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Incidence of tardive dyskinesia: a comparison of long-acting injectable and oral paliperidone clinical trial databases

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Disclosures
Drs. Bossie and Fu are employees of Janssen Scientific Affairs, LLC. Dr. Burón is an employee of Janssen Global Services. Drs. Hough, Gopal, Nuamah, Savitz and Xu are employees of Janssen Research & Development, LLC. All authors hold stocks in the company.

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SUMMARY

Background: To assess the tardive dyskinesia (TD) rate in studies of once-monthly long-acting injectable (LAI) paliperidone palmitate (PP) and once-daily oral paliperidone extended release (Pali ER). **Methods:** Completed schizophrenia and bipolar studies for PP and Pali ER (≥ 6 month duration with retrievable patient-level data) were included in this *post hoc* analysis. Schooler–Kane research criteria were applied using Abnormal Involuntary Movement Scale (AIMS) scores to categorise probable (qualifying AIMS scores persisting for ≥ 3 months) and persistent TD (score persisting ≥ 6 months). Spontaneously reported TD adverse events (AEs) were also summarised. Impact of exposure duration on dyskinesia (defined as AIMS total score ≥ 3) was assessed by summarising the monthly dyskinesia rate. **Results:** In the schizophrenia studies, TD rates for PP (four studies, $N = 1689$) vs. Pali ER (five studies, $N = 2054$), were: spontaneously reported AE, 0.18% (PP) vs. 0.10% (Pali ER); probable TD, 0.12% (PP) vs. 0.19% (Pali ER) and persistent TD, 0.12% (PP) vs. 0.05% (Pali ER). In the only bipolar study identified [Pali ER ($N = 614$)], TD rate was zero (spontaneously reported AE reporting, probable and persistent TD assessments). Dyskinesia rate was higher within the first month of treatment with both PP (13.1%) and Pali ER (11.7%) and steadily decreased over time (months 6–7: PP: 5.4%; Pali ER: 6.4%). Mean exposure: PP, 279.6 days; Pali ER, 187.2 days. **Conclusions:** Risk of TD with paliperidone was low (< 0.2%), regardless of the formulation (oral or LAI), in this clinical trial dataset. Longer cumulative exposure does not appear to increase the risk of dyskinesias.

What's known
Paliperidone extended release (ER), an oral once-daily tablet, and paliperidone palmitate, a once monthly injectable, are both approved for the treatment of schizophrenia in many countries. Tardive dyskinesia (TD) is one of the potential side effects of antipsychotic medications, particularly associated with long-term treatment with dopamine D2 receptor blockade. Paliperidone is a potent inhibitor of the dopamine D2 receptor. Chronic treatment with antipsychotic medication may result in TD.

What's new
This *post hoc* analysis suggests that the risk of TD from paliperidone appears to be similar regardless of administration route or release profiles (monthly long-acting injectable versus daily oral dosing) in the treatment of schizophrenia. The risk for TD with paliperidone treatment was observed to be low and similar to data from published literature with other atypical antipsychotics. Longer cumulative exposure does not appear to increase the risk of dyskinesias.

Introduction

Tardive dyskinesia (TD) is a serious movement disorder that manifests in many different forms, but typically involves repetitive uncontrolled involuntary movements of the face, jaw and lips. In more severe forms it can impact the trunk or limbs or both (1,2). The occurrence of TD is associated with long-term treatment with several medication classes, including antimuscarinics, toxins, substances of abuse and antipsychotic medications (3–7). Antipsychotic-associated TD has been the focus of research for decades, with varying TD rates reported because of differences in TD definitions, populations, treatment conditions, etc. (8). Potential risk factors for TD include demographic characteristics (e.g. increasing age, female sex, race), medication regimen (e.g. specific drug, higher dose, longer duration of treatment) and medical conditions [e.g. acute extrapyramidal symptoms (EPS), psychosis, mood disorders, diabetes mellitus and organic brain dysfunction or damage]. Multiple types of acute EPS, such as parkinsonism, dystonia, akathisia, as well as dyskinesia, appear to increase the risk for TD (9–13). The potential of TD to be irreversible and severe can contribute to significant disability and social stigma for afflicted patients.

Atypical antipsychotics have generally shown a better safety profile compared with conventional antipsychotics, particularly in terms of a lower risk for TD (14–18). Long-acting injectable (LAI) antipsychotics provide more continuous, effective blood levels than daily oral antipsychotic medications thus, eliminating the need for daily treatment and overcoming a significant barrier to optimal medication management for many patients. However, some reports suggest that compared with oral antipsychotics, LAI may increase acute EPS in patients with schizophrenia (19–21), and likely be a risk factor for

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TD (11,22,23). Thus, with the increasing availability and use of LAI atypical antipsychotics, TD associated with LAI formulations may be a concern for clinicians and patients. Well-designed comparative studies for TD incidence with oral and LAI formulations of atypical antipsychotics are limited.

Paliperidone ER (Pali ER), an oral once-daily tablet, and paliperidone palmitate (PP), a once-monthly injectable LAI, are approved for the acute and maintenance treatment of schizophrenia in USA, EU and many other countries (24–28). Paliperidone (9-hydroxyrisperidone) is the active ingredient in both formulations and is an active metabolite of another atypical antipsychotic, risperidone. Paliperidone is a potent inhibitor of the dopamine D2 receptor (26); according to the dopamine supersensitivity hypothesis, the blockade of striatal D2 receptors by antipsychotic drugs up-regulates the striatal dopaminergic system and subsequently, may result in TD (29,30). The objective of this *post hoc* analysis was to determine the incidence of TD in each paliperidone formulation and compare the incidence rates using both spontaneous reporting of adverse events (AE) and by applying standardised research criteria.

Methods

This was a *post hoc* analysis performed on pooled data from the acute and extension phases of 10 randomised controlled long-term clinical research studies (≥ 6 months), involving patients with schizophrenia or bipolar disorder treated with once-monthly injectable PP (25–150 mg eq.) or once-daily Pali ER (3–15 mg/day). Because doses of PP can be expressed both in terms of milligram equivalents (mg eq.) of paliperidone (the pharmacologically active fraction) and in milligrams of PP, the doses expressed as PP 25, 50, 100 and 150 mg eq. equate to 39, 78, 156 and 234 mg, respectively, of PP.

In all of the studies, patients were required to wash-out of their previous antipsychotic (typical/atypical) before starting paliperidone treatment. The duration of the screening/wash-out period varied from 1 to 3 weeks, depending on the study.

An Independent Ethics Committee or Institutional Review Board at each study site approved the protocols of the studies included in this analysis. The studies were conducted in accordance with the ethical principles originating in the Declaration of Helsinki and ICH Good Clinical Practice guidelines, applicable regulatory requirements and in compliance with the protocols. All patients provided written informed consent.

Analytical design

Studies of PP and Pali ER that met the following criteria were included: (i) Janssen Research & Development (formerly: Johnson & Johnson Pharmaceutical Research & Development) sponsored studies because access to patient-level data was required for these analyses; (ii) Assessed either PP or Pali ER and (iii) Conducted in adult patients (≥ 18 years old) diagnosed ≥ 1 year before screening with schizophrenia or bipolar disorder (defined by Diagnostic and Statistical Manual of Mental Disorders, 4th Edition criteria). In addition, only studies of sufficient duration (≥ 6 months) were included.

Based on the above criteria, 10 total studies were identified- PP: $n = 4$, all in patients with schizophrenia (pooled sample size; $n = 1689$) and Pali ER: $n = 6$ [5: in patients with schizophrenia, 1: in patients with bipolar disorder (pooled sample size; $n = 2668$)] (PP: NCT00111189, NCT00210717, NCT01150448, NCT00119756; Pali ER: NCT00086320, NCT00085748, NCT00650793, NCT00077714, NCT00668837, NCT00490971). The designs and the primary results of these studies are published in detail elsewhere (31–38).

Treatment-emergent tardive dyskinesia

Incidence of TD was evaluated by two methods: applying Schooler–Kane standardised research criteria for TD based on Abnormal Involuntary Movement Scale (AIMS) scores (39,40) and using spontaneous reporting of AE of TD.

Spontaneously reported TD

Investigator reported terms were coded using the Medical Dictionary for Regulatory Affairs (MedDRA). Events matching the preferred term 'tardive dyskinesia' were summarised descriptively.

Schooler–Kane standardised research criteria for TD

Case definitions for TD were based on the AIMS items 1–7, which specifically measure dyskinetic movements on a scale of 0–4. Patients who scored ≥ 2 on two or more items or ≥ 3 on a single item were considered to have qualifying scores. The AIMS assessments were performed at baseline, at regular intervals throughout the study, and at end of the study.

Schooler–Kane criteria were then applied to patients having qualifying AIMS scores to define probable or persistent TD. Schooler–Kane criteria require: (i) at least 3 months of cumulative exposure to neuroleptics; (ii) absence of other conditions that might cause involuntary movements and (iii) at least

moderate dyskinetic movements in one body area (≥ 3 on AIMS) or mild dyskinetic movements in two body areas (≥ 2 on AIMS) (40). Patients who had qualifying AIMS scores for at least 3 months while on treatment were classified as having probable TD and those patients whose qualifying scores persisted for an additional 3 months were classified as having persistent TD. Patients with qualifying scores for TD at screening or baseline visits (pre-existing), though included in the analysis, were not considered to have treatment-emergent TD as per Schooler–Kane criteria.

Statistical analyses

Pooled data from all patients in the safety analysis set (all randomised and treated patients who received at least one dose during the double-blind or open-label phases) from all 10 studies (four PP and six Pali ER studies) were included. Rates of treatment-emergent TD (probable TD and persistent TD) were summarised separately for the PP studies and Pali ER studies (by indication of schizophrenia and bipolar disorder). The incidences of spontaneously reported TD as AEs were summarised by treatment group.

All dyskinesias (including TD) were analysed over time by assessing the number of patients having an AIMS total score (items 1–7) ≥ 3 at each time point.

Table 1 Demographic and baseline characteristics of patients (safety analysis set)

Parameters	Paliperidone palmitate	Paliperidone ER
Gender (*N*)	1689	2668
Men, *n* (%)	1001 (59.3)	1573 (59)
Age (*N*), years	1689	2668
Mean (SD)	39.6 (11.34)	39.6 (12.53)
BMI (*N*), kg/m^2	1686	2664
Mean (SD)	27.3 (5.95)	26.5 (6.46)
Age at diagnosis (*N*), years	1685	2648
Mean (SD)	27.1 (9.01)	29.6 (11.45)
Duration of Pali Expo (*N*), days	1689	2668
Mean (SD)	279.6 (215.17)	187.2 (187.5)
Mean Pali Dose (*N*), mg/mg eq.	1688	2667
Mean (SD)*	79.5 (30.6)	9.4 (2.77)

*Unit is mg for Paliperidone ER, and is mg eq. for Paliperidone palmitate. Paliperidone ER, paliperidone extended release; SD, standard deviation; BMI, body mass index; Expo, exposure.

Results

Demographics and clinical characteristics

A total of 4357 schizophrenia (PP-treated group: *n* = 1689; Pali ER-treated group: *n* = 2054) and bipolar disorder (n=614) patients were included in this analysis (safety analysis set). Studies were conducted from 2004 to 2010. Baseline demographic and clinical characteristics appeared similar between both treatment groups (Tables 1 and 2). The mean length of drug exposure was 279.6 days for the PP patients and 187.2 days for the Pali ER patients.

Treatment-emergent tardive dyskinesia

Incidence of TD as spontaneously reported adverse events

Three (0.18%) of 1689 PP-treated schizophrenia patients and two (0.10%) of 2054 Pali ER-treated schizophrenia patients had spontaneously reported TD as AE. There were no cases of spontaneously reported TD as an AE in the bipolar study (Pali ER) (Table 3).

For these five patients, one PP-treated patient was on a fixed dose of 150 mg eq. (the highest tested dose), one Pali ER-treated patient was on a fixed dose of 9 mg; the other three patients were on flexible-dose regimen. Of these three patients on flexible dose, the mean exposures for the two PP-treated patients were 87.5 mg eq. and 47.6 mg eq. and for the Pali ER-treated patient, the mean exposure dose was 11.2 mg. At the end of study, TD was persisting in four patients (two each in PP and Pali ER groups), while it was resolved in one PP-treated patient.

None of the five patients (three in PP, two in Pali ER) discontinued the study because of TD. One PP-treated patient withdrew from the study because of AE (ejaculation delayed), and another PP-treated patient withdrew from the study because of lack of efficacy. One Pali ER-treated patient withdrew from the study because of AE (psychotic disorder). The remaining two patients completed the study.

Incidence of TD using Schooler–Kane criteria

According to Schooler–Kane criteria, 2 (0.12%) of 1689 PP-treated patients had persistent and probable TD. Among the Pali ER-treated patients (*n* = 2054), four (0.19%) had probable TD and one (0.05%) of four had persistent TD (Table 3). There were no cases of TD identified using Schooler–Kane criteria in the bipolar study.

The mean exposure was 50.0 mg eq. and 51.8 mg eq. for the two PP-treated patients and 6.7 mg, 9.0 mg, 9.2 mg and 7.7 mg for the four Pali ER-treated patients.

Table 2 Demographics and baseline characteristics of patients identified with tardive dyskinesia-safety analysis set

Treatment	Age (years)	Gender	BMI (kg/m^2)	Age at diagnosis of schizophrenia (years)	Duration of paliperidone exposure (days)	Mean dose (SD) (mg/mg eq.)	Actual Day of AE Onset	Time to Probable TD	Time to Persistent TD	Actual day of disposition	
										Double-blind	Open- label
TD as spontaneously reported adverse events											
Pali ER	29	Woman	36.0	24	402	11.2 (1.94)	157	–	–	45	402
Pali ER	54	Woman	31.2	31	4	9.0 (0)	4	–	–	5	-
PP	43	Man	32.6	26	197	150.0 (0)	92	–	–	–	197
PP	60	Man	18.4	31	197	87.5 (23.15)	64	–	–	–	197
PP	58	Woman	24.6	57	569	47.6 (7.52)	652*	–	–	–	652
TD using Schooler–Kane criteria											
Probable TD (Persistent TD marked with*)											
Pali ER*	53	Woman	34.5	46	417	9.2 (1.53)	–	316	417	43	417
PP*	43	Man	17.9	28	621	50.0 (0)	–	427	511	–	621
PP*	57	Man	32.5	26	372	51.8 (6.68)	–	176	372	372	–
Pali ER	79	Woman	24.7	NA	211	6.7 (1.95)	–	155	–	43	211
Pali ER	56	Man	21.6	54	200	9.0 (0)	–	155	–	43	204
Pali ER	57	Woman	19.8	25	336	7.7 (1.49)	–	309	–	41	378

TD, tardive dyskinesia; BMI, body mass index; Pali ER, paliperidone extended release; PP, paliperidone palmitate. *Persistent TD cases.

Table 3 Incidence of treatment-emergent tardive dyskinesia in paliperidone extended release and paliperidone palmitate studies

	Paliperidone palmitate studies		Paliperidone ER studies	
Schizophrenia studies*	***N* = 1689 *n* (%)**	**Event/Patient years**	***N* = 2054 *n* (%)**	**Event/Patient years**
Tardive dyskinesia (spontaneously reported adverse event)	3 (0.18)	3/1292.85 = 0.23%	2 (0.10)	2/1367.78 = 0.15%
Probable tardive dyskinesia (Schooler–Kane criteria)	2 (0.12)	2/1292.85 = 0.15%	4 (0.19)	4/1367.78 = 0.29%
Persistent tardive dyskinesia (Schooler–Kane criteria)	2 (0.12)	2/1292.85 = 0.15%	1 (0.05)	1/1367.78 = 0.07%

*There was no incidence of TD in the 1 bipolar study that met inclusion criteria and hence not represented in this table; The total patient years for PP studies were 1292.85; the total patient years for Pali ER studies were 1367.78.

Both the PP-treated patients completed the study, while only one Pali ER-treated patient (with probable TD) completed the study. For the three Pali ER-treated patients who did not complete the study, one (with persistent TD) withdrew because of scheduling problems, the second withdrew because of lost to follow-up and the remaining one withdrew because of adverse event of dyspnoea. None of the three patients withdrew because of reasons that could be directly linked to TD as defined by Schooler–Kane criteria.

There was no overlap of cases between the spontaneously reported TD as AE cases vs. those identified using Schooler–Kane criteria.

Incidence of dyskinesia over time

Incidence of all dyskinesia (total AIMS score ≥ 3 at any single visit) was highest within the first treatment month (Table 4) for both PP (13.1%) and Pali ER (11.7%) treated groups and steadily decreased over time (Figure 1).

Discussion

Atypical antipsychotics, effective in the control of both positive and negative symptoms of schizophrenia, provide clinical advantages over conventional antipsychotics in part by having a comparatively lower incidence of TD (4,41,42). The present *post hoc* analysis from 10 paliperidone studies was designed to compare the incidence of TD between the LAI (PP) and oral formulation (Pali ER) of paliperidone, a potent inhibitor of dopamine D2 receptor. Only studies of sufficient duration ($\geq$ 6 months) were included because TD is expected with a long-term treatment of antipsychotic medications and also the Schooler–Kane criteria used in this study requires a time component to accurately diagnose TD. This *post hoc* analysis revealed that irrespective of the formulation, paliperidone treatment has a low risk for TD ($<$ 0.2%). Our results were generally comparable whether TD was assessed by spontaneous AE reporting or by AIMS definition, according to the standardised Schooler–Kane criteria. The risk estimates for persistent TD in this limited dataset were 0.12% for PP and 0.05% for Pali ER. The low rates of TD reported in both the oral and LAI treatment groups may reflect the similar and expected rates of EPS seen with these two treatments in a recent pooled analysis since rates of EPS may predict future TD (43).

The TD incidence rate reported in this study is consistent with rates reported using another atypical antipsychotic where the annualised TD incidence was 3.9% for atypical antipsychotics and 5.5% for the conventional antipsychotics (16). A recently published systematic review showed that the TD rate with oral atypical antipsychotics was 0.8% (range: 0.0–1.5%) in adults with schizophrenia and schizoaffective disorder compared with 5.4% (range: 4.1–7.4%) among adult patients who received haloperidol (4). In another study with risperidone LAI, the rate of treatment-emergent TD was low (0.94%; 1.19% annually) and there was no evidence of a dose-dependent effect.

Notably, though the overall incidence rates were similar in this analysis, a disparity was observed between the TD cases revealed by Schooler–Kane criteria and those identified by spontaneous AE reports. These differences in individual cases may exist as AEs were defined clinically and there is a possibility that clinicians may not have focused on the persistence and classified them as dyskinesias. However, on the other hand, the Schooler–Kane criteria are widely accepted and utilised to define neuroleptic-induced TD, with 100% sensitivity and 99% specificity for identifying TD (44).

The incidence of dyskinesias based on AIMS score at a single time point in both the PP and Pali ER groups was highest in the first month of treatment and then steadily decreased over time. This comparatively high rate in the beginning may at least partly be

Table 4 Occurrences of dyskinesia: AIMS total score of at least 3 at a particular time point since medication initiation

	Paliperidone Palmitate		Paliperidone ER	
	Patients exposed ***N***	**AIMS Score ≥ 3** ***n* (%)**	**Patients exposed** ***N***	**AIMS Score ≥ 3** ***n* (%)**
≤ Day 1	1689	174 (10.30)	2663	187 (7.00)
> Day 1 to ≤ 1 month	122	16 (13.10)	2634	308 (11.70)
> 1 month to ≤ 2 months	668	71 (10.60)	2021	173 (8.60)
> 2 months to ≤ 3 months	921	67 (7.30)	1696	118 (7.00)
> 3 months to ≤ 4 months	280	37 (13.20)	1514	96 (6.30)
> 4 months to ≤ 5 months	236	24 (10.20)	1178	78 (6.60)
> 5 months to ≤ 6 months	430	45 (10.50)	1100	72 (6.50)
> 6 months to ≤ 7 months	222	12 (5.40)	922	59 (6.40)
> 7 months to ≤ 8 months	576	28 (4.90)	970	54 (5.60)
> 8 months to ≤ 9 months	221	9 (4.10)	793	33 (4.20)
> 9 months to ≤ 10 months	200	11 (5.50)	828	34 (4.10)
> 10 months to ≤ 11 months	348	20 (5.70)	786	28 (3.60)
> 11 months to ≤ 12 months	220	14 (6.40)	715	21 (2.90)
> 12 months to ≤ 13 months	378	31 (8.20)	725	24 (3.30)
> 13 months to ≤ 14 months	187	11 (5.90)	461	17 (3.70)
> 14 months to ≤ 15 months	122	5 (4.10)	214	6 (2.80)
> 15 months to ≤ 16 months	136	7 (5.10)	135	5 (3.70)
> 16 months to ≤ 17 months	157	6 (3.80)	136	4 (2.90)
> 17 months to ≤ 18 months	157	8 (5.10)	48	2 (4.20)
> 18 months to ≤ 19 months	137	6 (4.40)	82	2 (2.40)
> 19 months to ≤ 20 months	119	5 (4.20)	23	1 (4.30)
> 20 months to ≤ 21 months	107	9 (8.40)	64	1 (1.60)
> 21 months to ≤ 22 months	94	4 (4.30)	16	0 (0)
> 22 months to ≤ 23 months	88	7 (8.00)	52	0 (0)
> 23 months to ≤ 24 months	78	2 (2.60)	16	0 (0)
> 24 months	112	7 (6.30)	48	0 (0)

AIMS, Abnormal Involuntary Movement Scale.

attributable to early withdrawal dyskinesias, related to the rapid discontinuation of the previous antipsychotic medications by the patients. Longer cumulative exposure did not appear to increase the risk of dyskinesia in the populations assessed in this study. However, the same cannot be said for TD as there was not enough cases of TD with paliperidone to comment. This result is consistent with previous studies which showed most significant improvement in TD in the first month of risperidone and olanzapine treatment in patients previously treated with typical antipsychotics (45,46). The observation that both PP and Pali ER treatment result in similar, low incidence rates of TD that do not worsen over time, may aid clinicians in deciding whether to switch a patient between oral and LAI treatment if required, and depending on the patient's response to treatment.

The strength of this meta-analysis is that it used patient-level data from controlled clinical trials. However, there are several limitations. This was a *post hoc* analysis and meant to be hypothesis generating only and needs to be confirmed with prospectively designed trials. All the studies selected in the *post hoc* analysis were company sponsored studies with specific inclusion and exclusion criteria. Clinically significant TD was often an exclusion criteria in these studies, and hence there is a possibility that patients at higher risk for developing TD following paliperidone treatment may have been excluded from the study. There is also a possibility that patients with dyskinesias may have preferentially discontinued from the studies and thereby influencing the apparent incidence of TD in this study.

Earlier studies have indicated that the benefits of a lower TD risk with atypical antipsychotics may be reduced at higher doses (47,48), however we could not determine whether there is any association between dose and incidence of TD because of the flexible-dose design of some of the studies and the small number of TD cases detected overall. Another limitation of the current analysis is that no definite conclusions could be drawn about the comparative

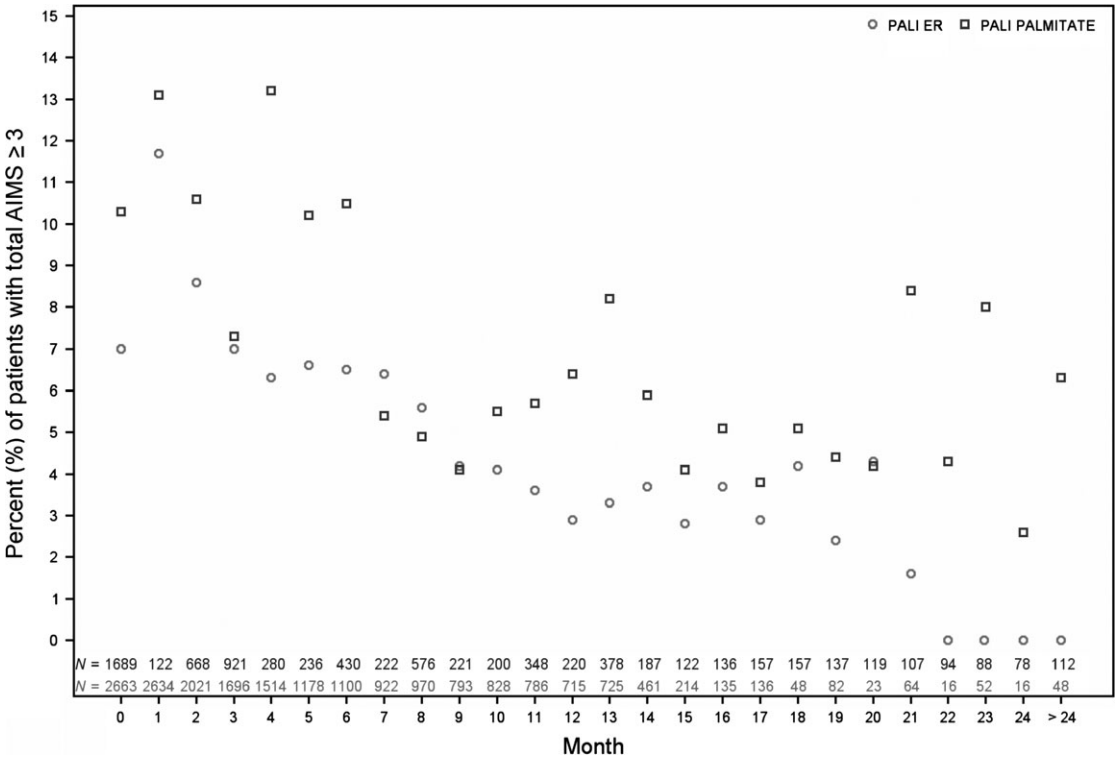

Figure 1 Incidence of dyskinesia over time. Dyskinesia defined as abnormal involuntary movement scale total score of at least 3.

risk for TD among patients with bipolar disorder because of the limited sample size or schizoaffective disorder because of no studies being of sufficient length. Several atypical antipsychotics are commonly used as adjunctive or even primary treatment for manic symptoms (49) and data to date suggest that patients suffering from mood disorders may be at higher risk for developing TD, compared with patients with schizophrenia (50). In addition, the lower risk for acute and chronic TD effects associated with paliperidone has to be weighed against other potential AEs, particularly weight gain, hyperglycaemia, hyperprolactinemia and dyslipidaemia, which may occur more frequently with second generation antipsychotic treatment. More robust and carefully designed, long-term studies across the entire age range, ethnic backgrounds and including more women are required to confirm these findings and to estimate the true risk of TD associated with paliperidone treatment.

Conclusion

In this *post hoc* analysis of two sets of studies with patient-level data, the risk for TD with paliperidone treatment with the oral or injectable formulation was low and comparable to data from published literature with other atypical antipsychotics. The risk of TD from paliperidone appears to be similar regardless of administration route or release profiles (monthly LAI vs. daily oral dosing) in the treatment of schizophrenia. Time to onset of dyskinesia was highest in the first month, and then steadily decreased over time. Longer cumulative exposure did not appear to increase the risk of dyskinesia in the populations assessed in this study. However, the same cannot be said for TD as there was not enough cases of TD with paliperidone to comment.

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Author contributions

Drs. Isaac Nuamah and Haiyan Xu were the statisticians for this *post hoc* analysis. All authors contributed to the data interpretation of the results,

development of this manuscript and approved the final manuscript for submission. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors met the International Council of Medical Journal Editors' criteria for authorship and all those who met those criteria are listed as authors.

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