic but waxing and waning disorder with periods of full remission that are more often temporary than sustained. The results support a more informed perspective on ADHD, its impairment, and its tendency to fluctuate over time in symptoms and impairment, perhaps in response to environmental or health-related factors. Providers should expect recurrence of clinically elevated ADHD symptoms and impairments in most patients who experience remission; continued periodic screening for recurrent symptoms and impairments should therefore be standard practice after successful treatment. Given these findings, assessing factors that may influence symptom fluctuations (e.g., environmental fit, physical health) should be central to evaluation and treatment of ADHD across the lifespan. Future research should investigate malleable biological and environmental factors that trigger symptom fluctuations and might serve as targets for new classes of environmental or health interventions (e.g., modifications to factors that may catalyze and maintain symptomatic periods). Based on these findings, clinicians can communicate to families that most adolescents and young adults with ADHD (~90%) experience at least intermittent relief from their ADHD symptoms over time that may be modulated by personal or life circumstances.

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REFERENCES

1. Barkley RA, Fischer M, Smallish L, et al: The persistence of attention-deficit/hyperactivity disorder into young adulthood as a function of reporting source and definition of disorder. J Abnorm Psychol 2002; 111:279–289

2. Sibley MH, Mitchell JT, Becker SP: Method of adult diagnosis influences estimated persistence of childhood ADHD: a systematic review of longitudinal studies. Lancet Psychiatry 2016; 3:1157–1165

3. Sibley MH, Swanson JM, Arnold LE, et al: Defining ADHD symptom persistence in adulthood: optimizing sensitivity and specificity. J Child Psychol Psychiatry 2017; 58:655–662

4. Agnew-Blais JC, Polanczyk GV, Danese A, et al: Evaluation of the persistence, remission, and emergence of attention-deficit/hyperactivity disorder in young adulthood. JAMA Psychiatry 2016; 73: 713–720

5. Biederman J, Faraone S, Milberger S, et al: Predictors of persistence and remission of ADHD into adolescence: results from a four-year prospective follow-up study. J Am Acad Child Adolesc Psychiatry 1996; 35:343–351

6. Karam RG, Breda V, Picon FA, et al: Persistence and remission of ADHD during adulthood: a 7-year clinical follow-up study. Psychol Med 2015; 45:2045–2056

7. Biederman J, Petty CR, Evans M, et al: How persistent is ADHD? A controlled 10-year follow-up study of boys with ADHD. Psychiatry Res 2010; 177:299–304

8. Biederman J, Petty CR, O'Connor KB, et al: Predictors of persistence in girls with attention deficit hyperactivity disorder: results from an 11-year controlled follow-up study. Acta Psychiatr Scand 2012; 125:147–156

9. Biederman J, Mick E, Faraone SV: Age-dependent decline of symptoms of attention deficit hyperactivity disorder: impact of remission definition and symptom type. Am J Psychiatry 2000; 157: 816–818

10. Hechtman L, Swanson JM, Sibley MH, et al: Functional adult outcomes 16 years after childhood diagnosis of attention-deficit/hyperactivity disorder: MTA results. J Am Acad Child Adolesc Psychiatry 2016; 55:945–952.e2

11. Swanson JM, Arnold LE, Molina BSG, et al: Young adult outcomes in the follow-up of the Multimodal Treatment Study of Attention-Deficit/Hyperactivity Disorder: symptom persistence, source discrepancy, and height suppression. J Child Psychol Psychiatry 2017; 58:663–678

12. MTA Cooperative Group, Multimodal Treatment Study of Children with ADHD: A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 1999; 56:1073–1086

13. Jensen PS, Arnold LE, Swanson JM, et al: 3-year follow-up of the NIMH MTA study. J Am Acad Child Adolesc Psychiatry 2007; 46: 989–1002

14. Molina BSG, Flory K, Hinshaw SP, et al: Delinquent behavior and emerging substance use in the MTA at 36 months: prevalence, course, and treatment effects. J Am Acad Child Adolesc Psychiatry 2007; 46:1028–1040

15. Molina BSG, Hinshaw SP, Swanson JM, et al: The MTA at 8 years: prospective follow-up of children treated for combined-type ADHD in a multisite study. J Am Acad Child Adolesc Psychiatry 2009; 48:484–500

16. Molina BS, Hinshaw SP, Eugene Arnold L, et al: Adolescent substance use in the Multimodal Treatment Study of Attention-Deficit/Hyperactivity Disorder (ADHD) (MTA) as a function of childhood ADHD, random assignment to childhood treatments, and subsequent medication. J Am Acad Child Adolesc Psychiatry 2013; 52:250–263

17. Swanson JM: School-Based Assessments and Interventions for ADD Students. Irvine, Calif, KC Publications, 1992

18. Swanson JM, Schuck S, Porter MM, et al: Categorical and dimensional definitions and evaluations of symptoms of ADHD: history of the SNAP and the SWAN rating scales. Int J Educ Psychol Assess 2012; 10:51–70

19. Conners CK, Erhardt D, Sparrow E: Conners' Adult ADHD Rating Scales (CAARS). Toronto, Multi-Health Systems, 1999

20. Swanson JM, Kraemer HC, Hinshaw SP, et al: Clinical relevance of the primary findings of the MTA: success rates based on severity of ADHD and ODD symptoms at the end of treatment. J Am Acad Child Adolesc Psychiatry 2001; 40:168–179

21. Bird HR, Shaffer D, Fisher P, et al: The Columbia Impairment Scale (CIS): pilot findings on a measure of global impairment for children and adolescents. Int J Meth Psychiatr Res 1993; 3:167–176

22. Bird HR, Andrews H, Schwab-Stone M, et al: Global measures of impairment for epidemiologic and clinical use with children and adolescents. Int J Meth Psychiatr Res 1996; 6:295–307

23. Fabiano GA, Pelham WE Jr, Waschbusch DA, et al: A practical measure of impairment: psychometric properties of the Impairment Rating Scale in samples of children with attention deficit hyperactivity disorder and two school-based samples. J Clin Child Adolesc Psychol 2006; 35:369–385

24. Bird HR, Gould MS, Staghezza B: Aggregating data from multiple informants in child psychiatry epidemiological research. J Am Acad Child Adolesc Psychiatry 1992; 31:78–85

25. Shaffer D, Fisher P, Lucas CP, et al: NIMH Diagnostic Interview Schedule for Children, Version IV (NIMH DISC-IV): description, differences from previous versions, and reliability of some common diagnoses. J Am Acad Child Adolesc Psychiatry 2000; 39:28–38

26. Jensen PS, Eaton Hoagwood K, Roper M, et al: The Services for Children and Adolescents–Parent Interview: development and performance characteristics. J Am Acad Child Adolesc Psychiatry 2004; 43:1334–1344

27. Sibley MH, Pelham WE Jr, Molina BSG, et al: Diagnosing ADHD in adolescence. J Consult Clin Psychol 2012; 80:139–150

28. Goodman R: The Strengths and Difficulties Questionnaire: a research note. J Child Psychol Psychiatry 1997; 38:581–586

29. Hanley JA, McNeil BJ: The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982; 143:29–36

30. Lahey BB, Pelham WE, Loney J, et al: Instability of the DSM-IV subtypes of ADHD from preschool through elementary school. Arch Gen Psychiatry 2005; 62:896–902

31. Kenny DA, Zautra A: The trait-state-error model for multiwave data. J Consult Clin Psychol 1995; 63:52–59

32. Larsson H, Chang Z, D'Onofrio BM, et al: The heritability of clinically diagnosed attention deficit hyperactivity disorder across the lifespan. Psychol Med 2014; 44:2223–2229

33. Langberg JM, Epstein JN, Altaye M, et al: The transition to middle school is associated with changes in the developmental trajectory of ADHD symptomatology in young adolescents with ADHD. J Clin Child Adolesc Psychol 2008; 37:651–663

34. Steele M, Jensen PS, Quinn DM: Remission versus response as the goal of therapy in ADHD: a new standard for the field? Clin Ther 2006; 28:1892–1908

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Examination Questions: Sibley et al.

1. **According to the results of this study, what is the definition of full remission from ADHD?**
   A. Full remission is defined as having zero symptoms of ADHD for at least six months
   B. Full remission is present in any case that does not meet full criteria for DSM-5 ADHD
   C. Full remission is defined as low symptoms (i.e., three or fewer) and little to no ADHD-related impairment without current use of medication to manage symptoms
   D. Full remission means zero symptoms of ADHD and zero impairment, as well as no current use of medication to manage symptoms

2. **Which was the most common longitudinal pattern of ADHD in the Multimodal Treatment Study?**
   A. Recovery from ADHD
   B. Fluctuating ADHD Status
   C. Sustained Persistence of ADHD
   D. Sustained Partial Remission from ADHD

3. **What percentage of the sample appeared to demonstrate recovery (sustained remission from ADHD) by age 25?**
   A. Less than 10%
   B. Approximately 20%
   C. Approximately 30%
   D. Approximately 50%