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Impact of dyskinesia on activities of daily living in Parkinson's disease: Results from pooled phase 3 ADS-5102 clinical trials

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ABSTRACT

Introduction: In Parkinson's disease, dyskinesias result from disease progression and chronic levodopa therapy. Using Unified Dyskinesia Rating Scale (UDysRS) data pooled from two pivotal trials of ADS-5102 (amantadine) extended-release capsules in dyskinetic patients, we assessed the impact of dyskinesia on activities of daily living (ADLs), and the effects of ADS-5102 versus placebo.

Methods: Patients had troublesome dyskinesia (≥1 h/day) and at least mild functional impact of dyskinesia per Movement Disorder Society Unified Parkinson's Disease Rating Scale, Part IV, item 4.2. UDysRS Parts 1B, 3, and 4 scores at baseline were summarized descriptively. Twelve-week changes in score distributions and total scores were tested for significant differences between treatments.

Results: Among 196 patients, the majority (63%–73%) characterized their dyskinesia at baseline as having at least a mild impact on *walking and balance*; *public and social settings*; *exciting or emotional settings*; *doing hobbies and other activities*; *handwriting*; and *dressing* (six of ten ADLs in UDysRS Part 1B). By clinician ratings (in Parts 3 and 4), greatest impairment was most often observed in the trunk (62% of patients) and occurred most often for the ADL of dressing (64% had at least moderate impairment). ADS-5102 significantly reduced the patient-rated impact of dyskinesia on six of ten ADLs in Part 1B, the clinician-rated intensity of dyskinesia in all seven body regions assessed in Part 3, and the clinician-rated disability during three of four ADL tasks assessed in Part 4. Improvements in Parts 1B, 3, and 4 total scores were also statistically significant.

Conclusion: Dyskinesia can impair multiple tasks of daily living. Further studies may help characterize its underreported impact. By several measures, ADS-5102 treatment was associated with significant improvement of dyskinesias.

1. Introduction

In patients with Parkinson's disease (PD), dyskinesias develop as a common, often disabling complication of disease progression and chronic levodopa therapy [1,2]. Levodopa continues to be the most effective oral agent for motor-symptom control in PD [3,4], but dyskinesia is a dose-limiting consequence [5]. Dyskinesias consist of involuntary, purposeless, non-rhythmic, choreiform movements, typically occurring at times of maximum levodopa-dose benefit (peak-dose dyskinesia) or at the beginning and end of dose benefit (biphasic dyskinesia) [6]. In a survey of the English-language PD medical literature, dyskinesias were found to increase in prevalence by approximately 10% of patients for each year of levodopa use, approaching 90% at 10 years [7]. Currently, the strategy most commonly used to manage dyskinesia

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is to manipulate the patient's regimen of levodopa and/or adjunctive drugs, usually at the cost of worsening PD [8,9]. Amantadine HCl immediate release is sometimes used off-label to treat levodopa induced dyskinesia in patients with PD. Immediate-release amantadine has been shown to reduce dyskinesia in some studies; although well-controlled clinical trials are lacking and different guidelines vary in their recommendations for its use [10,11]. In addition, more efficacious doses of immediate-release amantadine (> 200 mg per day amantadine HCl) produce a greater incidence of central nervous system side effects, such as hallucinations, sleep disruption and edema [12,13]. Patients (and their physicians) may fail to appreciate the impact dyskinesias have on their daily life. This may reflect, in part, a patient's aversion to the OFF state [14], undermining a full realization of the disability dyskinesias cause while the patient is ON [15]. Patients also may not distinguish between parkinsonian symptoms (e.g., tremor) and dyskinesia. Lack of controlled studies has led to a paucity of data regarding the impact of dyskinesias, and their anatomical patterns [14–16]. Nevertheless, dyskinesia has been found to worsen the negative impact PD has on a patient's quality of life (QoL) [14–16], as well as to increase the risk of falls [17,18] and health care costs [19]. In a large cross-sectional study of European PD patients [15], peak-dose dyskinesia was associated with significant worsening on the Activities of Daily Living (ADL) and cognition dimensions of the Parkinson's Disease Questionnaire-39 (PDQ-39), and biphasic dyskinesia with significant worsening on the stigma dimension. In a recent study of 177 PD outpatients [20], dyskinesia was associated with significant worsening of daily functioning, as measured by the PD-specific Schwab and England ADL Scale.

ADS-5102 (GOCOVRI™, Adamas Pharmaceuticals, Inc.) is an orally administered high-dose, extended-release formulation of amantadine specifically approved for the treatment of dyskinesia in patients with PD receiving levodopa-based therapy. It is the only medication approved by the United States Food and Drug Administration for this use [21]. ADS-5102 dosed at bedtime provides high plasma amantadine concentrations upon waking and throughout the day, with lower concentrations in the evening [22]. In dyskinetic PD patients, both of two pivotal phase 3 clinical trials of ADS-5102 (EASE LID [23] and EASE LID 3 [24]) demonstrated a reduction of dyskinesia, as measured by the primary endpoint (total score at Week 12 on the Unified Dyskinesia Rating Scale, the UDysRS [25,26]). PD home diaries [27] identified an additional benefit of reduced daily OFF time and increased ON time without troublesome dyskinesia.

The UDysRS is a four-part instrument designed to comprehensively capture the clinical features and the subjective and objective impact of dyskinesia [28,29]. It is the most robust tool available to assess dyskinesia [29]. Part 1B of the scale obtains a patient's perceptions of the impact of dyskinesia on ten ADLs. Part 3 obtains a clinician's ratings of dyskinesia-related impairment of seven body regions during four observed ADL tasks. Part 4 obtains the clinician's ratings of overall dyskinesia-related disability during each of those ADL tasks. Herein, we have pooled UDysRS data from EASE LID and EASE LID 3 to assess the baseline impact of dyskinesia on ADLs, and the effects of ADS-5102 treatment on these impairments.

2. Methods

2.1. Study designs and participants

The EASE LID trial [23] (ClinicalTrials.gov identifier: NCT02136914) was conducted at 44 North American sites between May 2014 and July 2015, and the EASE LID 3 trial [24](NCT02274766) at 39 sites in the US and Western Europe between October 2014 and December 2015. Both trials had the same design and the same criteria for patient selection [23,24]. All patients were required to be experiencing at least 1 h/day (two half-hour periods) of ON time with troublesome dyskinesia between 9 a.m. and 4 p.m., as documented in PD home diaries [27]. Dyskinesia had to be present on the two days preceding treatment day 1, and cause at least mild functional impairment, as documented at screening and baseline by a score ≥2 on item 4.2 of the Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [30]. The main difference between the studies was the duration of treatment: up to 25 weeks for EASE LID and up to 13 weeks for EASE LID 3.

2.2. Efficacy measures

In Part 1B of the UDysRS, the patient (and/or a caregiver) assesses, with reference to the preceding week, whether "jerking or twisting movements called on-dyskinesias usually cause problems" with ten ADLs (*speech; chewing and swallowing*; *eating tasks*; *dressing*; *hygiene*; *handwriting*; *doing hobbies and other activities*; *walking and balance*; *public and social settings*; and *exciting or emotional settings*). In Part 3, the clinician assesses the intensity of dyskinesia in seven regions of the patient's body (*face*, *neck*, *trunk*, *left arm/shoulder*, *right arm/shoulder*, *left leg/hip*, and *right leg/hip*) during each of four observed ADL tasks (*communication, drinking, dressing,* and *ambulation*). In Part 4, the clinician assesses the global disability caused by dyskinesia during each of these ADL tasks. For Parts 1B, 3, and 4, the available ratings are summarized in Supplementary Table 1. The pooled results presented here pertain to data obtained at baseline (pre-treatment) and during treatment Week 12—assessment time points common to both trials.

2.3. Efficacy analyses

In each trial, the modified intent-to-treat (mITT) population consisted of all randomized patients exposed to study drug who provided at least one post-baseline UDysRS assessment. Here, scores from UDysRS Parts 1B, 3, and 4 obtained at baseline are summarized descriptively in the pooled mITT population. To identify statistically significant differences between ADS-5102 and placebo, shifts in the distributions of scores during study-drug treatment of the mITT population are analyzed by the Cochran-Mantel-Haenszel test. Changes in total scores are analyzed by a linear mixed model with repeated measures, where baseline score is a covariate while treatment group, visit, and interaction between treatment group and visit are categorical effects. Statistical significance was set at $P < 0.05$ without adjustment for multiplicity. In addition, the proportions of patients with at least moderate impairment of a body region assessed in UDysRS Part 3 are summarized descriptively by treatment group in all patients who provided UDysRS data both at baseline and at Week 12.

2.4. Ethical conduct

Each study was conducted in accordance with the Declaration of Helsinki and with Good Clinical Practice guidelines. Before the start of each study, each study site received approval from an institutional review board, research ethics board, or independent ethics committee. Written informed consent was obtained from each patient before any study procedure.

3. Results

3.1. Study participants

Across studies, the pooled mITT population comprised 196 patients (100 for ADS-5102 and 96 for placebo). Baseline characteristics of the pooled mITT population have been previously presented [31], and are summarized by treatment group in Supplementary Table 2. On average, study participants were 64.7 years of age (range, 34–82), had a 9.7-year disease duration (range, 1.0–26.8), a 7.7-year duration of levodopa treatment (range, 0.1–14.0), and a 3.8-year duration of dyskinesia (range, 0.1–14.0). UDysRS scores at baseline were similar between treatment groups. In the pooled mITT population, baseline mean (range) UDysRS Part 1B, Part 3, and Part 4 scores were 16.0 (1–27), 10.6 (0–27), and 5.8 (0–14), respectively.

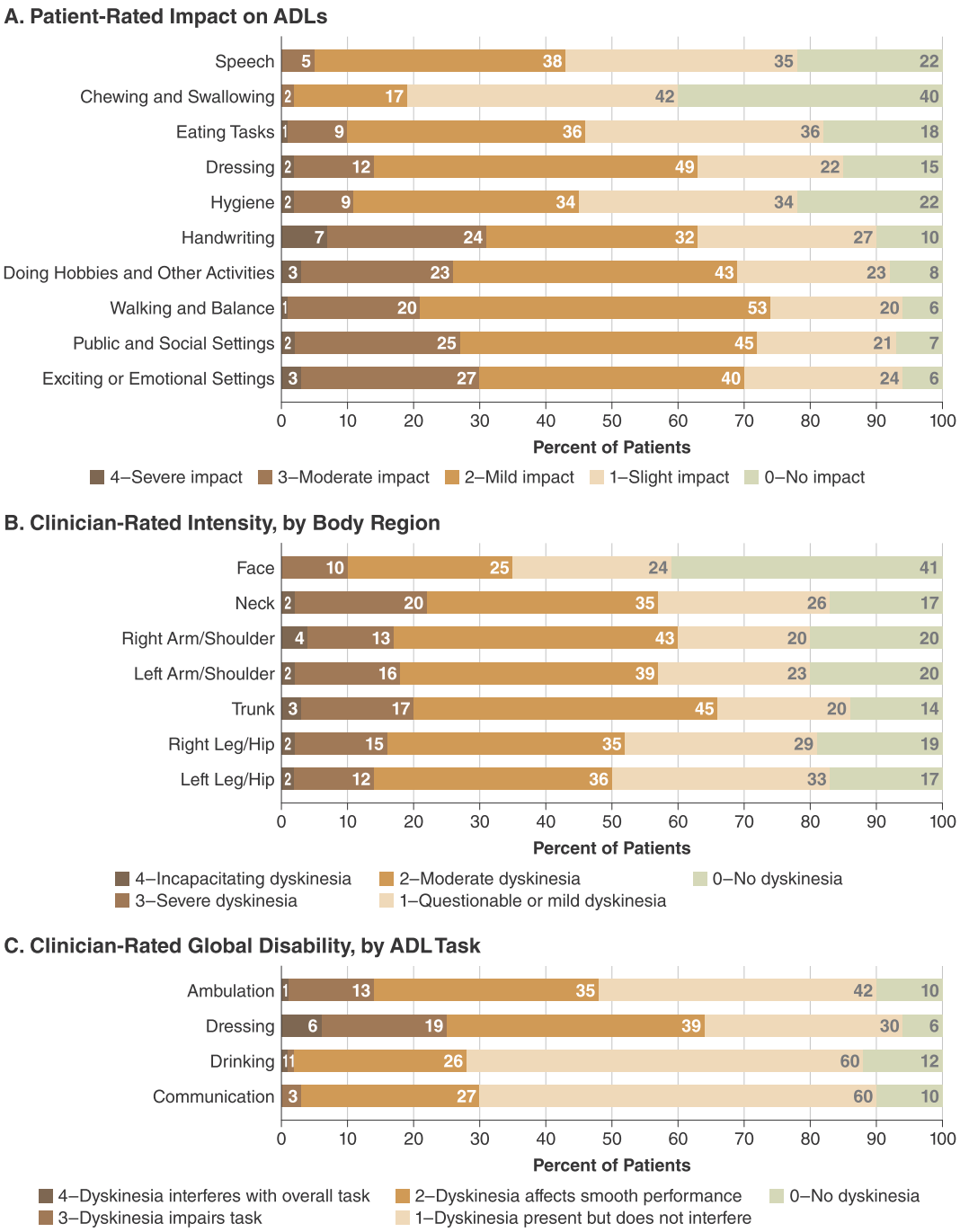

Fig. 1. Dyskinesia impact on ADLs at baseline: Distribution of scores for (A) patient-rated impact on ten ADLs, from UDysRS Part 1B; (B) clinician-rated intensity in seven body regions, measured as highest score across the four ADL tasks observed in UDysRS Part 3; and (C) clinician-rated global dyskinesia-related disability during each of these tasks, from UDysRS Part 4 (pooled mITT population[a]).
[a]N = 196.
[b]Supplementary Table 1 provides more detailed descriptions of the UDysRS Part 1B, Part 3, and Part 4 rating systems.
ADLs, activities of daily living; mITT, modified intent-to-treat; UDysRS, Unified Dyskinesia Rating Scale.

3.2. Baseline impact of dyskinesia

For each of the ADLs itemized in UDysRS Part 1B, the distribution of patient self-ratings at baseline in the mITT population is displayed in Fig. 1A. The proportion of patients characterizing their dyskinesia as having at least a mild impact (i.e., a score ≥2) was highest (≥70% of patients) for *walking and balance* (73%), for *public and social settings* (72%), and for *exciting or emotional settings* (70%), and lowest (≤20%) for *chewing and swallowing* (18%).

For each of the body regions itemized in UDysRS Part 3, the distribution of clinicians' ratings of the intensity of dyskinesia-related impairment at baseline, expressed as highest score across the four observed ADL tasks, is displayed in Fig. 1B. The proportions of patients rated at baseline as exhibiting at least a moderate impairment of a body region (i.e., a score ≥2) during each task are displayed in Fig. 2. For *communication* and for *drinking*, the proportion was highest for the neck (47% and 28% of patients, respectively); for *dressing*, the proportion was highest for the trunk (53%); and for *ambulation*, the proportion was

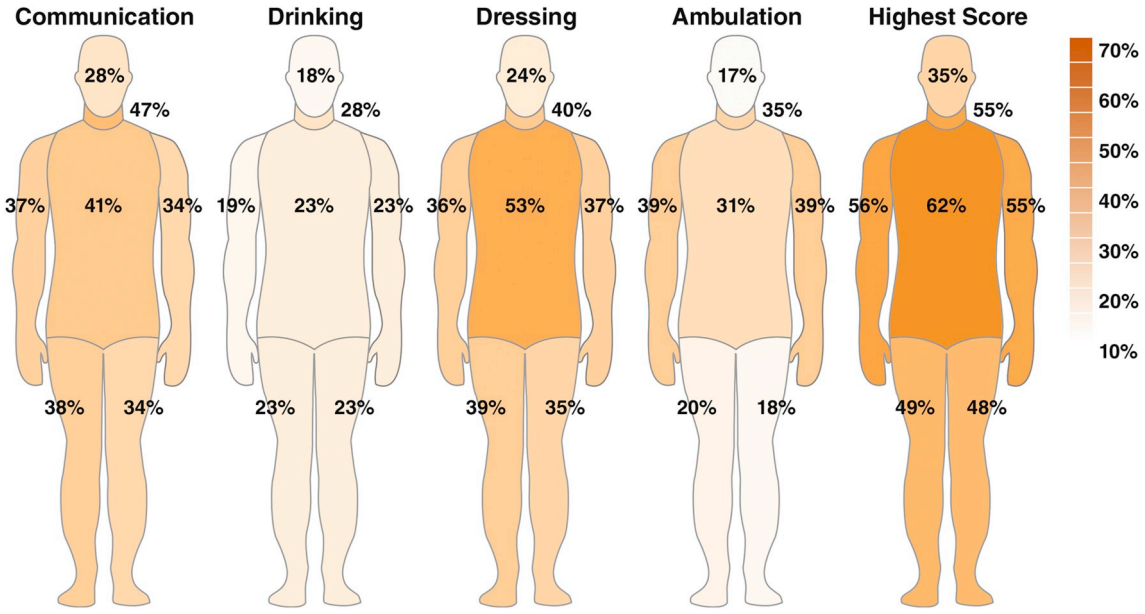

Fig. 2. Dyskinesia intensity during ADLs at baseline: Proportions of patients with a highest UDysRS Part 3 score ≥2 (at least moderate impairment), by body region[a] (pooled mITT population[b]).

[a]Right/left identifications are from the perspective of the homunculi. Because each figure faces the viewer, percentages for the right arm/shoulder and leg/hip are on the left of each drawing, and vice versa.

[b]N = 196.

ADLs, activities of daily living; UDysRS, Unified Dyskinesia Rating Scale.

highest for the *arms/shoulders* (39% for left and right). On all four ADL tasks, the proportion was lowest for the *face* (17%–28%, depending on task). Across all four ADL tasks (Fig. 2, right), the body region with the highest impairment score was most frequently the *trunk* (62% of patients) and least frequently the *face* (35%).

The distribution of clinicians' ratings of the global impact of dyskinesia on each of the ADL tasks (in UDysRS Part 4) is displayed in Fig. 1C. A score ≥2 was more frequent for *dressing* (64% of patients) than for *drinking*, *communication*, or *ambulation* (28%–49%, depending on task).

3.3. Effects of ADS-5102

For each of the ADLs itemized in UDysRS Part 1B, the distribution of shift from baseline to Week 12 in patients' self-ratings of dyskinesia impact is presented by treatment in Fig. 3A. The difference between ADS-5102 and placebo was statistically significant for six of the ten ADLs: *walking and balance* ($P < 0.0001$), *eating tasks* ($P = 0.0052$), *doing hobbies and other activities* ($P = 0.0159$), *public and social settings* ($P = 0.0165$), *exciting or emotional settings* ($P = 0.0310$), and *speech* ($P = 0.0494$).

For each of the body regions itemized in UDysRS Part 3, the distribution of shift from baseline to Week 12 in clinicians' ratings of the intensity of dyskinesia-related impairment, expressed as change in highest score for each body region across the four observed ADL tasks, is presented by treatment in Fig. 3B. The difference between ADS-5102 and placebo was statistically significant in all seven body regions, most markedly in the *arms/shoulders* ($P \leq 0.0001$).

For each of the ADL tasks, the distribution of shift from baseline to Week 12 in clinicians' ratings of the global impact of dyskinesia (in UDysRS Part 4) is presented by treatment in Fig. 3C. The difference between ADS-5102 and placebo was statistically significant for three of the four tasks: *ambulation* ($P = 0.0007$), *dressing* ($P = 0.0074$), and *drinking* ($P = 0.0112$).

3.4. Change in highest impairment score

For baseline and for Week 12, the proportion of patients with an impairment score of at least 2 (moderate impairment) as the patient's highest score across the ADL motor tasks observed in UDysRS Part 3 are displayed by body region and treatment group in Fig. 4A. Changes from baseline are displayed by body region and treatment group in Fig. 4B. In all body regions, the proportion of patients with a reduction in highest impairment score was greater in the ADS-5102 group than in the placebo group. In the ADS-5102 group, change from baseline was largest for the *neck* (25 percentage points) and both *arms/shoulders* (29 and 30 points).

3.5. Change in UDysRS total scores

The least-squares (LS) mean change in UDysRS Part 1B total score was −7.7 in the ADS-5102 group, compared with −3.7 in the placebo group, an LS mean difference of −3.9 ($P < 0.0001$). The LS mean change in Part 3 total score was −4.6 vs −1.5, an LS mean difference of −3.2 ($P < 0.0001$). The LS mean change in Part 4 total score was −2.4 vs −1.1, an LS mean difference of −1.3 ($P = 0.0006$).

4. Discussion

The impact of dyskinesia on the ADLs of patients with PD has not been extensively studied. To our knowledge, the findings presented here, from 196 dyskinetic PD patients, represent the largest sample of patients in whom the impact of dyskinesia has been reported to date. Thus, the findings expand substantially the available evidence concerning the impact of dyskinesia on a patient's daily life.

In the present sample, most patients (63% to 73%) judged their dyskinesia at baseline to be at least a mild problem impeding *walking and balance*, *public and social settings*, *exciting or emotional settings*, *doing hobbies and other activities*, *handwriting*, and *dressing*—a broad variety of the ADLs rated in UDysRS Part 1B. All of these ADLs are known to be

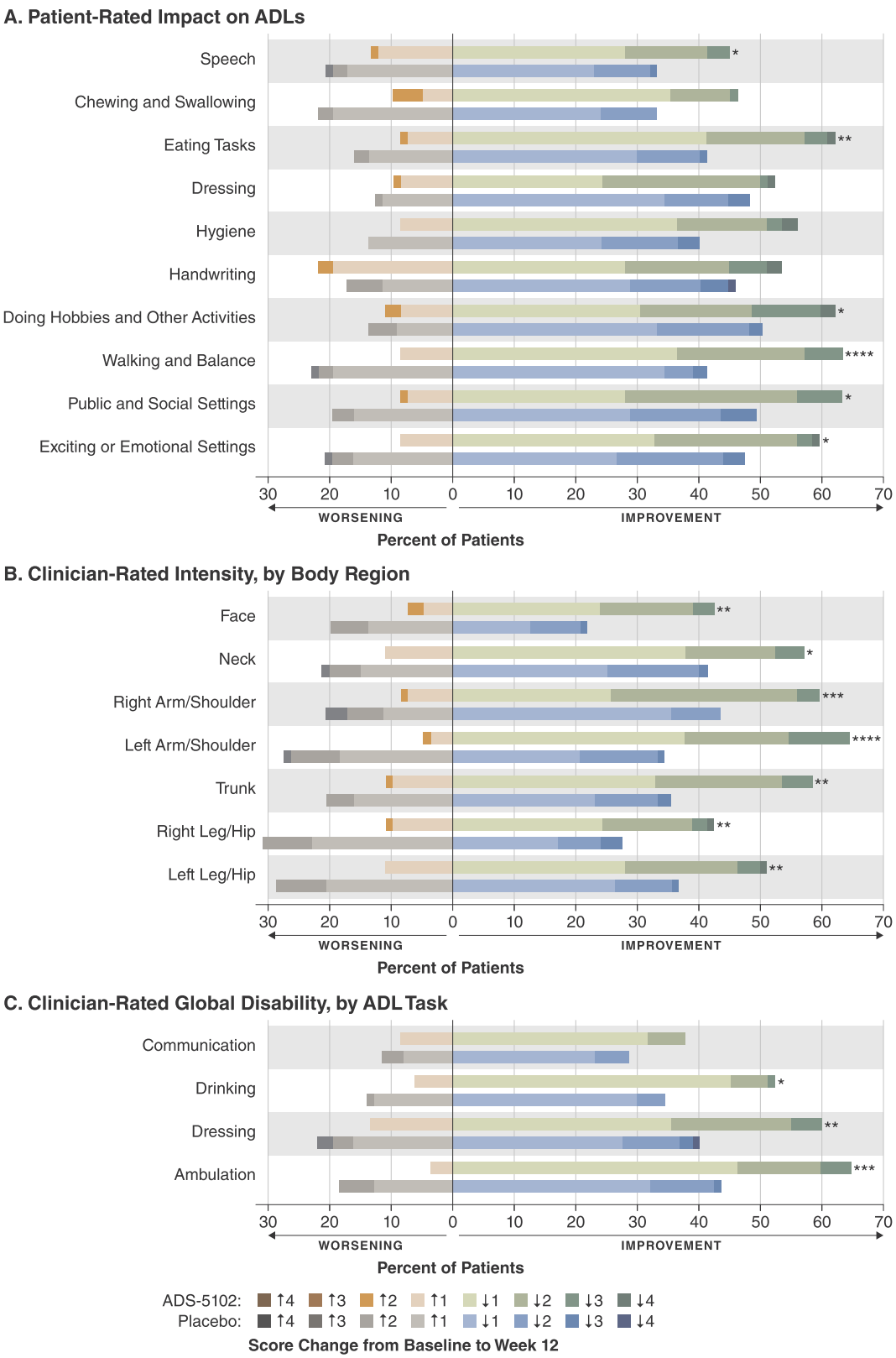

Fig. 3. Effects of ADS-5102 and placebo on ADLs: Distribution of shift from baseline to Week 12 in scores (excluding change of 0) for (A) patient-rated dyskinesia impact on each of ten ADLs, from UDysRS Part 1B; (B) clinician-rated dyskinesia intensity in seven body regions, measured as change in highest score for each body region across the four ADL tasks observed in UDysRS Part 3; and (C) clinician-rated global dyskinesia-related disability during each of these tasks, from UDysRS Part 4 (pooled mITT population[a]).

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; ****$P < 0.0001$ vs placebo, Cochran-Mantel-Haenszel test.

[a]N = 100 for ADS-5102 and 96 for placebo.

ADLs, activities of daily living; mITT, modified intent-to-treat; UDysRS, Unified Dyskinesia Rating Scale.

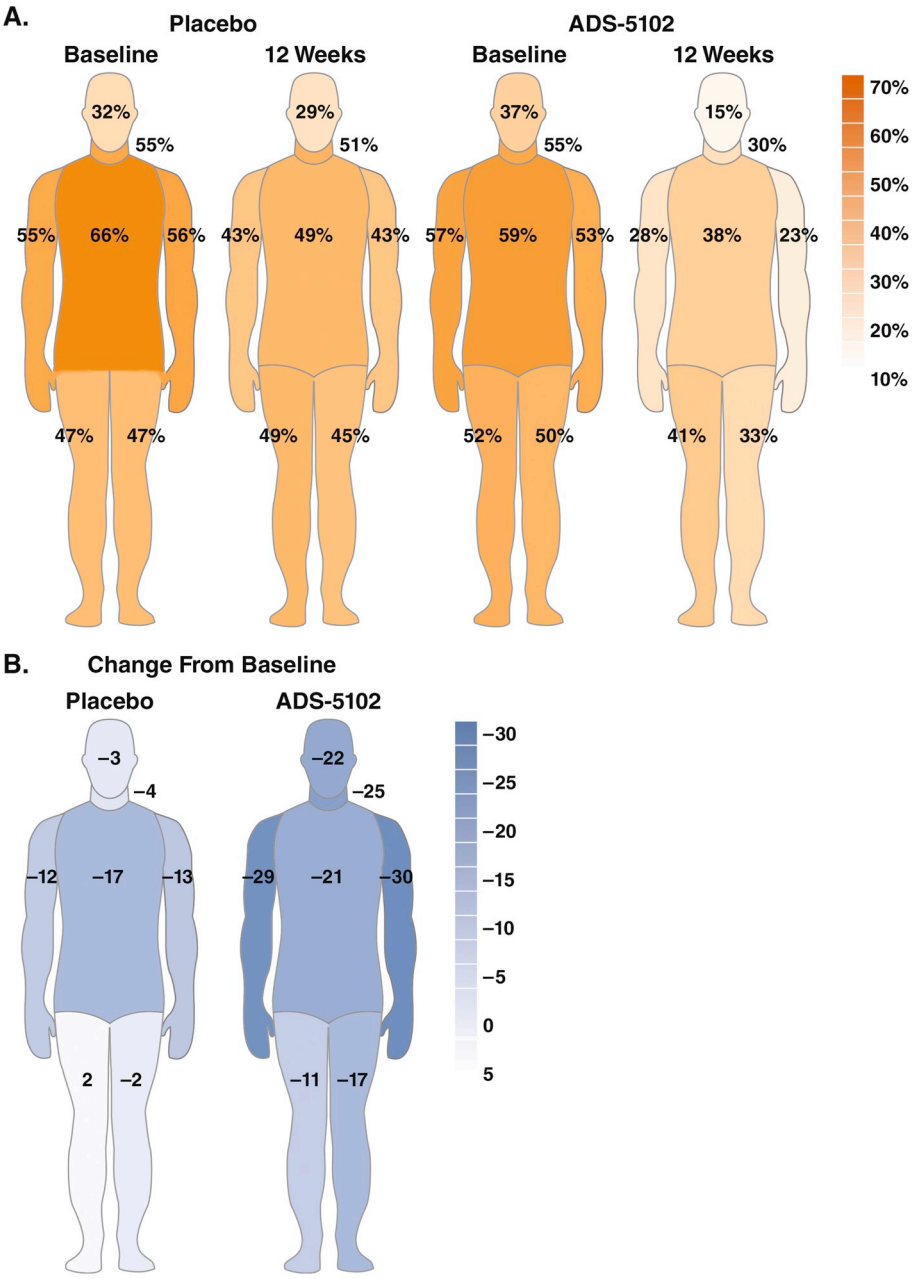

Fig. 4. Effects of ADS-5102 and placebo on dyskinesia intensity during ADL tasks: (A) Proportions of patients with a highest UDysRS Part 3 score ≥2 (at least moderate impairment), by body region[a] and treatment group at baseline and at 12 weeks among all patients who contributed data at both of these time points.[b] (B) Changes from baseline to Week 12 in percentage points, by body region and treatment group.

[a]Right/left identifications are from the perspective of the homunculi. Because each figure faces the viewer, percentages for the right arm/shoulder and leg/hip are on the left of each drawing, and vice versa.

[b]N = 82 for ADS-5102 and 87 for placebo.

ADLs, activities of daily living; UDysRS, Unified Dyskinesia Rating Scale.

affected by the parkinsonian state. Since UDysRS Part 1B instructs a patient to rate the impact of "jerking or twisting movements" occurring "when your Parkinson's disease medications were working" [22], the findings show that the ADLs are specifically worsened by dyskinesia in its typical forms.

To our knowledge, the findings reported here are also the first to characterize the anatomic distribution of dyskinesia intensity during ADLs. In the ADL tasks observed and scored by clinicians at baseline in UDysRS Part 3, the body regions with at least moderate dyskinesia-related impairment varied markedly, depending on task, with the *neck* most likely to be affected during *communication* and *drinking*, the *trunk* during *dressing*, and the *arms/shoulders* during *ambulation*. Overall, anatomic involvement in dyskinesia (assessed in UDysRS Part 3) was most frequent for the *trunk* and least frequent for the *face,* in contrast to dyskinesia seen in populations studied for tardive dyskinesia, which is most prominent in the oral-buccal region [32]. In the present PD population, relatively severe dyskinesia-related impairment (assessed in UDysRS Part 4) was most frequent for *dressing*.

In this population, 12-week treatment with ADS-5102 was associated with statistically significant shifts in several UDysRS scores, compared with those for placebo. The findings indicate that in dyskinetic PD patients, ADS-5102 reduced the patient-rated impact of dyskinesia on six of the ten ADLs assessed in UDysRS Part 1B (most markedly for *walking and balance*), the clinician-rated intensity of dyskinesia in all seven body regions assessed in UDysRS Part 3 (most markedly in the *arms/shoulders,* and the neck was most frequently the anatomic region where patients experienced improvement), and the clinician-rated disability during three of the four ADL tasks assessed in UDysRS Part 4 (most markedly for *ambulation*). Improvement in total scores on Parts 1B, 3, and 4 were also statistically significant.

The safety profile of ADS-5102 has been reported for patients in individual ADS-5102 trials [23,24,33,34], including the two trials pooled here [23,24], and for the pooled population analyzed here [31]. The most commonly observed adverse reactions occurring at a frequency of > 10% and greater than placebo were hallucination, dizziness, dry mouth, peripheral edema, constipation, fall, and orthostatic hypotension [31,35].

The present analyses have limitations. First, they were restricted to patients reporting at least mild dyskinesia at baseline (per MDS-UPDRS item 4.2) and at least 1 h/day of troublesome dyskinesia (per PD home diary). In addition, the patients were enrolled and treated in a clinical-trial setting, mostly at movement disorder centers. Hence, the analyses may not represent the full clinical spectrum of dyskinesia seen by community neurologists. For UDysRS Part 1B findings, the analyses relied on the patients' ability to differentiate between dyskinesia and the motor deficits intrinsic to their PD. Lastly, the studies' efficacy assessments did not include QoL tools, such as the disease-specific Parkinson's Disease Questionnaire (PDQ-39). Hence, changes in UDysRS scores could not be correlated with changes in QoL measures.

Further studies integrating QoL measures in broad samples of dyskinetic PD patients should be undertaken to more fully characterize the underreported impact of dyskinesia on patients' daily lives. Meanwhile, PD management should not primarily focus on patients' OFF time but should also consider dyskinesia and its impact on patients. The findings presented here show that dyskinesias can impair patients' ADLs across multiple tasks, and that treatment with ADS-5102 can ameliorate the impairment.

Authors' roles

Rajesh Pahwa participated in the conception and design of the study, the acquisition of data, the analysis and interpretation of data, and drafting the manuscript or revising it critically for important intellectual content.

Stuart Isaacson participated in the conception and design of the study, the acquisition of data, the analysis and interpretation of data, and drafting the manuscript or revising it critically for important intellectual content.

Joohi Jimenez-Shaheed participated in the interpretation of data and drafting the manuscript or revising it critically for important intellectual content.

Irene A. Malaty participated in the interpretation of data and drafting the manuscript or revising it critically for important intellectual content.

Andres Deik participated in the interpretation of data and drafting the manuscript or revising it critically for important intellectual content.

Reed Johnson participated in the conception and design of the study, the acquisition of data, the analysis and interpretation of data, and drafting the manuscript or revising it critically for important intellectual content.

Rajiv Patni participated in the conception and design of the study, the acquisition of data, the analysis and interpretation of data, and drafting the manuscript or revising it critically for important intellectual content.

All authors have approved the final version of the manuscript.

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Stuart Isaacson has received honoraria for CME, and has served as consultant, received research grants, and/or acted as promotional speaker on behalf of AbbVie, Acadia, Acorda, Adamas Pharmaceuticals, Addex, Allergan, Amarantus, Auspex, Avid, Axovant, AZ Therapies, Biogen, Biotie, Britannia, Cynapsus, Eisai, Eli Lilly, GE Healthcare, Impax, Intec Pharma, Ipsen, Kyowa, Lundbeck, Medtronic, Merz, Michael J. Fox Foundation, Neurocrine, Neuroderm, NINDS/NIH, Parkinson Study Group, Pfizer, Pharma2B, Prothena, Roche, Sanofi, Shire, Sunovion Pharmaceuticals, Teva, UCB, US WorldMeds, and XenoPort.

Joohi Jimenez-Shaheed has served as a consultant for Abbott, Medtronic, Teva, Nuvelution, and Bracket. She has also received research support from Biotie/Acorda, Abbott, Medtronic, Lilly, Nuvelution, and the Michael J. Fox Foundation.

Irene A. Malaty has participated in research funded by the Parkinson Foundation, Tourette Association, Dystonia Coalition, AbbVie, Auspex, Biogen, Biotie, Intrepid, Lundbeck, Merz, Neurocrine, Pfizer, and Revance, but has no owner interest in any pharmaceutical company.

Andres Deik has participated in advisory boards for Adamas Pharmaceuticals, Sunovion Pharmaceuticals (formerly Cynapsus), and US WorldMeds. He has worked as a consultant for ITF Pharma. He has been Site PI for clinical trials sponsored by Adamas Pharmaceuticals and Sunovion Pharmaceuticals, as well as a number of NIH-sponsored trials.

Reed Johnson and **Rajiv Patni** are employees of and own stock in Adamas Pharmaceuticals.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.parkreldis.2018.09.005.

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