

# Exploring real-world symptom impact and improvement in well-being domains for tardive dyskinesia in VMAT2 inhibitor-treated patients via clinician survey and chart review

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## Abstract

**Introduction:** Two vesicular monoamine transporter 2 (VMAT2) inhibitors are approved in the United States (US) for the treatment of tardive dyskinesia (TD). There is a paucity of information on the impact of VMAT2 inhibitor treatment on patient social and physical well-being. The study objective was to elucidate clinician-reported improvement in symptoms and any noticeable changes in social or physical well-being in patients receiving VMAT2 inhibitors.

**Methods:** A web-based survey was offered to physicians, nurse practitioners, and physician assistants based in the US who prescribed valbenazine for TD within the past 24 months. Clinicians reported data from the charts of patients who met the inclusion criteria and were allowed to recall missing information.

**Results:** Respondents included 163 clinicians who reviewed charts of 601 VMAT2-treated patients with TD: 47% had TD symptoms in  $\geq 2$  body regions, with the most common being in the head or face and upper extremities. Prior to treatment, 93% of patients showed impairment in  $\geq 1$  social domain, and 88% were impaired in  $\geq 1$  physical domain. Following treatment, among those with improvement in TD symptoms ( $n = 540$ ), 80% to 95% showed improvement in social domains, 90% to 95% showed improvement in physical domains, and 73% showed improvement in their primary psychiatric condition.

**Discussion:** In VMAT2-treated patients with TD symptom improvement, clinicians reported concomitant improvement in psychiatric disorder symptoms and in social and physical well-being. Regular assessment of TD impact on these types of domains should occur simultaneously with movement disorder ratings when evaluating the value of VMAT2 inhibitor therapy.

**Keywords:** tardive dyskinesia, valbenazine, deutetrabenazine, tetrabenazine, vesicular monoamine transport inhibitors, antipsychotics, psychiatric diseases, disease burden, patient awareness, patient-centric outcomes

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## Introduction

Tardive dyskinesia (TD) is an involuntary, hyperkinetic movement disorder associated with prolonged exposure to dopamine receptor-blocking agents, such as antipsychotics and metoclopramide.<sup>1</sup> The symptoms of TD often persist after discontinuing the offending drug and typically include excessive blinking, grimacing, lip puckering and smacking, or twisting and writhing in the upper and lower trunk and extremities.<sup>1,2</sup> The clinical burden of TD symptoms is associated with impaired social and physical capabilities, leading to negative outcomes such as social withdrawal, shame, embarrassment, and helplessness.<sup>3,4</sup> TD symptoms can also increase the stigma associated with mental illness and reduce patients' quality of life (QOL).<sup>5,6</sup> Vesicular monoamine transporter 2 (VMAT2) inhibitors show clinically meaningful improvement in TD symptoms regardless of underlying psychiatric diagnosis or patient characteristics and are considered the standard of care for TD.<sup>7-10</sup> Valbenazine and deutetrabenzazine are the 2 reversible VMAT2 inhibitors approved by the United States (US) Food and Drug Administration (FDA) for managing TD symptoms.<sup>11,12</sup> Although the phase 2 and 3 clinical studies for these 2 agents showed statistically significant improvements in TD severity using the Abnormal Involuntary Movement Scale (AIMS)<sup>13</sup> score (items 1-7), none of the clinical trials showed statistically significant improvement in patient-reported health-related QOL or indicators of social or physical well-being, as QOL was not consistently measured throughout the trials.<sup>8,14-18</sup>

Reduction in severity of TD motor symptoms represents one aspect of treatment-related changes, but additional measures

of social and physical well-being help capture the broader extent of patient benefit. Published case reports note that VMAT2 inhibitors provide improvement not only in clinical disease severity, but also in social and physical well-being.<sup>19,20</sup> Unfortunately, there is limited information on this topic from the prospective clinical trials of the new VMAT2 inhibitors. Additionally, retrospective data regarding the social and/or physical impact of the symptoms of TD or potential effect of treatment on social and physical capabilities are challenging to locate in electronic medical records or insurance claim databases.

To expand the understanding of this issue, Neurocrine Biosciences, Inc. sponsored the present hybrid study composed of a clinician survey and chart review by treating clinicians. The primary objective of this study was to assess if patients who showed improvement in TD movement-associated symptoms showed changes in 3 other aspects: (1) social capabilities, with individual domains of socialization and engagement with family and friends and ability to work or go to school; (2) physical capabilities, with individual domains of mobility, eating and speech, and activities of daily living; and (3) primary psychiatric condition. The goal was to provide real-world clinician-reported data to supplement the extant clinical trial data on VMAT2 inhibitors and to inform clinicians, patients, payers, and regulatory bodies about the overall potential benefits of VMAT2 inhibitors for the treatment of TD.

## Methods

The survey instrument was jointly developed by IQVIA and Neurocrine Biosciences, Inc. and was administered by IQVIA, who invited physicians, nurse practitioners, and physician assistants based in the US to complete the study. These clinicians who had prescribed valbenazine for TD within the past 24 months were asked to complete a web-based survey consisting of specific data of interest for VMAT2-treated patients. They may have also prescribed deutetrabenzazine or off-label tetrabenzazine for TD, as determined by IQVIA. Invitations were sent to 2359 individuals, and 240 responses were received for a 10.2% response rate. Survey participants had to provide consent to participate and were compensated for completing the survey. The survey participants were blinded to the sponsor, and the sponsor was blinded to the survey participants.

In this hybrid methodology, the clinician was asked to input data from the chart with recall allowed to complete items not directly found within the chart. Clinicians provided patient-specific information of interest consisting of both pre-VMAT2 inhibitor treatment and post-VMAT2 inhibitor treatment data. For testing clarity and clinical relevance of the survey, IQVIA obtained feedback from 4 clinicians in a pilot interview (via phone) that was used to

improve the clarity and content of the survey before it was extended to all survey participants.

Clinicians provided data from up to 10 patient charts for adult patients (aged  $\geq 18$  years) who started at least 1 VMAT2 inhibitor (valbenazine, deutetrabenazine, or off-label tetrabenazine) for TD on or after January 1, 2018, and completed at least 2 months of treatment. The study focused on the impact of TD symptom improvement on social and/or physical capabilities. Data provided by the clinicians were reviewed for quality (logic) and completeness before inclusion in the final analysis. The database contains no patient-identifiable data beyond age and gender. All patient-related data were protected in compliance with HIPAA rules on patient confidentiality.

Clinicians participating in the survey logged into a secure website to complete a survey (1 per patient), which included items related to TD symptom presentation (body location and severity), impact of TD on social and physical capabilities prior to treatment, and any improvements after VMAT2 inhibitor treatment. Clinician responses to the multiple-choice questions were based on their chart review of any documented patient-specific disease impact, clinician recall from patient interactions, and clinician judgment. Clinicians described characteristics of patient symptoms by identifying the body regions with TD symptoms, duration of TD symptoms, and awareness of symptoms. Disease severity was categorized as “asymptomatic,” “mild,” “moderate,” or “severe” based on their clinical perception. Clinicians categorized the pretreatment impact of TD symptoms on patient social and physical well-being into one of the following ratings: “no impact,” “somewhat impacted,” and “significantly impacted.” Likewise, clinicians categorized patient TD symptom improvements post-treatment into one of the following ratings: “none,” “somewhat improved,” and “significantly improved.” These defined categories allowed understanding of the observed impact of the disease before treatment compared to TD symptom improvements after treatment with a VMAT2 inhibitor. The study also collected information related to noticeable changes in psychiatric conditions based on clinician judgment as “none,” “somewhat improved,” or “significantly improved” after treatment with VMAT2 inhibitors. The survey was approved by the Western Institutional Review Board. Data, collected from July 24, 2019, to August 30, 2019, were analyzed and summarized with descriptive statistics. Statistics for frequencies of responses and measures of central tendency as means were reported.

## Results

### Respondent and Patient Characteristics

Of the 163 clinicians who responded to the survey, 113 (69%) practiced in psychiatry, 46 (28%) in neurology, and 4

(2%) in primary care, with the majority of respondents practicing as physicians ( $n = 158$ ). The responding clinicians reviewed charts of 601 patients prescribed a VMAT2 inhibitor for TD. Most charts were from psychiatrists (68%;  $n = 411$ ) and neurologists (30%;  $n = 181$ ), with the rest from primary care physicians (1%;  $n = 9$ ). The mean age of patients was 50.6 years, and 50% (299/601) were male.

### Antipsychotic Use and Psychiatric Conditions

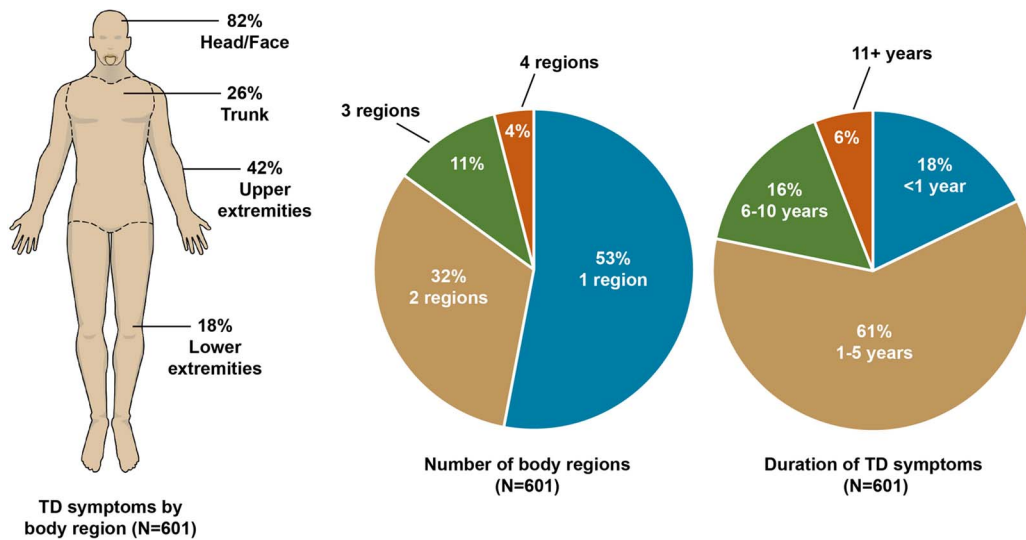
Of the 601 patients, 542 (90%) took an antipsychotic over the last 12 months; of these, 420 (77%) were still taking an antipsychotic at the time of data collection. Of the 542 patients exposed to antipsychotics, 74% (402/542) were exposed to second-generation antipsychotics (SGAs) and 15% (83/542) were taking first-generation antipsychotics (FGAs); the remainder (57/542, 11%) were taking both FGAs and SGAs (the survey did not capture the dosing, frequency, or specific antipsychotic drug[s] prescribed). Approximately 63% and 72% of patients were exposed to FGA and/or SGA medications for 1 to 10 years, respectively. The most common primary psychiatric conditions treated with an antipsychotic were schizophrenia (172/542; 32%), bipolar disorder (159/542; 29%), schizoaffective disorder (125/542; 23%), and major depressive disorder (61/542; 11%). Anxiety disorders (196/601; 33%) and substance use disorders (110/601; 18%) were common psychiatric comorbidities.

### Medications for TD

Most of the 601 patients were prescribed an FDA-approved VMAT2 inhibitor for TD (69% valbenazine, 28% deutetrabenazine) with the remaining 3% receiving tetrabenazine. In addition to a VMAT2 inhibitor, 231 (38%) patients had previously taken another medication for TD, and 85 (14%) were currently taking another medication. The most common non-VMAT2 inhibitor treatments were benzotropine (28% past, 5% current), benzodiazepines (17%, 5%), amantadine (11%, 3%), and vitamin E (11%, 3%).

### Location and Severity of TD Symptoms

The most commonly reported regions where TD symptoms were present included the head or face (82%) and upper extremities (42%), and 47% of the patients had symptoms in  $\geq 2$  body regions (Figure 1). More than half (61%) of patients experienced TD symptoms for 1 to 5 years, and 6% experienced symptoms for  $\geq 11$  years. Clinicians rated TD symptom severity to be mild (111/601; 18%), moderate (328/601; 55%), or severe (160/601; 27%). Clinician-reported patient awareness of TD symptoms was highest for lips (79%) and tongue (77%) and lowest for ankles (55%) and toes (55%).



**FIGURE 1:** Clinician-described location and duration of TD symptoms; TD = tardive dyskinesia

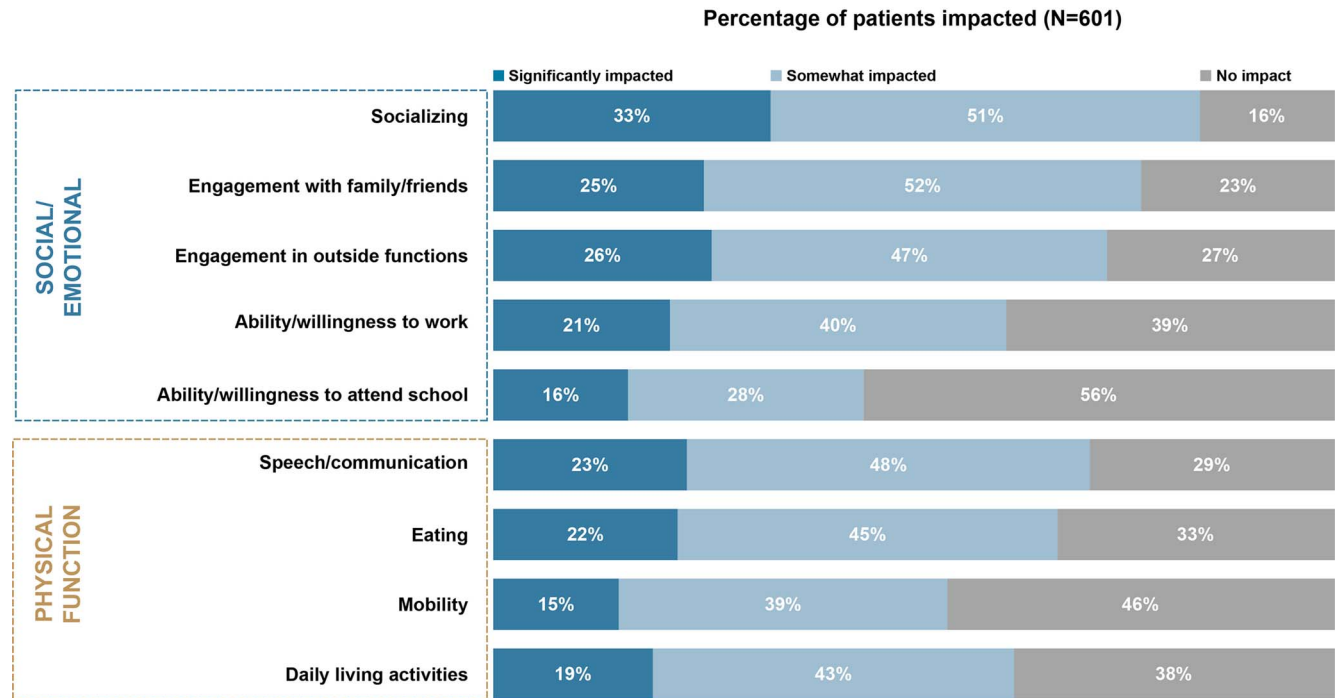
### Impact of TD Symptoms

Clinicians reported that nearly all patients had social or physical impacts from their TD symptoms (Figure 2). Most patients (93%; 560/601) were impacted in at least 1 social domain, and 88% (528/601) were impacted in at least 1 physical domain. Clinicians rated social domains as “significantly impacted” or “somewhat impacted” in 84% (504/601) of patients. In the social domains, clinicians most frequently reported “significantly impacted” or “somewhat impacted” for socializing (504/601; 84%) and engagement with family and friends (461/601; 77%).

Clinicians rated physical domains as “significantly impacted” or “somewhat impacted” in 71% (427/601) of patients. In the physical domains, clinicians most frequently reported “significantly impacted” or “somewhat impacted” for speech and communication (429/601; 71%) and eating (403/601; 67%).

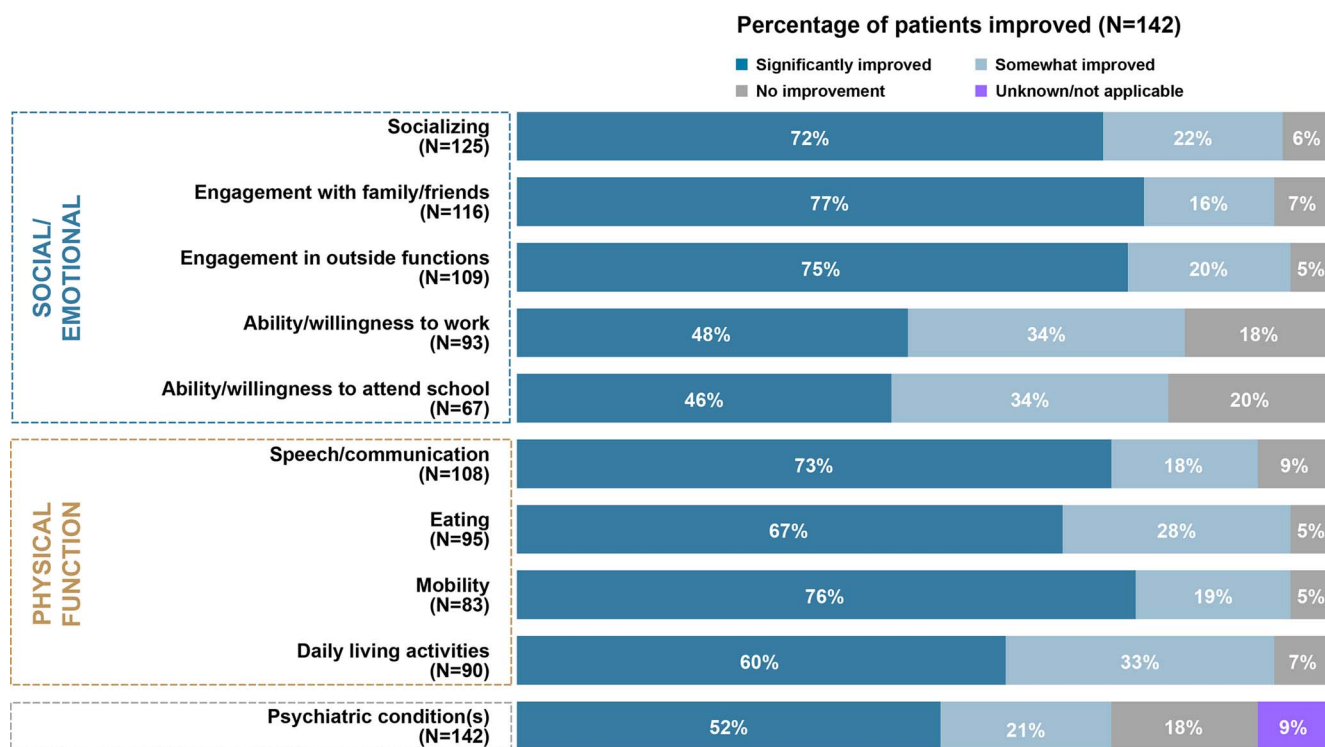
### Impact of VMAT2 Inhibitor Treatment on TD Symptoms

Clinicians reported improvement in TD symptoms since starting the most recent VMAT2 inhibitor treatment for



**FIGURE 2:** Clinician-determined impact of TD on social and physical well-being domains before treatment with VMAT2 inhibitors; TD = tardive dyskinesia; VMAT2 = vesicular monoamine transporter 2





**FIGURE 3:** Clinician perceptions of improvement in social and physical well-being domains and psychiatric conditions in patients with “significantly improved” TD symptoms after VMAT2 inhibitor treatment. The N under each domain represents the total number of patients where clinicians reported that TD symptoms had an impact on that domain or condition; TD = tardive dyskinesia; VMAT2 = vesicular monoamine transporter 2

540 (90% of 601) of the patients in the study. Respondents rated TD symptoms as “significantly improved” in 142 (24%) patients, “much improved” in 230 (38%) patients, and “somewhat improved” in 168 (28%) patients. Of the remaining 61 (10%) patients in the study, 36 (6%) were still “improving/titrating the dose [of VMAT2 inhibitor],” and 25 (4%) had “stopped taking the medication.”

### Impact of TD Symptom Improvement on Social and Physical Domains

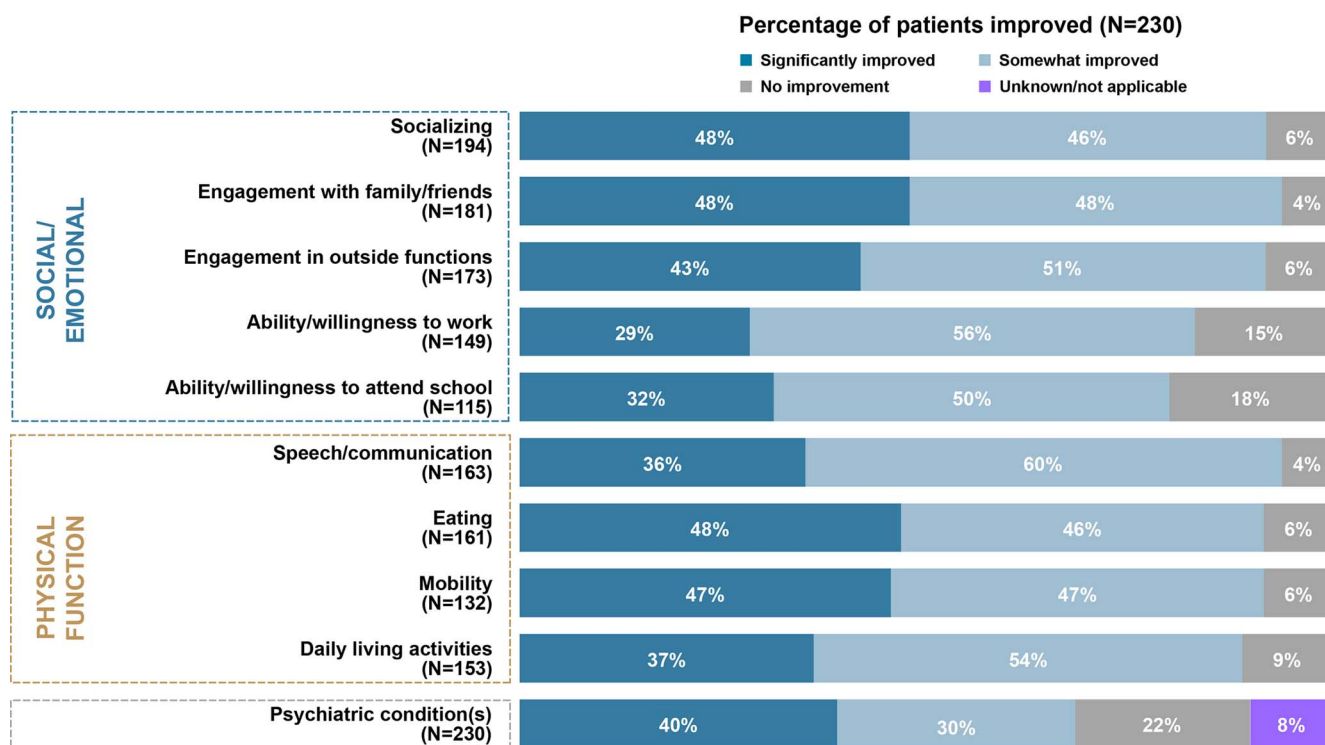
If clinicians reported improvement in TD symptoms, the survey sought to understand if there was a commensurate improvement in the social and physical domains that were negatively impacted by TD symptoms. For example, there were 142 patients in the study where TD symptoms “significantly improved” following VMAT2 treatment. Of those 142 patients with “significant improvement” in TD symptoms, there were 125 where TD symptoms impacted the socializing domain. For this subset of patients, clinicians indicated that 90 (72% of 125) had improved “significantly” in socializing after their TD symptoms improved following VMAT2 inhibitor treatment, 28 (22%) patients improved “somewhat,” and the remaining 7 (6%) had no observed improvement (Figure 3).

### Patients with “Significantly Improved” TD Symptoms

Many of the patients for whom clinicians reported “significant improvement” in TD symptoms with a VMAT2 inhibitor were also reported to have improvement in social and physical well-being, as well as psychiatric condition improvement. Of this group (n = 142), 96.5% (137/142) improved in at least 1 social domain, and 94% (134/142) improved in at least 1 physical domain. Psychiatric conditions were rated as improved in 73% (74/142) of these patients (Figure 3). Engagement with family and friends (89/116; 77%), engagement in outside function (82/109; 75%), mobility (63/83; 76%), and speech and communication (79/108; 73%) had the largest number of patients rated by clinicians as “significantly improved” in the social and physical domains.

### Patients with “Much Improved” TD Symptoms

Among 230 patients in the “much improved” TD symptoms category, 98% (226/230) showed improvement in at least 1 social domain, and 97% (224/230) in at least 1 physical domain while 70% were rated as having improvement in their primary psychiatric condition (Figure 4). Socializing, engagement with family and friends, eating, and mobility were rated by clinicians as “significantly improved” in nearly half of the patients (47%-48%).



**FIGURE 4:** Clinician perceptions of improvement in social and physical well-being domains and psychiatric conditions in patients with “much improved” TD symptoms after VMAT2 inhibitor treatment. The N under each domain represents the total number of patients where clinicians reported that TD symptoms had an impact on that domain or condition; TD = tardive dyskinesia; VMAT2 = vesicular monoamine transporter 2

### Patients with “Somewhat Improved” TD Symptoms

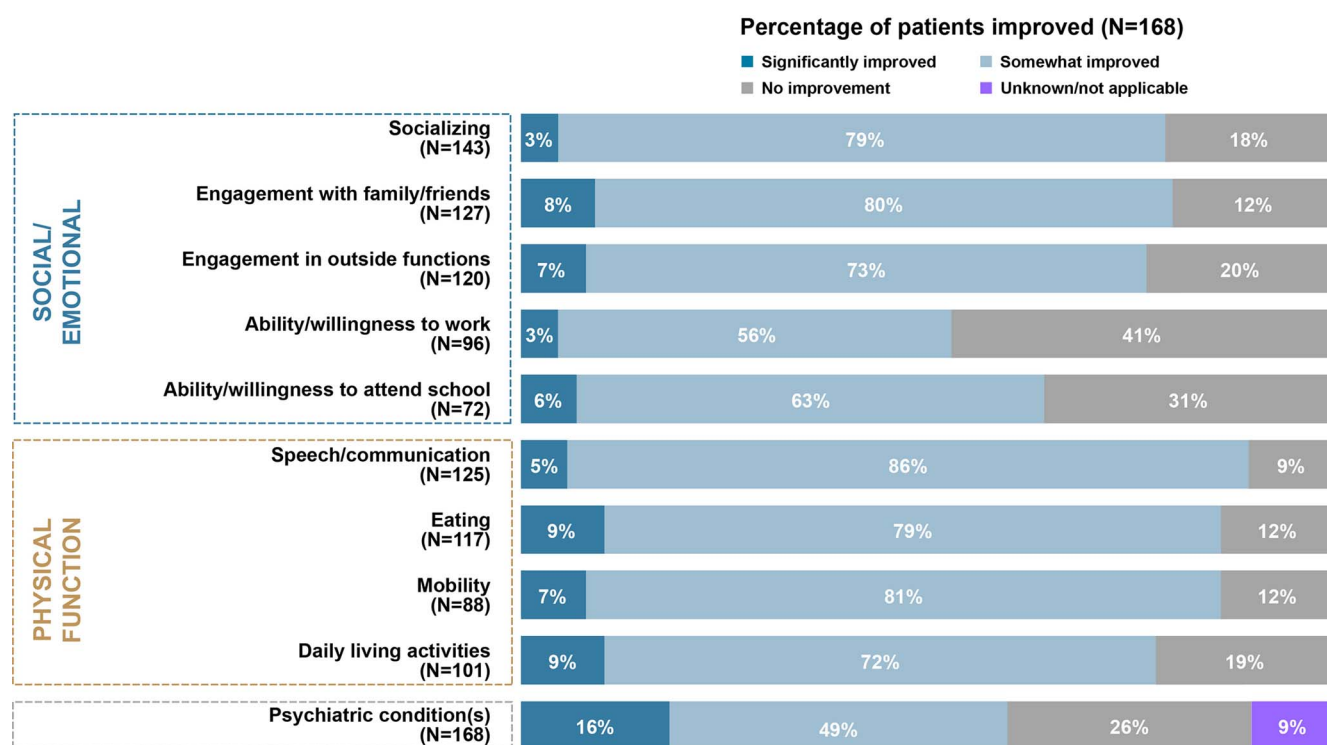
Of the 168 patients categorized as “somewhat improved” in TD symptoms, few (3%-9%) showed “significant improvement” in any of the social or physical well-being domains (Figure 5). Likewise, a smaller proportion of patients (16%; 27/168) were categorized as having “significant improvement” in their psychiatric conditions. These data support the linkage between TD symptom improvement and well-being change.

## Discussion

This retrospective real-world study describes clinician perceptions of clinical improvement in TD symptoms along with concurrent improvement in social and/or physical well-being in patients receiving VMAT2 inhibitors. Changes in AIMS score are often tracked during VMAT2 inhibitor treatment, but they do not reflect changes in social or physical impairment associated with TD<sup>21</sup> or its treatment. Given the potential impact of TD on social and physical functioning, it is important for clinicians to assess social and physical well-being function in patients on VMAT2 inhibitors as part of a holistic approach to gauging the impact of treating TD. While this survey was descriptive and retrospective in nature, the results are consistent with the data

on functional improvement after TD treatment published in case studies.<sup>19,20</sup>

In this survey, clinicians reported that 90% (n = 540) of patients on VMAT2 inhibitors showed improvement in TD symptoms and in their ability to socialize, engage with family and friends, work, or attend school. More than 90% reportedly showed improvements in the ability to perform physical activities such as speaking, eating, moving, or carrying out activities of daily living. In general, patients who were reported to have “significantly improved” TD symptoms with VMAT2 inhibitor treatment had a greater frequency of significant improvement in each domain, while patients who were reported to have “somewhat improved” had a lower frequency of significant improvement in each domain (compare Figures 3-5). The patients included in this study had similar characteristics to what has been observed in a real-world population of patients treated with antipsychotics and possible TD diagnosis. In the 204 patients with clinician-reported possible TD, 55% of patients had a mood disorder or other psychiatric condition (eg, anxiety disorder, major depressive disorder), and 83% had been exposed to an SGA.<sup>22</sup> In the current study, 40% of patients had bipolar disorder (29%) or major depressive disorder (11%), and 74% had been exposed to a SGA. This further supports that TD can occur in other psychiatric conditions and with exposure to SGAs.



**FIGURE 5:** Clinician perceptions of improvement in social and physical well-being domains and psychiatric conditions in patients with “somewhat improved” TD symptoms after VMAT2 inhibitor treatment. The N under each domain represents the total number of patients where clinicians reported that TD symptoms had an impact on that domain or condition; TD = tardive dyskinesia; VMAT2 = vesicular monoamine transporter 2

Inherent limitations exist for this study, partially due to the retrospective nature and use of the survey study design. The clinician sample is not necessarily representative of all those who treat TD patients, as only clinicians who had prescribed a VMAT2 inhibitor in the past 24 months based on pharmacy claims data were invited to participate, and the charts reviewed by the clinicians were prone to selection bias based on perceived treatment success. Second, improvements and outcomes were only captured by clinicians based on chart review and clinician recall. While standardized scales such as AIMS that prospectively measure TD signs are available, the survey did not capture clinicians’ use of the scale. Clinicians could have used AIMS-related data if it was recorded in the patient’s chart, but it was not a requirement for this study. As this study was a retrospective chart review, only data that were available in the charts could be used to complete the survey responses. Also, improvements in social and physical well-being reported in the study were not captured in a standardized manner; in order to reduce bias, a sample of qualified physicians pre-tested the survey before fieldwork, and the team designed the survey with close-ended responses to all of the questions. Finally, because this was intended to be a responder analysis, the survey did not collect information related to antipsychotic or VMAT2 inhibitor discontinuations or dose reductions due to adverse events or worsening TD

symptoms. Only use of FGAs or SGAs were recorded and not the use of a specific antipsychotic.

This hybrid study was conducted to gather data that are not systematically captured in this population nor part of clinical trial endpoints. Therefore, given the limited information on functional outcomes from VMAT2 inhibitor therapy, more prospective clinical data are needed to investigate patient improvements in well-being related to improvements in TD symptom severity to reinforce the understanding that TD is a disorder that potentially impacts multiple aspects of patient well-being.

## Conclusions

This retrospective clinician survey study provides preliminary real-world evidence suggesting that improvements in TD symptom severity with VMAT2 inhibitor treatment may be accompanied by improvements in social and physical well-being. Future prospective studies evaluating this relationship would further strengthen the value of VMAT2 inhibitors in treating TD. Therefore, a holistic approach to treating patients with TD that includes assessment of social and physical functioning is warranted. Such assessments should include patient perspective on impact of TD and

subsequent improvements after VMAT2 inhibitor treatment initiation to appreciate the true value of these therapies.

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RBB, LL, EGF, RD, BB, MB, and CY participated in the study's conception and design. RBB and BB participated in collection and acquisition of data. JMM, CC, RBB, MMP-R, LL, BB, MB, and CY participated in data analysis and interpretation. All authors contributed to drafting and critically revising the manuscript. All authors are accountable for the work and provided their agreement for submission to the journal and approval for publication.

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