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RE-KINECT

A Prospective Study of the Presence and Healthcare Burden of Tardive Dyskinesia in Clinical Practice Settings

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Abstract:

Purpose/Background: RE-KINECT (NCT03062033) was designed to assess the presence and impact of possible tardive dyskinesia (TD) in antipsychotic-treated outpatients.

Methods/Procedures: The study included adults with 3 or more months of lifetime antipsychotic exposure and 1 or more psychiatric disorder. Based on clinician observation and assessment, patients were assigned to cohort 1 (without involuntary movements or with non-TD involuntary movements) or cohort 2 (with involuntary movements confirmed by clinician as possible TD). Baseline assessments included the following: patient characteristics; location/severity of involuntary movements; and impact of possible TD on health-related quality of life, including the EuroQoL 5-Dimensions 5-Level questionnaire.

Findings/Results: Of 739 eligible patients, 204 (27.6%) had clinician-confirmed possible TD (cohort 2). Compared with cohort 1, patients in cohort 2 were significantly older ($P < 0.0001$), more likely to have schizophrenia or schizoaffective disorder ($P < 0.0001$) and longer lifetime exposure to antipsychotics ($P < 0.0001$), and less likely to be working or studying, based on clinician perception ($P = 0.0010$). Clinician- and patient-rated severity of possible TD movements was significantly correlated in each of 4 body regions (head/face, neck/trunk, upper extremities, lower extremities), for maximum severity in any region, and for total number of affected regions ($P < 0.001$ for all correlations). For the patient-rated EuroQoL 5-Dimensions 5-Level, the health state visual analog scale score was significantly lower (worse) in cohort 2 versus cohort 1 (66.8 vs 69.7; $P = 0.0002$), as was the utility index score (0.71 vs 0.76; $P < 0.0175$).

Implications/Conclusions: Results from this real-world population indicate that TD occurs frequently and can significantly reduce quality of life in patients with a psychiatric disorder.

Key Words: tardive dyskinesia, antipsychotics, movement disorders, schizophrenia, mood disorders

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Received September 12, 2019; accepted after revision February 14, 2020.

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Supplemental digital content is available for this article. Direct URL citation appears in the printed text and is provided in the HTML and PDF versions of this article on the journal's Web site (www.psychopharmacology.com).

ISSN: 0271-0749
DOI: 10.1097/JCP.0000000000001201

(*J Clin Psychopharmacol* 2020;40: 259–268)

Patients treated with first-generation antipsychotics (FGAs) or second-generation antipsychotics (SGAs) are at risk for developing tardive dyskinesia (TD), an often persistent and potentially debilitating disorder characterized by involuntary hyperkinetic movements of the face, trunk, and extremities.[1–4] It was originally assumed that the advent of SGAs would eliminate the risk of TD, but that has not been proven to be the case, and increased use of antipsychotics in mood-related disorders (eg, major depressive disorder, bipolar disorder) and in patients of varying ages (eg, behavioral disturbances in elderly patients) has resulted in more patients at risk for TD.[5–7] A recent meta-analysis found the prevalence of TD to be 25.3% in patients treated with any antipsychotic medication.[8]

Because of this risk associated with antipsychotics, it is highly encouraged that screening for TD becomes routine practice among all patients who receive these medications,[9] especially now that approved treatments for TD are available. Standardized and structured assessments such as the Abnormal Involuntary Movement Scale (AIMS)[10] are valid instruments for evaluating TD in research trials under controlled conditions and for objectively documenting changes in severity of TD in clinical settings.[9,11,12] However, implementing regularly scheduled and structured screening protocols has been challenging for many clinicians and facilities. In a 1990 survey of community mental health center directors, 92.6% of the 160 responding centers reported that they performed some type of TD screening (eg, visual observation, AIMS examination); however, only 41.3% of the responding centers had a formal screening policy.[13] Comments from survey respondents suggested that one disincentive to implementing a formal screening policy was the concern that screening might raise alarm among patients and increase antipsychotic noncompliance although a systematic study refuted this fear.[14] Another published report suggests that in the context of busy practices, administering validated screening instruments can be too time-consuming and that implementing informal observations of patients' movements during clinical visits may be a more realistic approach.[11]

Understanding the burden of TD is another important aspect of patient management. Several studies have reported the negative effects of TD on health-related quality of life and daily functioning, but these were mostly focused on patients taking FGAs[15] or patients with schizophrenia.[16,17] Given the expanding use of SGAs in different populations (eg, patients with mood disorders, children, and the elderly), studies that assess the impact and burden of TD need to be more comprehensive in scope. Too often, it is assumed that patients are unaware of or unconcerned about having TD, and therefore, it is not worth screening for or treating this disorder.[18] However, with the increasing use of SGAs in patients who are highly functional (eg, can work, go to school, manage a household), it has been reported that TD symptoms are more

likely be considered bothersome or disruptive even in "mild" cases.[11,18] Moving beyond old stereotypes of TD, understanding the current landscape of antipsychotic use, and implementing reliable measures of impairment make it important to assess the impact of TD on quality of life and daily functioning.[19]

The RE-KINECT study (NCT03062033) was designed to document the presence of possible TD in patients recruited from a broad range of outpatient psychiatry clinics across the United States, which varied in terms of setting (eg, research institutions, community health centers, private practice), size, and geographic region. The overall objective of this study was to document the presence and impact of involuntary movements in a real-world cohort of patients taking antipsychotics. This report, which presents baseline results from the study, focuses on the characterization of patients with and without possible TD, including socio-demographics, clinical characteristics, healthcare utilization, disease burden, and quality of life.

MATERIALS AND METHODS

Study Design and Patient Population

This prospective, observational, multicenter study was conducted at 37 clinical sites in the United States from April 2017 to January 2018. Sites were selected based on their available patient population and ability to meet study protocol requirements. Institutional review board approval was obtained at each site before the conduct of any study procedures; all study documentation was approved for central ethics review. Study design, data management, and analyses were conducted by Evidera (Bethesda, Md).

At each site, all clinical staff members were required to complete an online training course that included the following: videos illustrating the presentation and severity of TD symptoms in 4 key body regions (ie, head/face, neck/trunk, upper extremities, lower extremities) and videos of non-TD movements (eg, parkinsonism, tremor). After training, clinical staff members were asked to assess all patients who presented for a 2-week enrollment period. During this period, patients attending their usual care visit (ie, RE-KINECT baseline visit) were prescreened for eligibility per the following criteria, based on review of the patient's medical records: 18 years or older; 3 or more months of cumulative lifetime exposure to antipsychotic medication; and 1 or more clinician-confirmed psychiatric disorder diagnosis per the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* criteria.[20] Patients who met selection criteria, were capable of consent per clinician judgment, and provided voluntary written informed consent were enrolled in the study.

During the patient's usual care visit, the clinician looked for involuntary movements in any region of the body. Based on the clinician's observation and assessment of whether the movements were consistent with possible TD, patients were assigned to cohort 1 (without involuntary movements or with involuntary movements not deemed consistent with TD) or cohort 2 (with involuntary movements and clinician-confirmed possible TD). After cohort assignment, nonpaid caregivers of patients in cohort 2 were invited to participate in the study; the data collected from caregivers will be reported separately. A longitudinal 12-month follow-up of cohort 2 is ongoing, and the results of this phase will also be reported separately.

Study Measures

For all patients (cohort 1 and cohort 2), a retrospective medical chart review for the 12-month period before baseline was conducted to capture demographic information, psychiatric conditions, cumulative lifetime exposure to antipsychotic medication and current antipsychotic use, comorbid medical conditions, and healthcare resource utilization and hospitalizations. Patients provided information on marital status, domestic/living situation, education level, and employment status. Clinicians were asked to rate the severity of patients' psychiatric conditions ("normal/not at all ill" to "among the most severely ill").

For cohort 2, clinician- and patient-rated assessments included the following: severity of involuntary movements in each of 4 body regions (head/face, neck/trunk, upper extremities, lower extremities), rated using a simplified scale of "none," "some," or "a lot," and awareness of possible TD symptoms. Patients who reported being aware of involuntary movements they could not control within the past 4 weeks were also asked to rate the following: impact of involuntary movements on daily activities, using the same simplified scale ("none," "some," or "a lot"), and self-consciousness or embarrassment about involuntary movements.

Functional status and health-related quality of life were evaluated in all patients (cohort 1 and cohort 2). Patients were asked to provide their perspective on the following health-related issues: overall health status ("no health problems" to "health as bad as you can imagine"); health conditions that caused the most worry or concern; and health conditions that required the most time to manage. Clinicians were asked to indicate (to the best of their knowledge) whether patients were able to work, study, and/or manage a household ("independently," "with assistance," or "not been working or studying an in any capacity and not managing own household").

In addition, while waiting for their usual care visit (ie, before clinician assessment of involuntary movements and cohort determination), all patients completed the EuroQOL 5-Dimension 5-Level questionnaire (EQ-5D-5L)[21] and the Sheehan Disability Scale (SDS).[22] The EQ-5D-5L includes 5 domains (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), each of which is rated using a 5-point scale (range, 1 = no problems [or no pain/anxiety] to 5 = unable to perform [or extreme pain/anxiety]). The EQ-5D-5L also includes a 100-mm visual analog scale (VAS: range, 0 = "worst health you can imagine" to 100 = "best health that you can imagine") and a utility index score derived from domain scores (range, 0 = health state equivalent to death to 1 = perfect health). The SDS includes 3 domains (work/school, social life, family life/home responsibilities), each of which is rated using an 11-point scale (range, 0 = not at all disruptive to 10 = extremely disruptive). The SDS total score was calculated for patients who had a score in at least 2 of the 3 domains. When only 1 domain was missing, the average of his/her observed scores was imputed to the missing record.

Data Collection and Statistical Analyses

Statistical Analysis Software (SAS) Version 9.4 was used to conduct the study analyses. For continuous variables, the number of participants, mean, and standard deviation (SD) were calculated. When applicable, a two-tailed, Student *t* test was performed (for cohort 2 vs cohort 1). If the distribution of data suggested a deviation from normality, an equivalent, nonparametric test (eg, Wilcoxon-Mann-Whitney test) was used. For categorical variables, the number of participants and percent distribution by category were calculated. When applicable, a Pearson χ^2 test (or Fisher exact test in cases of low sample size) was performed (for cohort 2 vs cohort 1).

Comparisons between cohorts were adjusted for age (<55 vs ≥55 years), sex (male vs female), and psychiatric diagnosis (schizophrenia or schizoaffective disorder vs other) when appropriate. The 55-year threshold for older age has been used in other TD studies, based on the decreased life expectancy in patients with schizophrenia and other serious mental illnesses.[23–25] For the adjusted comparison of categorical variables, a logistic regression (binary, ordinal, or nominal, as applicable) was used. For

continuous variables, an analysis of variance was performed. When applicable, associations between patient- and clinician-reported outcomes were assessed using Spearman correlation.[26] Statistical significance was evaluated for exploratory purposes at an α level of 5%, and no adjustment was applied for multiple comparisons.

Imputation for missing observations was not performed, except for measures associated with validated instruments (ie, EQ-5D-5L and SDS). Missing items from these instruments were handled according to instructions from the relevant scoring manuals.

RESULTS

Patient Characteristics (Cohorts 1 and 2)

A total of 1148 patients from 37 clinical sites in 19 states were screened (Fig. 1). These sites included research-focused institutions (n = 23), community health centers (n = 11), and private practices (n = 3). After screening, 739 patients met eligibility criteria, provided informed consent, and were clinically evaluated. Per clinician confirmation of possible TD, 204 (27.6%) patients were assigned to cohort 2. The remaining 535 (72.4%) patients were assigned to cohort 1, which included 508 with no involuntary movements and 27 with movements that were not consistent with TD per clinician judgment.

There were no statistically significant differences between cohorts in terms of sex, race, or marital status, but cohort 2 patients were significantly older than cohort 1 patients ($P < 0.0001$; Table 1). Cohort 2 patients were more likely than cohort 1 patients to be living alone or in a facility and less likely to be living with a partner, spouse, family, or friends, but this was not significant when adjusted for age, sex, and psychiatric diagnosis. Similarly, cohort 2 patients were less likely to be employed full time or college-educated and more likely to be retired or disabled, but these differences were not statistically significant.

Severity of patients' psychiatric conditions, as rated by clinicians, was similar between cohorts, with no significant difference when adjusted for age, sex, and psychiatric diagnosis. Schizophrenia or schizoaffective disorder was significantly more prevalent in cohort 2 than cohort 1 ($P < 0.0001$); mood and other psychiatric disorders were more prevalent in cohort 1 than cohort 2 ($P = 0.0255$; Table 1). Among all 285 patients with a diagnosis of schizophrenia or schizoaffective disorder (cohort 1 and cohort 2), 38.9% had possible TD (cohort 2); among all 513 patients with a mood or other psychiatric disorder, 21.8% had possible TD. Lifetime exposure to antipsychotics was statistically significantly longer in cohort 2 than cohort 1 ($P < 0.0001$), but there was no statistically significant difference for total number of antipsychotics used in the prior 12 months or SGA use.

No statistically significant differences between cohorts were found for pre-existing comorbid medical conditions (Table S1, http://links.lww.com/JCP/A666). For healthcare utilization, significant differences between cohort 2 and cohort 1 (after adjustment for age, sex, and diagnosis) included the following: more healthcare visits or referrals due to any movement disorder (TD or non-TD; $P = 0.0022$); more hospitalizations due to a psychiatric condition ($P = 0.0199$); fewer hospitalizations due to a nonpsychiatric or nonmovement-related condition ($P = 0.0209$); and more hospitalizations in a psychiatric ward ($P = 0.0203$; Table S2, http://links.lww.com/JCP/A666).

Severity and Impact of Possible TD on Daily Activities (Cohort 2)

According to clinicians, 75.5% of all cohort 2 patients (n = 204) were aware of their possible TD symptoms, with higher

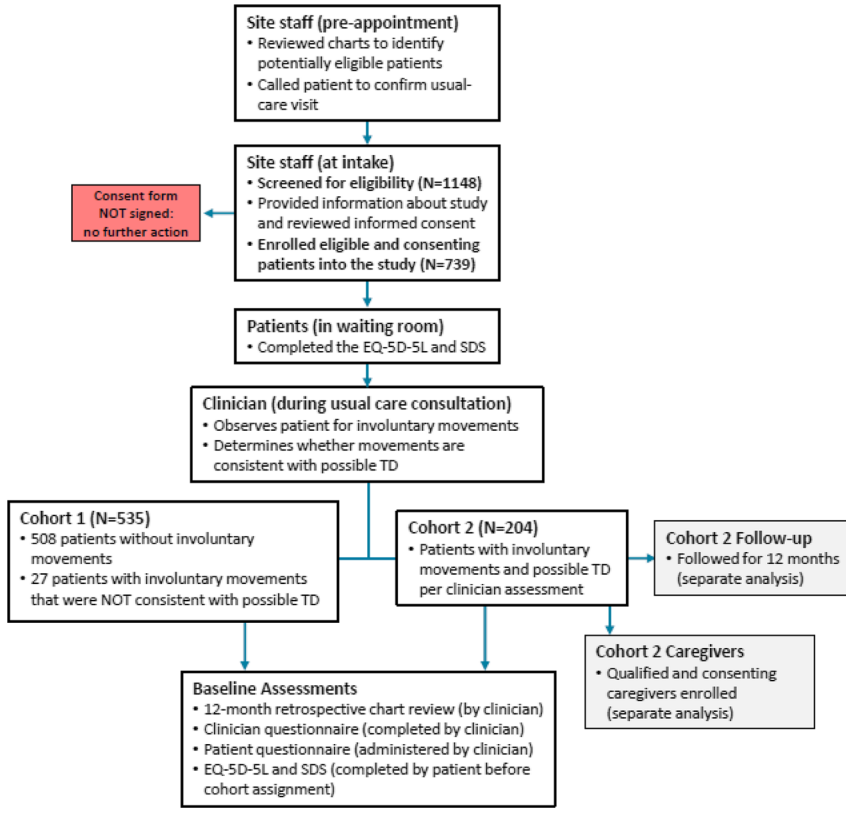

FIGURE 1. Study overview and cohort assignment.

TABLE 1. Demographics and Clinical Characteristics

	Cohort 1 (n = 535)	Cohort 2 (n = 204)	*P**	Adjusted *P**[†]
Age, mean (SD)	47.6 (14.6)	54.6 (13.6)	<0.0001	
Sex, n (%)			0.0920	
Male	225 (42.1)	100 (49.0)		
Female	309 (57.8)	104 (51.0)		
Race, n (%)				
White	385 (72.0)	149 (73.0)	0.7981	
Black	89 (16.6)	36 (17.6)	0.7508	
Asian	22 (4.1)	8 (3.9)	0.9029	
Indian/Alaska Native	10 (1.9)	2 (1.0)	0.5267	
Other	31 (5.8)	9 (4.4)	0.4546	
Missing	5 (0.9)	2 (1.0)		
Marital status, n (%)			0.0524	0.6329
Single	253 (47.3)	97 (47.5)		
Married	152 (28.4)	43 (21.1)		
Divorced	86 (16.1)	46 (22.5)		
Widowed	20 (3.7)	6 (2.9)		
Separated	18 (3.4)	12 (5.9)		
Other	5 (0.9)	0		
Missing	1 (0.2)	0		
Current living/domestic situation, n (%)			0.0009	0.1874
Living alone	120 (22.4)	57 (27.9)		
Living with a partner, spouse, family, or friends	351 (65.6)	105 (51.5)		
Other[‡]	63 (11.8)	41 (20.1)		
Missing	1 (0.2)	1 (0.5)		
Employment status, n (%)				
Employed, full-time	85 (15.9)	14 (6.9)	0.0012	0.1226
Employed, part-time	61 (11.4)	25 (12.3)	0.7528	0.3720
Homemaker	16 (3.0)	3 (1.5)	0.3062	0.2648
Student	22 (4.1)	1 (0.5)	0.0081	0.1155
Unemployed	85 (15.9)	19 (9.3)	0.0211	0.0132
Retired	48 (9.0)	32 (15.7)	0.0089	0.1676
Disabled	225 (42.1)	111 (54.4)	0.0027	0.0553
Other	8 (1.5)	3 (1.5)	>0.9999	0.7350
Missing	1 (0.2)	1 (0.5)		
Education level, n (%)				
Elementary/primary school	31 (5.8)	12 (5.9)	0.9681	0.9094
High school	165 (30.8)	89 (43.6)	0.0011	0.0211
Some college	172 (32.1)	58 (28.4)	0.3216	0.7012
College degree	113 (21.1)	31 (15.2)	0.0674	0.1157
Postgraduate degree	44 (8.2)	8 (3.9)	0.0404	0.0995
Other	24 (4.5)	11 (5.4)	0.6078	0.4785
Missing	1 (0.2)	0		
Psychiatric condition, n (%)				
Schizophrenia or schizoaffective disorder	174 (32.5)	111 (54.4)	<0.0001	<0.0001
Mood disorder or other psychiatric disorder[§]	401 (75.0)	112 (54.9)	<0.0001	0.0255
Severity of psychiatric condition per clinician impression, n (%)			0.0022	0.0682
Normal, not ill	57 (10.7)	7 (3.4)		
Minimally ill	115 (21.5)	27 (13.2)		
Mildly ill	135 (25.2)	68 (33.3)		
Moderately ill	152 (28.4)	67 (32.8)		
Markedly ill	54 (10.1)	26 (12.7)		
Severely ill	20 (3.7)	9 (4.4)		
Among the most severely ill	2 (0.4)	0		

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TABLE 1. *(Continued)*

	Cohort 1 (n = 535)	Cohort 2 (n = 204)	*P**	Adjusted *P**†
Lifetime exposure to antipsychotics, mean (SD), y	7.8 (8.6)	15.0 (13.9)	<0.0001	<0.0001
No. antipsychotics, n (%)			0.2607	0.1591
1	73 (13.6)	24 (11.8)		
2	120 (22.4)	35 (17.2)		
≥3	334 (62.4)	140 (68.6)		
Missing	8 (1.5)	5 (2.5)		
Use of second-generation antipsychotics, n (%)	442 (82.6)	169 (82.8)	0.9421	0.8138

*For questions or items that allowed more than 1 response (ie, categories not mutually exclusive), *P* values are provided for each response.

†Adjusted for age (<55 vs ≥55 years), sex (male vs female), and diagnosis (schizophrenia or schizoaffective disorder vs other). Psychiatric diagnosis was adjusted for age and sex.

‡Includes assisted living, group home, or living with other caregiver.

§Includes anxiety disorder or symptoms, bipolar disorder, major depressive disorder, posttraumatic stress disorder, personality disorder, attention-deficit/hyperactivity disorder, substance use disorder, and other psychotic disorder.

rates of awareness among patients with a mood or other disorder (80.6%) as compared with schizophrenia or schizoaffective disorder (71.2%), although the difference was not statistically significant. Consistent with clinicians' impressions, 78.4% of all cohort 2 patients reported having noticed involuntary movements in the past 4 weeks; 53.9% reported having involuntary movements in the past 4 weeks that they could not suppress or control (n = 110).

Clinician-rated assessments of involuntary movements were conducted in all 204 cohort 2 patients; patient-rated assessments were only conducted in the 110 patients who reported having involuntary movements in the past 4 weeks that they could not control. Based on these available assessments, there were statistically significant positive correlations between clinician and patient ratings (all $P < 0.001$) as follows: severity of involuntary movements in *each* body region (ie, head/face, neck/trunk, upper extremities, lower extremities); maximum severity score in *any* body region; and total number of body regions with an involuntary movement (Fig. 2). Based on clinician and patient ratings, respectively, 52.9% and 63.6% of cohort 2 patients had involuntary movements in 2 or more body regions. In addition, more than 40% of the cohort 2 patients with uncontrollable movements reported that involuntary movements had "some" or "a lot" of impact on their ability to continue usual activities, talk, be productive, and socialize (Fig. 3). In addition, 75.5% affirmed that they have felt self-conscious or embarrassed about involuntary movements that they could not seem to control.

Functional Status and Health-Related Quality of Life (Cohorts 1 and 2)

No statistically significant difference between cohorts was found for patient-reported overall health status (Table 2). More than 50% of patients in both cohorts were most worried or concerned about mental health and reported spending the most time managing this condition, but these results were also not statistically significant. However, a significantly higher percentage of cohort 2 patients were worried or concerned about movement disorders (TD or non-TD) than cohort 1 ($P < 0.0001$), and more cohort 2 patients reported spending the most time managing this condition ($P < 0.0001$).

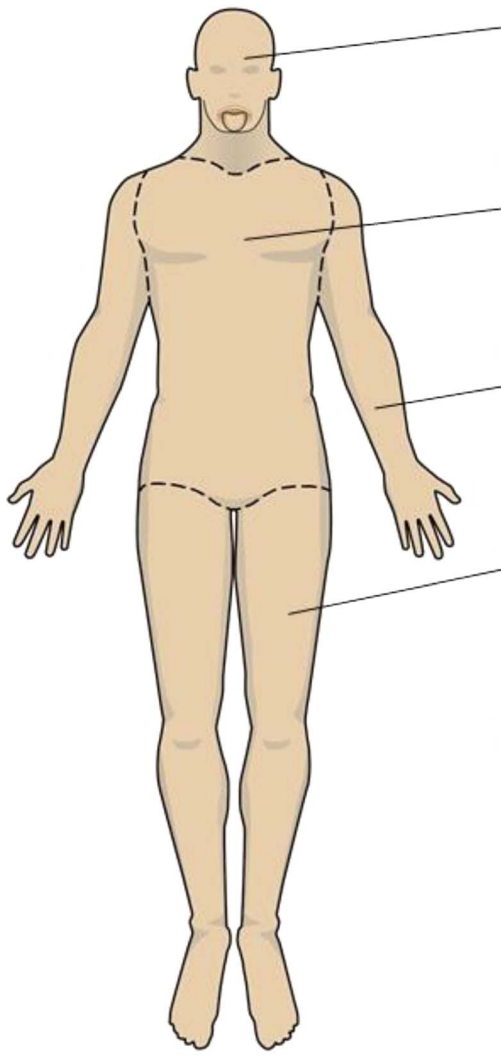
Based on clinicians' perceptions, a statistically significant difference between cohorts was observed for overall functional status, even when adjusted for age, sex, and psychiatric diagnosis ($P = 0.0010$; Table 3). More specifically, clinicians thought that fewer cohort 2 patients were "working/studying independently" as compared with cohort 1 and that 46.1% of cohort 2 patients were "not working/studying," which was comparable with the 54.4% of cohort 2 patients who self-reported their employment status was categorized as "disabled" (Table 1). However, differences between cohort 2 and cohort 1 for the patient-rated SDS (including the work/school domain) were not statistically significant (Table 3).

For all EQ-5D-5L dimensions, a higher percentage of cohort 2 patients had moderate problems or worse (score ≥3) as compared with cohort 1, with a statistically significant difference for self-care ($P < 0.05$; Table S3, http://links.lww.com/JCP/A666). The mean health VAS score was lower (worse) in cohort 2 than in cohort 1, with the difference being statistically significant when adjusted for age, sex, and diagnosis ($P = 0.0002$; Table 3). The mean utility index score, derived from the dimension scores, was also significantly lower (worse) in cohort 2 than in cohort 1 ($P = 0.0175$).

DISCUSSION

Estimates for the prevalence of drug-induced TD vary widely,[27] which may be partly due to the different types of studies and patient populations that have been analyzed. In a comprehensive meta-analysis that included randomized clinical trials, prevalence studies, genetic studies, and cohort studies, the global prevalence of TD was estimated to be 25.3% in patients taking an FGA or SGA.[8] Because RE-KINECT was not designed as a prevalence study, epidemiologic methods were not implemented and a formal diagnosis of TD was not required. However, as a real-world screening study for possible TD, RE-KINECT provides important information about the presence and frequency of involuntary movements in psychiatric outpatients from across the United States who received antipsychotic treatment for various disorders. Based on clinician assessment, 27.6% (204/739) of eligible patients in this study were considered to have possible TD.

One goal of RE-KINECT was to assess the potential utility of a simplified rating scale for TD (ie, "none," "some," or "a lot") that clinicians could use while observing patients during usual care visits. Given the similarity between the 27.6% of patients with possible TD in this study and the 25.3% global prevalence of TD, the methods used in RE-KINECT (ie, online video training for office staff, visual observation, and a simplified severity scale) may offer a reliable way for clinicians and/or staff to look for involuntary movements during every patient encounter. Per American Psychiatric Association guidelines, routine monitoring



	Percentage of Cohort 2 Patients		
	Per Clinician Report (N=204)	Per Patient Report (N=110)	Spearman Correlation, ρ
Head/face: facial muscles, lips, tongue, jaw			
None	33.8	30.0	0.76*
Some	45.6	43.6	
A lot	20.1	25.5	
Missing	0.5	0.9	
Neck/trunk: neck, shoulders, chest, hips			
None	77.9	75.5	0.61*
Some	16.2	16.4	
A lot	4.4	7.3	
Missing	1.5	0.9	
Upper extremities: arms, hands, fingers			
None	40.7	36.4	0.75*
Some	48.5	41.8	
A lot	10.3	20.9	
Missing	0.5	0.9	
Lower extremities: legs, feet, toes			
None	57.4	54.5	0.75*
Some	34.3	31.8	
A lot	7.8	13.6	
Missing	0.5	0	
Maximum rating in any body region			
None	0	0	0.50*
Some	66.7	52.7	
A lot	33.3	47.3	
Missing	0	0	
Total number of body regions			
One	47.1	36.4	0.24*
Two	28.4	36.4	
Three	14.7	17.3	
Four	9.8	10.0	

FIGURE 2. Location and severity of uncontrollable involuntary movements (cohort 2). The maximum symptom severity score represents the highest rating reported in any of the 4 body regions. Patient-reported ratings include patients who were aware of involuntary movements in the past 4 weeks that they could not control. Correlation analyses were based on available clinician- and patient-reported ratings. *$P < 0.001$ for correlation between clinician and patient report.

for abnormal involuntary movements should be conducted every 6 to 12 months in all patients treated with an antipsychotic, and every 3 to 6 months in patients at higher risk for TD (eg, older patients).[28] Although it has been shown that the AIMS can improve early detection of TD,[29] conducting a formal AIMS assessment at every visit may not be possible because of limited time or resources. Instead, a simplified screening tool, as used in this study, may be adequate as a quick, ongoing "check" throughout a patient's treatment with antipsychotics.

For cohort 2, a majority of both clinicians and those patients who were aware of and could not control their movements reported the presence of "some" or "a lot" of involuntary movements in at least 2 body regions, which may be comparable with the Schooler-Kane criteria of mild or worse dyskinetic movements in 2 areas (ie, score ≥2 in 2 AIMS items).[30] In addition, 33.3% of clinicians and 47.3% of these patients reported a maximum rating of "a lot" in at least 1 body region, which may correspond to the Schooler-Kane criteria of moderate or worse dyskinetic movements in 1 area (ie, score ≥3 in 1 AIMS item[30]). However, 35.8% and 24.5% of clinicians and patients, respectively, reported "some" movements in only 1 body region; these patients with possible TD may not meet the threshold of Schooler-Kane criteria but nevertheless should be considered by practicing clinicians as having TD. In addition, the maximum rating of "a lot" may be a proxy for AIMS item 8 (global severity), but a more formal examination of the congruence between RE-KINECT severity ratings and the AIMS would be needed.

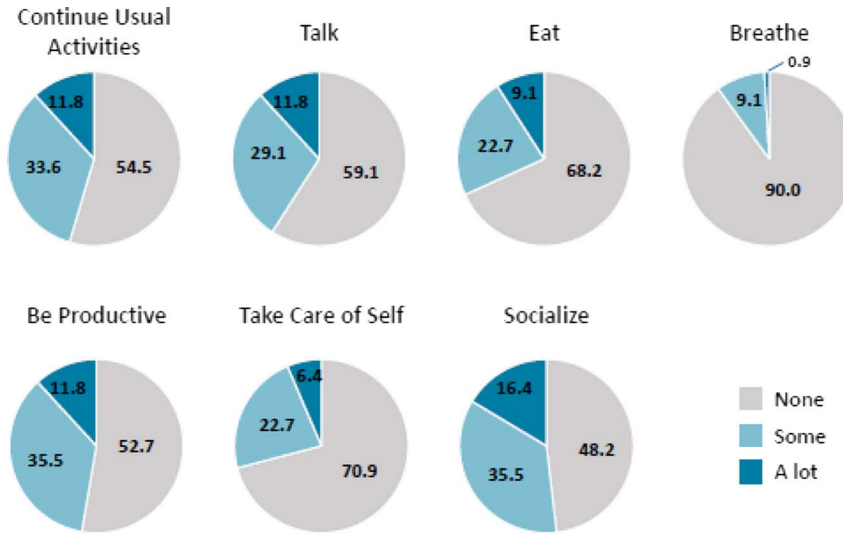


FIGURE 3. Impact of involuntary movements on daily activities (cohort 2). Patient-reported impact of involuntary movements on daily activities for the past 4 weeks. It includes patients who were aware of involuntary movements in the past 4 weeks that they could not control (n = 110).

The head/face was the most commonly reported region for involuntary movements. However, because movements were found in all 4 body regions, looking only at the head/face may cause TD to be missed. Statistically significant but only modest correlations were found between patient and clinician ratings for the total number of affected body regions, suggesting that healthcare providers may want to ask patients about their movements in addition to conducting their own assessments to get a fuller picture of the patient's TD. Some patients may not be aware of their involuntary movements, as indicated by both clinicians and patients. In these cases, caregivers may provide valuable information about the location, severity, and impact of involuntary movements. It has been reported that compared with patients with schizophrenia, patients with a mood disorder may be more functional and have higher levels of awareness.[31] However, awareness in RE-KINECT (per clinician judgment) did not significantly differ between cohort 2 patients who had a mood or other disorder and those who had schizophrenia or schizoaffective disorder. For all patients who are aware of their TD symptoms (regardless of underlying psychiatric diagnosis), even relatively "mild" involuntary

TABLE 2. Overall Health and Health Conditions (Patient Reported)

	Cohort 1 (n = 535)	Cohort 2 (n = 204)	*P**
Overall health, mean (SD)[†]	4.4 (2.8)	4.7 (2.8)	0.1251
Health conditions that caused the most concern or worry, n (%)			
Mental health	325 (60.7)	121 (59.3)	0.7217
Movement disorder (TD or non-TD)	24 (4.5)	53 (26.0)	<0.0001
Physical activity and nutrition	126 (23.6)	51 (25.0)	0.6800
Pain management	131 (24.5)	44 (21.6)	0.4043
Serious long-term disease/disorder	112 (20.9)	41 (20.1)	0.8019
Mild or short-term condition	58 (10.8)	26 (12.7)	0.4660
Other	66 (12.3)	16 (7.8)	0.0821
None	67 (12.5)	19 (9.3)	0.2238
Health conditions that were the most time-consuming, n (%)			
Mental health	329 (61.5)	112 (54.9)	0.1024
Physical activity and nutrition	94 (17.6)	39 (19.1)	0.6245
Movement disorder (TD or non-TD)	9 (1.7)	36 (17.6)	<0.0001
Pain management	98 (18.3)	36 (17.6)	0.8325
Serious long-term disease/disorder	95 (17.8)	30 (14.7)	0.3226
Mild or short-term condition	47 (8.8)	14 (6.9)	0.3959
Other	49 (9.2)	10 (4.9)	0.0563
None	62 (11.6)	24 (11.8)	0.9468

*For cohort 2 vs cohort 1, unadjusted comparison. For questions or items that allowed more than 1 response (categories not mutually exclusive), *P* values are provided for each response.

[†]Range, 0 (no health problems) to 10 (health as bad as you can imagine); based on available assessments (cohort 1, n = 531; cohort 2, n = 203).

TABLE 3. Functional Status and Health-Related Quality of Life

	Cohort 1 (n = 535)		Cohort 2 (n = 204)		*P**	Adjusted *P**†
Overall Functional Status‡	N_0	n (%)	N_0	n (%)	<0.0001	0.0010
Working/studying independently	535	276 (51.6)	204	66 (32.4)		
Working/studying with assistance	535	119 (22.2)	204	44 (21.6)		
Not working/studying	535	140 (26.2)	204	94 (46.1)		
Sheehan Disability Scale§		Mean (SD)		Mean (SD)		
Work/school	363	3.7 (3.5)	111	4.2 (3.4)	0.2358	0.2316
Social life	531	3.7 (3.3)	203	4.0 (3.4)	0.3262	0.2008
Family life/home responsibilities	530	3.7 (3.3)	203	3.8 (3.3)	0.7380	0.3863
Total score	530	11.1 (9.2)	203	11.7 (9.3)	0.4262	0.1880
EQ-5D-5L‖		Mean (SD)		Mean (SD)		
Health state VAS	531	69.7 (21.7)	204	66.8 (25.1)	0.1501	0.0002
Utility index score	526	0.76 (0.19)	197	0.71 (0.21)	0.0029	0.0175

*For cohort 2 vs cohort 1 unadjusted comparison. For questions or items that allowed more than 1 response (categories not mutually exclusive), *P* values are provided for each response.

†Adjusted for age (<55 vs ≥55 years), sex (male vs female), and diagnosis (schizophrenia or schizoaffective disorder vs other).

‡ Status since the last usual care visit, based on the clinician's best knowledge.

§Patient reported. Domain scores ranged from 0 (no problems) to 10 (extreme problems). Total score (ie, sum of domain scores) was calculated for patients who had ≥2 available domains. When only 1 domain was missing, the average of his/her observed scores was imputed to the missing record.

‖Patient reported. Health state VAS scores ranged from 0 (worst health you can imagine) to 100 (best health you can imagine). Utility index scores, derived from dimension scores, ranged from 0 (health state equivalent to death) to 1 (perfect health).

N_0, number of available assessments.

movements—especially if present in visible regions of the body—may be embarrassing or distressing. Among cohort 2 patients in RE-KINECT, 75.5% reported being self-conscious or embarrassed about involuntary movements that they could not control. Such feelings can exacerbate existing psychiatric symptoms (eg, depressed mood, anxiousness) and contribute to a sense of stigmatization and social isolation.

Characteristics that have been associated with a higher risk for TD include older age, female sex (with a possible interaction between age and sex), white or black/African-American race, longer illness duration, cognitive disability, schizophrenia or mood disorder diagnosis, treatment with FGAs or SGAs, and longer duration of antipsychotic use.[32] Although higher antipsychotic dosages and FGA use have also been associated with TD,[33] it may be problematic to conclude that patients who take lower doses of adjunctive SGAs (eg, for major depressive disorder) have a lower risk of TD because mood disorders are a risk factor[32] and overall use of SGAs continues to increase. Consistent with some of these risk factors, cohort 2 patients were statistically significantly older than cohort 1 patients and had a longer lifetime exposure to antipsychotics. However, there was no significant difference between cohorts in terms of sex or race.

Patients with negative symptoms of schizophrenia, as well as patients with a primary mood disorder or mood symptoms, may also be at higher risk for TD.[32] It should be noted, however, that published analyses of TD risk by psychiatric diagnosis are generally from earlier studies including the use of high-dose FGAs, which may be a confounding factor for risk.[34–36] In RE-KINECT, both cohorts seemed to have patients with multiple psychiatric diagnoses documented in their medical records, which is typical of real-world studies and can reflect diagnostic uncertainties, psychiatric comorbidities, or the difficulty of determining which symptoms (eg, psychotic episodes, depressed mood, anxiousness) are predominant. The relatively lower percentage of cohort 2 patients with a mood disorder was contrary to the conventional wisdom that these patients may be more at risk for developing TD. However, other confounding factors such as patient age, type of antipsychotic treatment (FGA or SGA), severity, and/or duration of mood disorder need to be considered.

The impact of TD on quality of life and daily functioning is an important treatment consideration, but recent TD treatment trials were not designed to include such outcomes. Therefore, another main goal of RE-KINECT was to understand patients' perspectives on how involuntary movements affect their daily lives. In recognition of the potentially confounding effects of age, sex, and psychiatric diagnosis on quality of life and daily functioning, comparisons between cohorts were adjusted for these factors. The importance of such adjustments can be seen in the shift from statistical significance to nonsignificance for cohort 2 versus cohort 1, as was the case for employment disability which suggests that age, sex, and psychiatric diagnosis may have been important factors of difference. On other critical measures, however, significance was maintained, as was the case for EQ-5D-5L health state VAS, suggesting that possible TD may have been the primary driving factor of difference.

Evaluating the impact of TD on quality of life may also be affected by the methods used for assessment. For example, the EQ-5D-5L utility score indicated significantly worse quality of life in cohort 2 compared with cohort 1, whereas SDS scores were not statistically significant in either analysis. One possible reason for this disparity is that the EQ-5D-5L has been used in many different psychiatric and medical conditions and incorporates national general population norms. In contrast, the SDS was developed for (and validated in) relatively higher functioning patients with mood or anxiety disorders. However, patient-reported responses regarding the impact of involuntary movements clearly indicate that TD can negatively affect a patient's ability to perform daily activities (Fig. 3). Therefore, it may be informative to ask

patients whether TD has had any impact on their ability to continue usual activities, be productive, take care of self, or socialize. For patients with visible or reported involuntary movements in the face or mouth, questions about their ability to talk, eat, and breathe might also be helpful.

Some of the limitations of this study have already been addressed. First, RE-KINECT was not designed to be a formal prevalence study, although results from the screening phase provide real-world data about the pervasiveness of possible TD in antipsychotic-treated outpatients. Second, the psychiatric and medical conditions were based on clinical records and were not standardized for reporting. In addition, the psychiatric conditions captured via retrospective chart review do not distinguish between primary and secondary/comorbid disorders, although they reflect the types of patients who are currently being treated with antipsychotics. Third, cohorts were not matched for demographic, geographic, socioeconomic, or illness-related variables; adjustments based on age, sex, and psychiatric diagnosis may mitigate some of these potential incongruities, but all comparisons between cohort 2 and cohort 1 should be interpreted with some caution. Finally, although the use of standardized patient-reported outcomes such as the EQ-5D-5L and SDS in TD populations is long overdue, it should be noted that neither of these scales (nor any of the self-reported items on the patient questionnaire) has been validated specifically in patients with TD. More research is needed to understand which scales are most appropriate for assessing the burden of TD. Moreover, patients in both cohorts had psychiatric and medical conditions that could affect quality of life and functional ability. Because the EQ-5D-5L and SDS were not "anchored" to possible TD or any movements, further analysis is required to try and isolate the role of TD in quality of life. Nonetheless, some of the results in this study suggest that possible TD may have had an independent effect on quality of life and functioning.

CONCLUSIONS

Although antipsychotic medications are necessary to treat various psychiatric disorders, they also carry some risk for TD. In concordance with recently published literature, the results of this real-world screening study indicate that approximately 25% of antipsychotic-treated patients have involuntary movements consistent with TD. The simplified rating scale used in this study may be appropriate for informal assessments of TD severity during regular patient visits. However, more formal and structured assessments should be conducted at prespecified time points and if signs of TD emerge. In this study, clinicians and patients often reported involuntary movements in more than 1 body region, suggesting that a visual scan of the entire body (not just the face or hands) should be included in the screening process.

In addition to assessing the location and severity of TD movements, the results presented in this report emphasize the importance of asking patients about the impact of TD on their lives. With the expanding use of antipsychotics in different types of psychiatric patients, many of whom are highly functioning and aware of their symptoms, even "some" TD may have "a lot" of impact on their ability to participate in regular daily activities. Social isolation due to embarrassment or stigma can exacerbate psychiatric symptoms that a patient might already be experiencing, such as anxiety or depressed mood.

Given the findings of this study—from the relatively frequent occurrence of possible TD, to the location and severity of involuntary movements, to the impact of these movements on patients' lives—routine screening is imperative for all patients treated with an antipsychotic. This study shows that from a research perspective, more work is needed to validate patient-reported outcomes in TD and/or develop objective scales that capture the impact of TD on patient quality of life and activities of daily living. From a clinical perspective, this study demonstrates that there may be an opportunity during routine office visits to incorporate patient self-assessment tools before clinical evaluation to elicit their perspectives on disease burden and severity of symptoms.

ACKNOWLEDGMENTS

The authors thank Amanda Ford, PhD, at PPD (Morrisville, NC) and Michael Serbin, PharmD, at Neurocrine Biosciences, Inc (San Diego, CA) for their contributions to this work. Writing and editorial assistance were provided by Gina Daniel, PhD, and Mildred Bahn, MA, at Prescott Medical Communications Group (Chicago, IL) with support from Neurocrine Biosciences, Inc.

AUTHOR DISCLOSURE INFORMATION

This study was conducted by Evidera (Bethesda, MD) with support from Neurocrine Biosciences, Inc (San Diego, CA). S.N.C. has served as a consultant to Neurocrine Biosciences, Inc, Teva Pharmaceuticals Industries, Ltd, Osmotica Pharmaceuticals, and Dispersol Technologies and received a separate research grant from Neurocrine Biosciences, Inc. C.M.T. receives grants from the Michael J. Fox Foundation, the Parkinson's Foundation, the Department of Defense, BioElectron, Roche/Genentech, Biogen, and the National Institutes of Health, compensation for serving on Data Monitoring Committees from Biotie Therapeutics, Voyager Therapeutics, and Intec Pharma and personal fees for consulting from Neurocrine Biosciences, Adamas Therapeutics, Biogen, 23andMe, Alexza, Gray Matter, Acadia, and CNS Ratings. A.J.C. has served as a consultant to, received research grants from, and is on the speaker bureau for ACADIA, Avanir, Neurocrine, Otsuka, and Teva, is a consultant to MedAvante-Prophase, and is on the Board of the Neuroscience Research Institute. W.R.L., K.Y., H.S., V.P., and J.C. are full-time employees of Evidera and served as consultants on this work. C.Y. and E.F. are full-time employees of Neurocrine Biosciences, Inc.

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