Tardive Dyskinesia Prevalence in the Period of Second-Generation Antipsychotic Use: A Meta-Analysis

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ABSTRACT

Objective: Comparison of tardive dyskinesia (TD) prevalence during contemporaneous treatment with first-generation antipsychotics (FGAs) and/or second-generation antipsychotics (SGAs).

Data Sources: PubMed/MEDLINE/Google Scholar search (January 1, 2000–September 30, 2015) without language restriction using (*tardive dyskinesia* OR *tardive*) AND (*antipsychotic**) plus specific names of SGAs.

Study Selection: Of 8,895 hits, we screened 203 full-text articles for cross-sectional, rating scale–based TD rates during SGA, FGA, or FGA+SGA treatment. Forty-one studies were used for random effects meta-analysis and meta-regression.

Data Extraction: Two authors independently extracted data on overall and antipsychotic class–wise TD rates and on TD moderators.

Results: The global mean TD prevalence was 25.3% (95% CI = 22.7%–28.1%) across all 41 studies (N = 11,493, mean age = 42.8 years, male = 66.4%, schizophrenia-spectrum disorders = 77.1%). TD prevalence varied greatly: Rates were lower with current SGA treatment (20.7%; 95% CI = 16.6%–25.4%, N = 5,103) vs current FGA treatment (30.0%; 95% CI = 26.4%–33.8%, N = 5,062; $Q = 9.17$, $P = .002$). This difference remained significant after controlling for moderators: higher age ($Z = 2.85$, $P = .004$; number of studies = 39) and region (39 studies; Asia vs Europe, $Z = 1.55$, $P = .12$; Asia lower than United States, $Z = 2.6$, $P = .009$; Asia lower than other regions, $Z = 2.42$, $P = .015$). Additional moderators of TD prevalence included longer illness duration ($R^2 = 0.15$; $P = .03$; 21 studies) and frequency of parkinsonism ($R^2 = 0.23$, $P = .017$; number of studies = 19). Particularly low TD prevalence (7.2%; number of studies = 4) was found in the treatment arms with FGA-naive subjects relative to SGA-treated cohorts with likely prior FGA exposure (23.4%; $P < .001$; 28 studies). Lower TD prevalence of SGA relative to FGA was also confirmed in the subgroup of studies reporting on ≥ 2 antipsychotic classes/combinations; this was found for both SGAs vs FGAs (risk ratio = 0.80; 95% CI = 0.67–0.95, $Z = -2.55$, $P = .011$) and FGA + SGA vs FGAs (risk ratio = 0.80, 95% CI = 0.71–0.90, $Z = -3.56$, $P < .001$). Reports on TD severity, provided by 10 studies, were of insufficient quality for meta-analysis.

Conclusions: Rating scale–based TD remains highly prevalent, with higher rates during FGA than during SGA treatment. However, TD severity was insufficiently reported to allow for interpretation of the clinical impact of identified TD cases with SGAs and FGAs. Reasons for high geographical variation warrant future research.

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Tardive dyskinesia (TD) is a movement disorder characterized classically by involuntary, repetitive orofacial movements, often accompanied by choreiform movements of the upper extremities. Other tardive syndromes, such as dystonia, akathisia, tics, tremor, or myoclonus, may occur alone or coexist with the dyskinetic movements.[1] While many patients with TD are not aware of their condition,[2] severe tardive syndromes reduce quality of life,[3] lead to functional impairment,[4] and are often difficult to treat.[1] All dopamine-receptor blocking agents can cause TD, but antipsychotic exposure is the most frequently associated etiology.[5]

TD incidence reported for first-generation antipsychotics (FGAs) reached up to 49% for 10-year exposure to FGAs.[6] In analogy to pathophysiologic concepts of other dyskinesias that were primarily centered on dopaminergic neurotransmission,[7] second-generation antipsychotics (SGAs) were thought to carry only a limited TD risk. Moreover, with TD risk estimates for SGAs being one fifth or less of the FGA risk, TD was even expected to be "eliminated."[8] This expectation was based on (1) low rates of early parkinsonism with SGAs,[9] (2) the reduced risk of treatment-emergent probable TD in early randomized controlled studies,[10] and (3) the potential of SGAs to reduce symptoms of TD due to FGA exposure (either when switched to an SGA or when an SGA is added on to FGAs).[11]

In an overview on TD prevalence in studies published between 2004 and 2008, TD prevalence was 13.1% for SGAs and 32.4% for FGAs.[12] Nevertheless, conflicting data have been published since. Surprisingly, in a representative US-based cohort study of psychiatric outpatients, with a median observation time of 2.5 years rates of incident persistent TD for FGAs and SGAs did not differ.[13] Moreover, the expected SGA-mediated reduction of TD rates was found neither in the UK-based Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS-1)[14] nor in the US-based Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), but methodological issues could have accounted for this unexpected finding.[15] One explanation for this lack of advantage of SGAs in current treatment regimens is the use of higher than currently recommended doses of FGAs as

Clinical Points

- Evidence regarding rates of tardive dyskinesia (TD) in current real-world care is conflicting. Although TD rates were expected to drop dramatically with the broad use of second-generation antipsychotics (SGAs), some studies found similar rates for SGA or first-generation antipsychotic (FGA) users.
- Our meta-analysis of studies that used systematic screening for TD demonstrated that one-third of patients currently treated with FGAs and one-fifth of patients currently treated with SGAs showed at least mild TD. The latter observation seemingly contrasts with the clinical perception of TD as a rare side effect. Indeed, research criteria for TD do not reflect the subjective burden of TD, but signal the start of a potentially irreversible, stigmatizing disorder.
- Physicians should screen regularly for signs of TD in order to modify treatment prior to development of the full-blown clinical picture of TD.

comparators in earlier clinical trials.[10,16] Additionally, however, randomized controlled trials (RCTs) increasingly focus exclusively on metabolic side effect screening,[17] are generally short, have stopped using FGA comparators, and include restricted populations. The latter aspect supports a lopsided perspective, ignoring severely affected subjects, who are not able to consent and participate in RCTs but who may be most vulnerable to TD. Thus, the preponderance of RCT data in decision-making processes bears the risk of an underestimate of TD. Therefore, prevalence studies in unselected, representative cohorts of real-world psychiatric patients are valuable to assess whether TD currently remains a clinically relevant issue and whether RCT results, showing minimal TD risk with SGAs or comparable TD risk with SGAs and FGAs, translate into usual care settings.

To assess the burden of TD in the psychiatric population and to compare TD prevalence in psychiatric groups with current FGA or SGA treatment, we searched for studies published since 2000. We focused on this period to exclude earlier studies during the era of high-dose FGA use. We included all studies that reported cross-sectional TD rates based on standardized TD ratings in clinical cohorts treated with FGAs, SGAs, or both and collected studywise information on potential TD moderators. Due to the cross-sectional nature of prevalence studies, a single examination was typically used in unselected hospital or outpatient groups, which did not allow for estimates of persistent tardive dyskinesia, but rather only of probable tardive dyskinesia.

As prevalence studies are not suited for a comprehensive risk estimate, future articles will address TD incidence data.

METHODS

Literature Search

Two authors (C.-H.H., M.C.) independently conducted a PubMed/MEDLINE/Google Scholar search without language restriction for studies published 2000–2015 (last search update September 30, 2015) reporting on TD prevalence in patients receiving FGAs, SGAs, or their combination. The year 2000 was chosen as the limit since the TD risk of SGAs was recognized by that time due to accumulating case reports.[18,19] The following search terms were used: (*tardive dyskinesia* OR *tardive*) AND (*antipsychotic** OR *neuroleptic** OR *risperidone* OR *olanzapine* OR *aripiprazole* OR *quetiapine* OR *perospirone* OR *ziprasidone* OR *clozapine* OR *amisulpride* OR *asenapine* OR *lurasidone* OR *iloperidone* OR *blonanserin* OR *clothiapine* OR *iloperidone* OR *lurasidone, mosapramine* OR *paliperidone* OR *remoxipride* OR *sertindole* OR *sulpiride* OR *tiapride* OR *chlorpromazine* OR *thioridazine* OR *mesoridazine* OR *loxapine* OR *molindone* OR *perphenazine, thiothixene* OR *trifluoperazine* OR *haloperidol* OR *fluphenazine* OR *droperidol* OR *zuclopenthixol, pimozide* OR *flupenthixol* OR *prochlorperazine*). The electronic search was complemented by a manual search of reference lists of eligible articles and reviews and of websites of leading psychiatric journals to include conference contributions. Whenever data needed for the meta-analysis were missing, we contacted authors for additional information.

Inclusion Criteria

We included studies that (1) provided cross-sectional data from ≥ 15 FGA-, SGA-, or FGA + SGA-treated subjects to avoid the inclusion of case series and (2) used a standardized rating scale to evaluate TD. No age or language restrictions were applied. To correctly reflect the point prevalence in the psychiatric population exposed to antipsychotics, the recruitment strategy had to explicitly state that a clinical/usual care sample was assessed. We excluded all studies of enriched samples.

Data Extraction

Two authors (C.-H. H., M.C.) independently checked eligibility and extracted data. Any disagreement was resolved by discussion. From prospective studies, only baseline data were included.

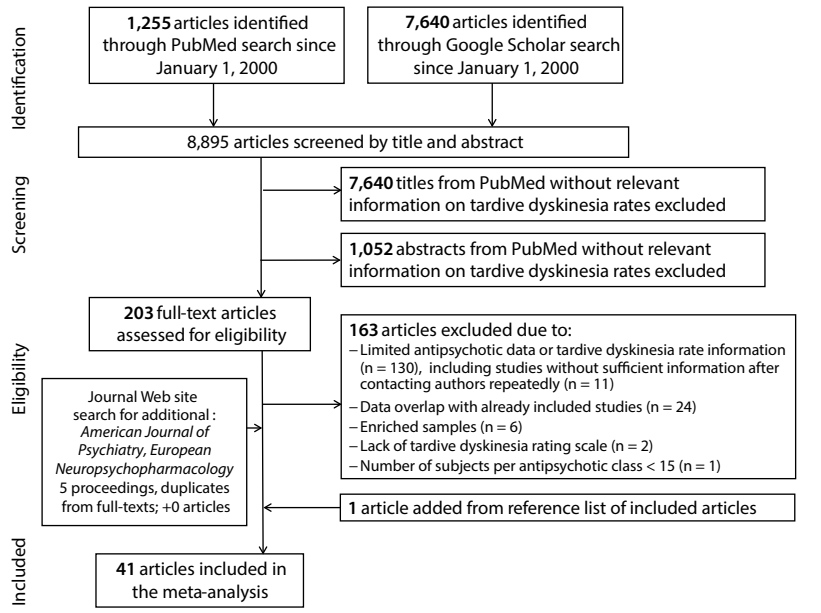
In addition to overall and antipsychotic class–wise TD rates, we extracted publication year, study design, and geographic region; patient sex, age, and race; and clinical diagnoses, illness duration, comorbid parkinsonism, chlorpromazine equivalent dose, prior FGA exposure, TD rating scale, diagnostic TD criteria, and TD severity.

Statistical Analysis

For each study (and analogously for each treatment group), prevalence was computed as the ratio of TD cases to sample size.

We conducted 2 sets of analyses. For the first set, we extracted data for 33 FGA groups, 12 FGA + SGA groups, and 28 SGA groups, treating them as independent of each other. Then we compared the prevalence across treatment groups using subgroup comparisons and meta-regression. Univariate regression analyses were calculated for relevant variables that could be obtained from > 10 studies. A

Figure 1. Data Search Flowchart



multivariable analysis was performed including significant moderators, which were available for the majority of studies (>35).

For the second analysis set, we limited the analyses to studies that included ≥2 antipsychotic treatment groups (FGAs, SGAs, FGA + SGA) and thus had the advantage of assessing different treatments with the same methodology in the same environment. In this subset, we computed the relative risk (RR) of TD as a function of drug class.

All analyses used a random effects model[20] and were 2-sided, with α = .05. Data were analyzed with Comprehensive Meta-Analysis Version 3 (http://www.meta-analysis.com).

To identify potential moderators of TD prevalence, subgroup and meta-regression analyses were conducted with the following study-level characteristics: patient source, study design, TD rating scale, diagnostic criteria for TD, geographic region (for subgroup comparisons); and mean age, male sex percentage, Caucasian percentage, illness duration, parkinsonism comorbidity percentage, percentage of anticholinergic use, and publication year (for regression analyses).

RESULTS

Search Results

Of 8,895 hits in PubMed and Google Scholar, 203 full-text articles were screened, resulting in 41 articles that fulfilled all inclusion criteria (Figure 1).

Sample Characteristics

Study characteristics. Forty-one studies reporting on TD prevalence by drug class were included in the analysis (see Table 1 for details).[13,21–60] In 13 studies, patients received FGAs at the time of TD screening*; in 5 studies, SGAs[34,35,47,49,54]; the other studies included more than 1 treatment group, resulting in a total of 73 treatment arms (33 FGA arms [N = 5,062], 28 SGA arms [N = 5,103], 12 FGA + SGA arms [N = 1,328]). The vast majority of studies did not provide specific TD rates per individual antipsychotic agent (as opposed to antipsychotic class).

Thirty-one studies were cross-sectional (N = 6,422),† and 10 represented baseline information of prospective studies (N = 5,071),‡ including the baseline information of 3 randomized[22,30,50] and 7 nonrandomized trials.[13,23,24,27,32,36,47] Additional information exceeding published data was provided from the authors for 12 studies.§

The mean chlorpromazine equivalent dose of FGA treatment was 440 mg/d (range, 264–676 mg/d) in 9 of 33 studies reporting TD rates for FGAs.¶ There were insufficient data on SGA doses.

Patient characteristics. The 41 studies included 11,493 patients (mean age = 42.8 years [39 studies[21–52,54–60]], male = 66.4% [39 studies[21–52,54–60]], Caucasian = 40.2% [32 studies**]). Two studies[35,59] included youth (N = 211; mean age = 15.3 years), 12†† included only adults (N = 2,592; mean age = 39.6 years), and the remaining 27 studies consisted of both adult and elderly subjects. Altogether, 15 studies‡‡ included inpatients, 7[26,30,42,45,54,58,59] included outpatients, and the remaining 19 studies consisted of both

*References 25,27–30,33,37,41,42,44,45,52,55
†References 21,25,26,28,29,31,33–35,37–46,48,49,51–60
‡References 13,22–24,27,30,32,36,47,50
§References 13,23,24,31,32,35,39,41,43,44,46,57
¶References 28,29,37,41,51,52,55,57,58
**References 21–27,29–31,34,36,37,39–50,52,54,56–60
††References 22,25,43,44,47,48,50,53–55,58,60
‡‡References 24,27–29,34,35,37,41,43,44,48,51,53,57,60

Table 1. Study and Patient Characteristics of Included Tardive Dyskinesia (TD) Prevalence Studies

Author	Study Design	Region	Diagnosis; (Setting, if Available)	Antipsychotic Class	N	Male (%)	Caucasian (%)	Mean Age (y)	Illness Duration (y)	EPS (%)	Anticholinergic Use (%)	Industry Sponsor	TD Scale; Threshold	TD Prevalence (%)
Achalia et al, 2014[21]	Prevalence study	AS	SCZ	AP-Total SGA (including FGA naive) FGA	160 90 (74) 70	67.5	0	35.9 32.9 39.8	8.8	…	…	No	AIMS S-K	26.3 20.0 (16.3) 34.3
Adam et al, 2014[22]	Baseline of an RCT	AS	SCZ, schizoaffective disorder, or schizophreniform disorder	AP-Total SGA FGA	86 31 55	52.3	0	25.9 25.1 26.3	…	…	65.1	No	AIMS S-K	29.1 25.8 30.9
Ascher-Svanum et al, 2008[23]	Baseline of a 3-year cohort study	US	SCZ, schizoaffective disorder, or schizophreniform disorder (inpatients + outpatients)	AP-Total SGA FGA FGA + SGA	2,084[a] 792[a] 778[a] 514[a]	61.4[b]	50.3[a]	42.1[b]	21.6[a]	24.3[c]	49.1[b]	Yes	AIMS S-K	29.6[a] 23.5[a] 36.9[a] 28.0[a]
Bakker et al, 2011[24]	Baseline of a 4-year cohort study	EU	SCZ, psychosis, affective disorder, other Axis I or II diagnosis (inpatients)	AP-Total SGA FGA SGA + FGA	201[a] 67[a] 76[a] 58[a]	60.9[d]	85.0[d]	47.4[d]	…	56.2[d]	…	No	AIMS S-K	26.4[a] 25.4[a] 26.3[a] 27.6[a]
Bhatia et al, 2004[25]	Genetic study	OT	SCZ	FGA (Israeli sample)	151	52.3	100	47.6	22.7	…	…	No	AIMS S-K	40.4
Boke et al, 2007[26]	Genetic study	EU	SCZ (outpatients)	AP-Total SGA FGA	127 81 36	59.1	100	39.6	15.7	…	…	No	AIMS S-K	37.0 32.1 44.4
Brar et al, 2008[27]	Baseline of a clinical trial	US	SCZ, schizoaffective disorder, or bipolar disorder (inpatients)	FGA	63	50.8	69.8	42.5	18.3	…	…	No	AIMS S-K	44.4
Brousse et al, 2007[28]	Experimental study	EU	SCZ (inpatients)	FGA (65% within-class polypharmacy)	69	49.3	…	42.0	…	…	58.0	No	AIMS ≥ 6	39.1
Chong et al, 2002[29]	Prevalence study	AS	SCZ (inpatients)	AP-Total FGA	602 596	76.7	0	53.0	…	64.4	61.0	No	AIMS S-K	39.2 38.6
Covell et al, 2012[30]	Baseline of an RCT	US	SCZ, schizoaffective disorder (outpatients)	FGA	62	71.0	37.1	47.9	…	35.5	…	No	AIMS S- K	35.5
de Leon, 2007[31]	Genetic study	US	SCZ, schizoaffective disorder, bipolar disorder, MDD	AP-Total SGA FGA FGA+SGA	516 439[a] 18[a] 51[a]	53.9	81.2[a]	42.4	…	44.4[a]	16.9	Yes	AIMS S-K	31.4 31.2[a] 44.4[a] 25.5[a]
Eberhard et al, 2006[32]	Baseline of a 5-year clinical trial	EU	SCZ, schizoaffective disorder, delusional disorder, or psychotic disorder NOS	AP-Total SGA SGA + FGA	166 132[a] 24[a]	58.4	…	37.9	11.6	…	…	Yes	AIMS S-K	13.9 14.4[a] 16.7[a]
Ellingrod et al, 2002[33]	Genetic study	US	SCZ	FGA	37	91.9	…	38.7	…	…	…	No	AIMS S-K	40.5
Fodstad et al, 2010[34]	Prevalence study	US	Autism-spectrum disorder, bipolar disorders, SCZ in subjects with intellectual disability (inpatients)	SGA	166	54.2	79.2	51.3	…	…	2.4	No	MEDS	42.2
Gebhardt et al, 2006[35]	Prevalence study	EU	SCZ and schizoaffective disorder adolescent (inpatients)	AP-Total SGA	93 74	55.9	…	19.6	4.0	25.8	8.6	Yes	AIMS S-K	5.4 5.4[a]

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Table 1 (continued). Study and Patient Characteristics of Included Tardive Dyskinesia (TD) Prevalence Studies

Author	Study Design	Region	Diagnosis; (Setting, if Available)	Antipsychotic Class	N	Male (%)	Caucasian (%)	Mean Age (y)	Illness Duration (y)	EPS (%)	Anticholinergic Use (%)	Industry Sponsor	TD Scale; Threshold	TD Prevalence (%)
Gharabawi et al, 2005[36]	Baseline of an open-label trial	US	SCZ or schizoaffective disorder	AP-Total SGA FGA	654[e] 333 212	65.4[f]	92.3[f]	42.3[f]	…	…	…	Yes	ESRS S-K	20.0 12.9 29.2
Güzey, 2007[37]	Genetic study	EU	SCZ (inpatients)	FGA	119	83.2	100	50.0	…	31.1	30.3	No	AIMS	12.6
Halliday et al, 2002[38]	Prevalence study	EU	SCZ (outpatients)	AP-Total SGA FGA AP-Total	121 48 73	53.7[g]	…	48[g]	20.6[g]	34.6[g]	…	No	AIMS S-K	45.5 52.1 41.1
Hansen et al, 2013[39]	Prevalence study	EU	SCZ	AP-Total SGA SGA+FGA	72[a] 34[a] 31[a]	77.1	98.6	38	11.9[a]	47.1	24.3[a]	No	AIMS S-K	11.1[a] 11.8[a] 6.5[a]
Hitzeroth et al, 2007[40]	Genetic study	OT	SCZ	AP-Total SGA FGA	233 26 207	79.8[h]	0	34.1[h]	10.4[h]	…	…	No	AIMS score ≥ 2	21.0 23.1 20.8
Hsieh et al, 2011[41]	Genetic study	AS	SCZ (inpatients)	FGA	167	47.9[a]	0	50.6	…	…	…	No	AIMS S-K	19.2
Jaanson et al, 2002[42]	Genetic study	EU	SCZ or schizoaffective disorder (outpatients)	FGA (zuclopenthixol)	52	36.5	100	43.0	15.4	61.5	48.1	No	AIMS S-K	21.2
Janno et al, 2004[43]	Prevalence study	EU	SCZ or schizoaffective disorder (inpatients)	AP-Total SGA (CLZ) FGA	99 19[a] 79[a]	45.5	100[a]	49.7	…	23.2	14.2	Yes	AIMS S-K	31.3 31.6[a] 31.6[a]
Kim and Byun, 2003[44]	Prevalence study	AS	SCZ (inpatients)	AP-Total FGA	142 132[a]	43.0	0[a]	37.5	10.7	65.5	79.6	No	AIMS S-K	28.2 28.0[a]
Koola et al, 2014[45]	Genetic study	EU	SCZ (outpatients)	FGA	70	54.3	100	41.6	…	50.0	…	Yes	AIMS S-K	18.6
Lee et al, 2010[46]	Prevalence study	AS	SCZ	AP-Total SGA FGA FGA+SGA	781[a] 137[a] 544[a] 100[a]	65.7[i]	0[i]	48.3[i]	20.1[a,i]	28.9[i]	68.0[i]	No	AIMS S-K	20.9[a] 15.3[a] 23.7[a] 13.0[a]
Lee et al, 2015[47]	Baseline of 4 clinical trials	AS	SCZ	SGA (RIS)	167	56.2	0	35.0	7[j]	22.5	…	Yes	AIMS score ≥ 2	12.6
Leung et al, 2003[48]	Prevalence study	AS	SCZ (inpatients)	AP-Total SGA FGA	225 24 201	71.1	0	41.7	20.4	26.2	58.7	No	AIMS S-K	6.7 8.3 6.5
Li et al, 2009[49]	Prevalence study	AS	SCZ, bipolar disorder	SGA (CLZ)	101	71.3	0	38.9	12.9	…	8.9	No	ESRS S-K	4.0
Miller et al, 2005[50]	Baseline of an RCT	US	SCZ (inpatients)	AP-Total SGA FGA[k]	969 757 212	74.6[l]	60.0[l]	40.2[l]	…	…	16.2[l]	No	AIMS S-K[m]	16.3 13.1 27.8
Modestin et al, 2000[51]	Prevalence study	EU	Various diagnoses, 50% SCZ (inpatients)	AP-Total SGA (CLZ) FGA FGA+SGA	200 46 127 27	57.0	…	48.4 53.0 49.1	16.6	20.0	27.1	No	AIMS S-K	22.5 31.8 19.7 14.8
Patterson et al, 2005[52]	Prevalence study	OT	SCZ, mood disorder, intellectual disability, dementia	AP-Total FGA	102 96	68.6	0	43.7	…	…	26.5	No	AIMS G-M	28.4 23.9

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Table 1 (continued). Study and Patient Characteristics of Included Tardive Dyskinesia (TD) Prevalence Studies

Author	Study Design	Region	Diagnosis; (Setting, if Available)	Antipsychotic Class	N	Male (%)	Caucasian (%)	Mean Age (y)	Illness Duration (y)	EPS (%)	Anticholinergic Use (%)	Industry Sponsor	TD Scale; Threshold	TD Prevalence (%)
Ross et al, 2005[53]	Prevalence study	US	Psychotic disorders, bipolar disorder	AP-Total	152	…	…	…	…	49	…	…	IMS, S-K	40.8
				SGA	79									39.2
				FGA	38									39.5
				SGA+FGA	35									45.7
Ryu et al, 2015[54]	Prevalence study	AS	SCZ or schizoaffective disorder (outpatients)	SGA	80	50.0	0	33.1	8.6	…	…	No	AIMS S-K	5.0
Sejil et al, 2013[55]	Prevalence study	OT	SCZ (outpatients)	FGA	157	100	…	37.0	8.0	…	74.5	No	Clinical, *DSM-IV-TR*	35.0
Souza et al, 2010[56]	Genetic study	US	SCZ	AP-Total	215	66.9	80.0	37.6	…	…	…	No	AIMS	37.7
				SGA	109								S-K	38.5
				FGA	106									36.8
Sun et al, 2013[57]	Genetic study	AS	SCZ (inpatients)	AP-Total	931[a]	84.7[n]	0[n]	48.0[n]	24.6[n]	…	57.2[a]	No	AIMS	39.5[a]
				SGA	698[a]								S-K	40.7[a]
				FGA	186[a]									37.6[a]
				FGA+SGA	47[a]									29.8[a]
Sundram et al, 2008[58]	Prevalence study	OT	SCZ or schizoaffective disorder (outpatients)	AP-Total	40	67.5	100	39.4	13.0	85.0	…	No	AIMS	57.5
				SGA[o]	16								G-M	31.3
				FGA	19									73.7
Wonodi et al, 2007[59]	Prevalence study	US	ADHD, mood disorder, or psychotic disorder	AP-Total	118	77.1	44.1	11.9	…	…	…	No	IMS	9.3
				SGA	81								score ≥ 10	6.2
				SGA+FGA	37									16.2
Woods et al, 2010[13]	Baseline of a 4-year cohort study	US	SCZ, schizoaffective disorder, or affective disorder outpatients	AP-Total	619	…	…	…	…	…	…	No	AIMS	31.5
				SGA	316[a]								G-M	29.1[a]
				FGA	148[a]									45.9[a]
				FGA+SGA	83[a]									42.2[a]
Yoon et al, 2004[60]	Prevalence study	AS	Adult inpatients with SCZ, schizoaffective disorder, or bipolar disorder	AP-Total	324	66.7	0	39.7	…	…	76.5	…	AIMS	6.2
				SGA	162								S-K	8.0
				FGA	106									3.8
				SGA+FGA	56									5.4

[a]Study data exceeding the published data, additional information received from the authors. [b]Based on published data of the sample (n = 2,175). [c]Based on published data of the sample (n = 1,583). [d]Based on published data of the sample (n = 207). [e]Among 654 patients, 109 on multiple antipsychotics were not included for TD rate analyses of treatment groups due to insufficient data. [f]Based on published data of the sample (n = 662). [g]Based on published data of the sample (n = 136). [h]Based on published data of the sample (n = 258). [i]Based on published data of the sample (n = 790). [j]Median duration of illness (years). [k]All subjects with FGA + SGA were categorized as FGA in this study. [l]Based on sufficient data on the sample (n = 1,310). [m]S-K criteria were used to define TD, but additionally a non-TD category was defined, excluding patients at risk for TD with minor dyskinesia. The non-TD group listed patients with no history of TD and no single AIMS item rated greater than 1 = minimal. [n]Based on sufficient data on the sample (n = 784). [o]Clozapine was not included in SGA group.

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; AIMS = Abnormal Involuntary Movement Scale; AP = antipsychotic; AS = Asia; CLZ = clozapine; *DSM-IV-TR* = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; EPS = extrapyramidal symptoms; ESRS = Extrapyramidal Symptom Rating Scale; EU = Europe; FGA = first-generation antipsychotic; G-M = Glazer-Morgenstern criteria for TD; IMS = Involuntary Movement Scale; MDD = major depressive disorder; MEDS = Matson Evaluation of Drug Side Effects; OT = other regions; RCT = randomized controlled trial; RIS = risperidone; SCZ = schizophrenia; SGA = second-generation antipsychotic; S-K = Schooler-Kane criteria for TD; TD = tardive dyskinesia; US = United States.

Symbol: … = no information given.

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inpatients and outpatients or did not specify the setting. Thirty studies* included predominantly patients with schizophrenia-spectrum disorders (N = 8,866, 77.1%). The other 11 studies included subjects with various psychiatric diagnoses (N = 2,627, 22.9%).

Screening Scales and Definitions for Tardive Dyskinesia

As per inclusion criteria, all studies used a standardized TD rating scale. The majority of studies (36 studies = 87.8%) used the Abnormal Involuntary Movement Scale (AIMS; Table 1). Less frequently used scales included the Extrapyramidal Symptom Rating Scale,[36,49] Involuntary Movement Scale,[53,59] and the dyskinesia subscale of the Matson Evaluation of Drug Side Effects[34] (see Table 1). Thirty studies used Schooler-Kane criteria† to define TD, where probable TD is present when a score of 2 is noted in at least 2 items or when a score of > 2 (ie, 3 or 4) is noted in at least 1 item, and 3 used the minimally more inclusive Glazer-Morgenstern criteria[13,52,58] (see Table 1).

Full Sample Analyses: Mean TD Prevalence and Modulators of Prevalence

The estimated weighted mean prevalence of TD across all treatment groups was 25.3% (95% CI = 22.7%–28.1%) for all 41 studies (73 treatment arms) including 11,493 subjects (Figure 2). However, there was substantial variation around this mean, including some strong outliers driven by the lack of prior FGA exposure (Figure 3). Extrapolating from all included studies and assuming that the TD prevalence is normally distributed (in logit units), we estimated that TD prevalence ranged from 8.5% in some populations to 75.3% in others. Some of this variation was associated with the moderators listed below.

Antipsychotic class. The estimated weighted mean TD prevalence differed significantly between antipsychotic classes ($Q = 10.51$, $P = .005$; number of treatment arms = 73). TD prevalence was significantly lower with SGAs (20.7%, 95% CI = 16.6%–25.4%) compared with FGAs (30.0%, 95% CI = 26.4%–33.8%) ($Q = 9.17$, $P = .002$). TD prevalence was 22.7% (95% CI = 16.9%–29.6%) for the FGA + SGA cotreatment groups, which was not significantly different from FGAs ($Q = 3.40$, $P = .07$) or SGAs ($Q = 0.26$, $P = .61$). While the mean prevalence varied by group, there was substantial variation within groups and overlap across groups (Figure 2).

Other clinical parameters. TD prevalence increased with mean age ($R^2 = 0.173$, $P = .0037$; number of studies = 39). Higher TD prevalence was associated with longer psychiatric illness duration (mean duration = 18.7 years, $R^2 = 0.154$, $P = .034$; number of studies = 21) and baseline parkinsonism rates ($R^2 = 0.226$, $P = .017$; number of studies = 19). Higher TD prevalence was near-significantly associated with Caucasian race ($R^2 = 0.078$, $P = .053$; number of studies = 32).

Data on dosage were available only for 9‡ of 33 FGA studies (mean chlorpromazine equivalent = 440 mg/d). The TD prevalence in these studies did not differ significantly from that of the other 24 studies,§ which did not provide dosage information (30.2% vs 29.9%, $P = .96$). Moreover, TD prevalence still differed significantly between the 9 studies of FGAs with available dosage information and the studies reporting on SGAs ($Q = 4.75$, $P = .029$).

Among 28 SGA arms,¶ only 4[21,49,54,59] specified TD rates in patients who had not been treated previously with FGAs. The TD prevalence was significantly lower in patients without prior FGA use (7.2%; 95% CI = 3.4%–14.5%. vs 23.4%; 95% CI = 18.8%–28.7%; $P < .001$; Figure 3).

Additionally, 8 of 41 studies included only patients treated with a stable antipsychotic dose for ≥ 3 months prior to study entry or with the same type of antipsychotic since the first episode or for the previous year.[25,26,28,41,45,49,54,57] TD prevalence in these studies did not differ from the remaining 33 studies that did not restrict inclusion in this way (23.5% vs 24.8%; $P = .79$).

No significant effect on TD prevalence rates was found for the variables sex ($P = .52$; number of studies = 39), concurrent anticholinergic use ($P = .48$; number of studies = 21), and treatment setting ($P = .66$; number of studies = 29).

Data on TD severity were provided in very heterogeneous formats, which did not allow for the use of this variable in the meta-analysis. Five studies provided mean total AIMS scores (sum of items 1–7) per treatment arm regardless of TD presence, a reporting format that does not allow for an estimate of the severity of affected subjects, unless affected subjects dominate the group (mean global AIMS total score = 2.9 ± 0.83; 95% CI = 1.3–4.6).[22,27,32,51,55] Five other studies[36,49,50,53,54] provided severity information on TD in affected subjects, regardless in part, however, of current AP treatment. These latter studies reported mild to moderate TD severity for a combined group of FGA- or SGA-exposed, TD-affected subjects (n = 64,[53] n = 132[36]) as well as for the TD cases related to clozapine exposure (mean AIMS total score = 4.75; n = 4[49] and mean AIMS total score = 6; n = 4[54]). The mean AIMS total score of 7.6 for the TD-affected subjects (FGA- and SGA-exposed) at baseline in the CATIE trial clustered slightly more toward the moderate side of that generally mild-to-moderate range.[50]

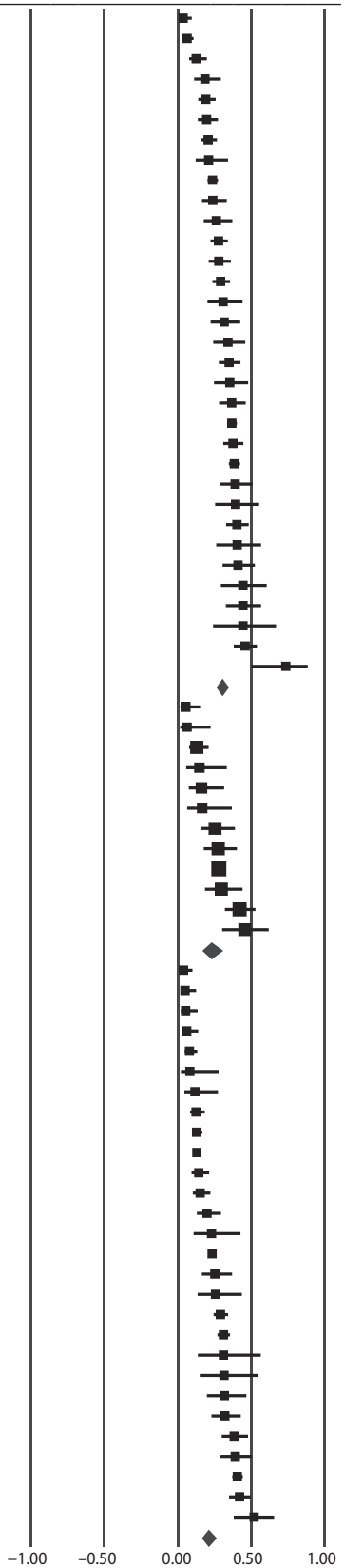
Geographical region. TD prevalence differed significantly among the major geographical regions ($Q = 11.91$, $P = .008$; number of studies = 41): 17.3% in Asia (95% CI = 12.0%–24.2%; number of studies = 12), 22.3% in Europe (95% CI = 16.5%–29.5%; number of studies = 12), 31.3% in the United States (95% CI = 25.8%–37.3%; number of studies = 11), and 31.8% in the other parts of the world (Australia, Africa, Middle East) (95% CI = 23.0%–42.1%; number of studies = 6).

Study design. Study design characteristics did not significantly moderate TD prevalence. This included general

*References 21–23,25,26,28–30,33,35–50,54–58
†References 29–39,41–46,48–51,53,54,56,57,60
‡References 28,29,37,41,51,52,55,57,58
§References 13,21–27,30,31,33,36,38,40,42–46,48,50,53,56,60
¶References 13,21–24,26,31,32,34–36,38–40,43,46–51,53,54,56–60

Figure 2. Overall Tardive Dyskinesia (TD) Prevalence in 41 Studies, Additionally Grouped by Antipsychotic Class (73 Treatment Arms), With Lower Rates in Second-Generation Antipsychotics (SGAs) Than in First-Generation Antipsychotics (FGAs)[a]

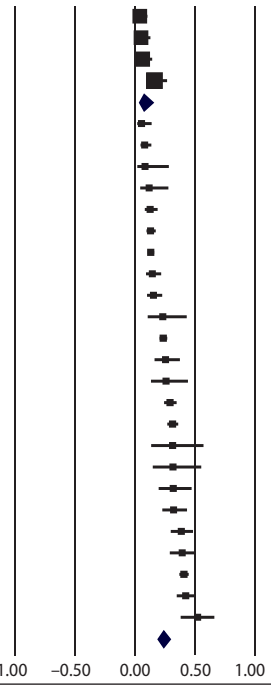
Group by Antipsychotic Types	Study Name	Statistics for Each Study: Event Rate	Lower Limit	Upper Limit
FGA	Yoon 2004[60]	0.038	0.014	0.096
FGA	Leung 2003[48]	0.065	0.038	0.108
FGA	Guzey 2007[37]	0.126	0.077	0.199
FGA	Koola 2014[45]	0.186	0.111	0.294
FGA	Hsieh 2011[41]	0.192	0.139	0.258
FGA	Modestin 2000[51]	0.197	0.137	0.275
FGA	Hizeroth 2007[40]	0.208	0.158	0.268
FGA	Jaanson 2002[42]	0.212	0.121	0.343
FGA	Lee 2010[46]	0.237	0.203	0.275
FGA	Patterson 2005[52]	0.240	0.165	0.335
FGA	Bakker 2011[24]	0.263	0.177	0.373
FGA	Miller 2005[50]	0.278	0.222	0.342
FGA	Kim 2003[44]	0.280	0.210	0.363
FGA	Gharabawi 2005[36]	0.292	0.235	0.357
FGA	Adam 2014[22]	0.309	0.202	0.442
FGA	Janno 2004[43]	0.316	0.224	0.427
FGA	Achalia 2014[21]	0.343	0.242	0.461
FGA	Sejil 2013[55]	0.350	0.280	0.428
FGA	Covell 2012[30]	0.355	0.246	0.481
FGA	Souza 2010[56]	0.368	0.282	0.463
FGA	Ascher-Svanum 2008[23]	0.369	0.336	0.403
FGA	Sun 2013[57]	0.376	0.310	0.448
FGA	Chong 2002[29]	0.386	0.348	0.426
FGA	Brousse 2007[28]	0.391	0.284	0.510
FGA	Ross 2005[53]	0.395	0.254	0.556
FGA	Bhatia 2004[25]	0.404	0.329	0.484
FGA	Ellingrod 2002[33]	0.405	0.261	0.568
FGA	Halliday 2002[38]	0.411	0.304	0.527
FGA	Boke 2007[26]	0.444	0.293	0.607
FGA	Brar 2008[27]	0.444	0.327	0.568
FGA	de Leon 2007[31]	0.444	0.240	0.670
FGA	Woods 2010[13]	0.459	0.381	0.540
FGA	Sundram 2008[58]	0.737	0.502	0.886
FGA		**0.300**	**0.264**	**0.338**
FGA+SGA	Yoon 2004[60]	0.054	0.017	0.153
FGA+SGA	Hansen 2013[39]	0.065	0.016	0.224
FGA+SGA	Lee 2010[46]	0.130	0.077	0.211
FGA+SGA	Modestin 2000[51]	0.148	0.057	0.335
FGA+SGA	Wonodi 2007[59]	0.162	0.075	0.317
FGA+SGA	Eberhard 2006 [32]	0.167	0.064	0.369
FGA+SGA	de Leon 2007 [31]	0.255	0.154	0.391
FGA+SGA	Bakker 2011[24]	0.276	0.176	0.404
FGA+SGA	Ascher-Svanum 2008[23]	0.280	0.243	0.321
FGA+SGA	Sun 2013[57]	0.298	0.185	0.442
FGA+SGA	Woods 2010[13]	0.422	0.320	0.530
FGA+SGA	Ross 2005[53]	0.457	0.302	0.621
FGA+SGA		**0.227**	**0.169**	**0.296**
SGA	Li 2009[49]	0.040	0.015	0.101
SGA	Ryu 2015[54]	0.050	0.019	0.126
SGA	Gebhardt 2006[35]	0.054	0.020	0.135
SGA	Wonodi 2007[59]	0.062	0.026	0.140
SGA	Yoon 2004[60]	0.080	0.047	0.133
SGA	Leung 2003[48]	0.083	0.021	0.279
SGA	Hansen 2013[39]	0.118	0.045	0.275
SGA	Lee 2015[47]	0.126	0.083	0.185
SGA	Gharabawi 2005[36]	0.129	0.097	0.170
SGA	Miller 2005[50]	0.131	0.109	0.157
SGA	Eberhard 2006[32]	0.144	0.094	0.215
SGA	Lee 2010[46]	0.153	0.102	0.224
SGA	Achalia 2014[21]	0.200	0.130	0.295
SGA	Hizeroth 2007[40]	0.231	0.108	0.428
SGA	Ascher-Svanum 2008[23]	0.235	0.207	0.266
SGA	Bakker 2011[24]	0.254	0.164	0.371
SGA	Adam 2014[22]	0.258	0.135	0.437
SGA	Woods 2010[13]	0.291	0.244	0.344
SGA	deLeon 2007[31]	0.312	0.270	0.357
SGA	Sundram 2008[58]	0.313	0.136	0.567
SGA	Janno 2004[43]	0.316	0.149	0.548
SGA	Modestin 2000[51]	0.318	0.198	0.468
SGA	Boke 2007[26]	0.321	0.229	0.430
SGA	Souza 2010[56]	0.385	0.299	0.480
SGA	Ross 2005[53]	0.392	0.291	0.504
SGA	Sun 2013[57]	0.407	0.371	0.444
SGA	Fodstad 2010[34]	0.422	0.349	0.498
SGA	Halliday 2002[38]	0.521	0.382	0.657
SGA		**0.207**	**0.166**	**0.254**



[a]References 13, 21–60.

Figure 3. Tardive Dyskinesia Prevalence in 4 Second-Generation Antipsychotic (SGA) Treatment Arms Without Prior First-Generation Antipsychotic (FGA) Exposure Compared to the Remaining 24 Treatment Arms in Which Prior FGA Exposure Was Not Specified[a]

Group by Prior FGA use	Study Name	Event Rate	Lower Limit	Upper Limit
No	Li 2009[49]	0.040	0.015	0.101
No	Ryu 2015[54]	0.050	0.019	0.126
No	Wonodi 2007[59]	0.062	0.026	0.140
No	Achalia 2014[21,b]	0.162	0.094	0.264
No		**0.072**	**0.034**	**0.145**
Unspecified	Gebhardt 2006[35]	0.054	0.020	0.135
Unspecified	Yoon 2004[60]	0.080	0.047	0.133
Unspecified	Leung 2003[48]	0.083	0.021	0.279
Unspecified	Hansen 2013[39]	0.118	0.045	0.275
Unspecified	Lee 2015[47]	0.126	0.083	0.185
Unspecified	Gharabawi 2005[36]	0.129	0.097	0.170
Unspecified	Miller 2005[50]	0.131	0.109	0.157
Unspecified	Eberhard 2006[32]	0.144	0.094	0.215
Unspecified	Lee 2010[46]	0.153	0.102	0.224
Unspecified	Hizeroth 2007[40]	0.231	0.108	0.428
Unspecified	Ascher-Svanum 2008[23]	0.235	0.207	0.266
Unspecified	Bakker 2011[24]	0.254	0.164	0.371
Unspecified	Adam 2014[22]	0.258	0.135	0.437
Unspecified	Woods 2010[13]	0.291	0.244	0.344
Unspecified	de Leon 2007[31]	0.312	0.270	0.357
Unspecified	Sundram 2008[58]	0.313	0.136	0.567
Unspecified	Janno 2004[43]	0.316	0.149	0.548
Unspecified	Modestin 2000[51]	0.318	0.198	0.468
Unspecified	Boke 2007[26]	0.321	0.229	0.430
Unspecified	Souza 2010[56]	0.385	0.299	0.480
Unspecified	Ross 2005[53]	0.392	0.291	0.504
Unspecified	Sun 2013[57]	0.407	0.371	0.444
Unspecified	Fodstad 2010[34]	0.422	0.349	0.498
Unspecified	Halliday 2002[38]	0.521	0.382	0.657
Unspecified		**0.234**	**0.188**	**0.287**



[a]References 13, 21–24, 26, 31, 32, 34–36, 38–40, 43, 46–51, 53, 54, 56–60.
[b]FGA-naive subgroup.

study design (baseline data from prospective clinical studies vs cross-sectional studies; $P = .91$; number of studies = 41), publication year ($P = .53$; number of studies = 41), concurrent reporting of TD prevalence in > 1 antipsychotic class vs single-class studies ($P = .89$; number of studies = 41), TD rating scale (AIMS vs non-AIMS; $P = .48$; number of studies = 41), TD diagnostic criteria (Schooler-Kane criteria yes vs no; $P = .55$; number of studies = 41), and sponsorship (industry vs nonindustry; $P = .07$; number of studies = 39).

Multivariable Model of TD Prevalence

A multivariable model was constructed to assess the independent effects of the main moderators on the difference in TD frequency between antipsychotic classes. The final model included significant moderators from the univariate analyses for which information was present from the majority of studies ($R^2 = 0.262$; $P = .0001$; number of studies = 39; 67 treatment arms).

Significant moderators in this model included antipsychotic class (FGA, SGA, FGA+SGA), age, and region. Importantly, the discrimination of antipsychotic classes remained significant when controlling for the significant moderators age and geographical region (antipsychotic class: FGA vs SGA; $Z = -2.09$; $P = .037$; FGA vs FGA + SGA; $Z = -2.12$, $P = .034$; region: Asia vs Europe, $Z = 1.55$, $P = .12$; Asia vs United States, $Z = 2.6$, $P = .009$; Asia vs other parts of world, $Z = 2.42$, $P = .015$; age: $Z = 2.85$, $P = .004$).

When adding the variable study sponsorship that was near-significant in univariate analysis into the multivariable model, sponsorship remained nonsignificant ($Z = 1.26$, $P = .21$).

Studies Reporting TD Prevalence for ≥ 2 Antipsychotic Classes

In the 20 studies* that contained both SGA and FGA treatment groups, TD prevalence with SGAs was lower than with FGAs (25.3%, 95% CI = 20.3%–31.1% vs 30.1%, 95% CI = 25.3%–35.4%; $Z = -2.55$, $P = .011$; Figure 4A). The mean RR was 0.80 (95% CI = 0.67–0.95) in favor of SGAs. However, there was substantial dispersion in the RRs, and the predicted RR in any single study could fall in the range of 0.41–1.55.

In the 9 studies† that included patients with FGA monotherapy and FGA+SGA combination, the TD prevalence was significantly lower for FGA + SGA (RR = 0.80; 95% CI = 0.71–0.90, $Z = -3.56$, $P < .001$; Figure 4B). There was no evidence of dispersion in the effect size.

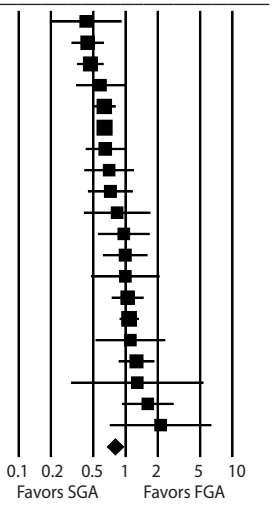
In the 12 studies‡ that included SGA monotherapy and FGA+SGA combination, there was no significant difference in TD prevalence. The mean risk ratio was 0.95 (95%

*References 13,21–24,26,31,36,38,40,43,46,48,50,51,53,56–58,60
†References 13,23,24,31,46,51,53,57,60
‡References 13,23,24,31,32,39,46,51,53,57,59,60

Figure 4. Tardive Dyskinesia Prevalence in Studies Including More Than 1 Antipsychotic Treatment Group Corroborates Lower Rates With Second-Generation Antipsychotic (SGA) Treatment

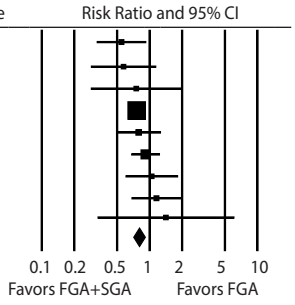
A. Second-Generation Antipsychotics (SGAs) vs First-Generation Antipsychotics (FGAs)[a]

	Statistics for Each Study				
Study Name	Risk Ratio	Lower Limit	Upper Limit	*Z* Value	*P* Value
Sundram 2008[58]	0.424	0.195	0.920	−2.170	.030
Gharabawi 2005[36]	0.442	0.312	0.626	−4.594	.000
Miller 2005[50]	0.470	0.354	0.624	−5.210	.000
Achalia 2014[21]	0.583	0.345	0.986	−2.011	.044
Woods 2010[13]	0.634	0.496	0.810	−3.647	.000
Ascher-Svanum 2008[23]	0.637	0.545	0.744	−5.684	.000
Lee 2010[46]	0.646	0.424	0.985	−2.029	.042
de Leon 2007[31]	0.702	0.411	1.199	−1.296	.195
Boke 2007[26]	0.722	0.445	1.171	−1.319	.187
Adam 2014[22]	0.835	0.408	1.708	−0.494	.621
Bakker 2011[24]	0.964	0.552	1.683	−0.128	.898
Ross 2005[53]	0.994	0.615	1.606	−0.024	.981
Janno 2004[43]	0.998	0.478	2.085	−0.006	.996
Souza 2010[56]	1.047	0.742	1.478	0.263	.793
Sun 2013[57]	1.081	0.880	1.328	0.744	.457
Hitzeroth 2007[40]	1.111	0.524	2.353	0.275	.784
Halliday 2002[38]	1.267	0.861	1.865	1.203	.229
Leung 2003[48]	1.288	0.309	5.369	0.348	.728
Modestin 2000[51]	1.616	0.926	2.822	1.689	.091
Yoon 2004[60]	2.127	0.712	6.348	1.352	.176
	0.797	0.669	0.949	−2.554	.011



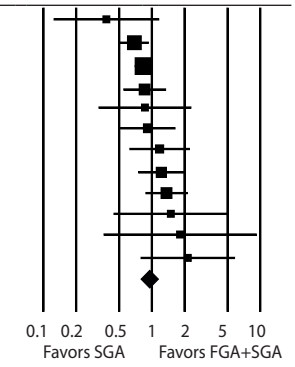
B. FGAs vs FGA + SGA[b]

	Statistics for Each Study				
Study Name	Risk Ratio	Lower Limit	Upper Limit	*Z* Value	*P* Value
Lee 2010[46]	0.548	0.323	0.930	−2.227	.026
de Leon 2007[31]	0.574	0.285	1.152	−1.562	.118
Modestin 2000[51]	0.753	0.285	1.986	−0.574	.566
Ascher-Svanum 2008[23]	0.759	0.643	0.897	−3.243	.001
Sun 2013[57]	0.791	0.492	1.274	−0.962	.336
Woods 2010[13]	0.918	0.675	1.247	−0.548	.583
Bakker 2011[24]	1.048	0.598	1.838	0.165	.869
Ross 2005[53]	1.158	0.679	1.976	0.539	.590
Yoon 2004[60]	1.420	0.329	6.122	0.470	.638
	0.798	0.705	0.904	−3.562	.000



C. SGAs vs FGA + SGA[c]

	Statistics for Each Study				
Study Name	Risk Ratio	Lower Limit	Upper Limit	*Z* Value	*P* Value
Wonodi 2007[59]	0.381	0.124	1.168	−1.688	.091
Woods 2010[13]	0.690	0.509	0.937	−2.380	.017
Ascher-Svanum 2008[23]	0.838	0.695	1.011	−1.848	.065
Ross 2005[53]	0.858	0.545	1.351	−0.660	.509
Eberhard 2006[32]	0.864	0.322	2.316	−0.291	.771
Bakker 2011[24]	0.920	0.512	1.651	−0.280	.779
Lee 2010[46]	1.179	0.621	2.240	0.503	.615
de Leon 2007[31]	1.224	0.751	1.997	0.810	.418
Sun 2013[57]	1.366	0.873	2.138	1.364	.172
Yoon 2004[60]	1.498	0.443	5.064	0.650	.516
Hansen 2013[39]	1.824	0.359	9.271	0.724	.469
Modestin 2000[51]	2.148	0.788	5.853	1.494	.135
	0.946	0.788	1.136	−0.593	.553



[a]References 13, 21–24, 26, 31, 36, 38, 40, 43, 46, 48, 50, 51, 56–58, 60. In cohorts that specified subgroups with different treatment conditions, tardive dyskinesia prevalence was significantly lower in SGAs relative to FGAs.
[b]References 13, 23, 31, 46, 51, 53, 57, 60. In cohorts that specified subgroups with different treatment conditions, tardive dyskinesia prevalence was lower in FGA + SGA vs FGAs.
[c]References 13, 23, 24, 31, 32, 39, 46, 51, 53, 57, 59, 60. In cohorts that specified subgroups with different treatment conditions, tardive dyskinesia prevalence was comparable in FGA + SGA vs SGAs.

CI = 0.79–1.14, $Z = -0.59$, $P = .55$; Figure 4C). However, there was substantial dispersion in the RRs, and the predicted RR in any single study could fall in the range of 0.51–1.76.

DISCUSSION

In this meta-analysis of 41 studies published since 2000, capturing contemporaneously used SGAs and FGAs, we found an overall mean TD prevalence of 25.3% in patients exposed to antipsychotics. Class-wide TD prevalence was significantly lower with current SGA treatment (20.7%) relative to FGA treatment (30.0%). This superiority was confirmed in the subsample of studies that included multiple antipsychotic classes and persisted when controlling for age and study region, the 2 major moderators of TD prevalence, which were available for the vast majority of studies.

Remarkably, these data illustrate that—despite high expectations[8]—the introduction of SGAs has not led to a marginalization of TD. The current results differ from our earlier report on trials published 2004–2008, with substantially higher rates during SGA treatment and slightly lower rates during FGA treatment.[12] The frequency of screening-based probable TD associated with current SGA treatment was twice as high as the baseline prevalence of TD of 9.4% in the Schizophrenia Outpatient Health Outcomes (SOHO) study,[61] where only spontaneous observations were recorded. Prior to the introduction of SGAs, Kane and Smith found a prevalence of around 20% of clinically recorded TD in a review of 56 studies conducted between 1959 and 1979.[62] It is surprising how closely this rate *seems* to match the one found for current treatment regimens, despite treatment guidelines favoring lower daily doses of FGAs[63,64] and despite high utilization of SGAs that were associated with 6-fold lower annualized incidence rates than FGAs in RCTs.[10] Importantly, however, TD ratings in our meta-analysis were based on *systematic screening* with standardized rating scales, using mostly the presence of only mild symptoms in 2 body parts as a cutoff. By contrast, earlier reports,[62,65] predating the introduction of these scales and thresholds, mostly reflected clinical assessments with far less sensitive thresholds, which quite likely identified only moderately to severely affected patients with TD.

How does the notion of a 25.3% overall prevalence of scale-based probable TD translate into an estimate of a clinical problem? To answer this question, complete data about severity and persistence of TD would be needed, but these aspects were reported in only the minority of studies.[22,27,32,36,49–51,53–55] Importantly, the percentage of severely affected subjects would need to be known, as well as the functional and/or social consequences of TD (eg, section IV of the AIMS), but this information was not provided in these contemporaneous TD studies. However, the sparse data that exist suggest rather mild TD severity in subjects on current SGA treatment, even in cohorts with prior FGA exposure, and it is likely that the mild cases would remain undiagnosed in routine clinical care. The distribution of clinical severity strata within TD reported earlier has varied greatly, ranging for moderate-severe TD with FGAs from 11%[66] to 30%[67] and up to 45%–50%[68,69]; and for SGAs from 22%[32] to 24%[70] and up to 27% with clozapine (which may have been prescribed to reduce TD).[68] Cross-sectional comparisons of TD severity by antipsychotic class are scarce, but clearly favor SGAs over FGAs.[22,27]

Indeed, this observation matches the robustly reported improvement in TD symptoms and the reduction of TD rates in earlier studies in which patients were switched from FGAs to SGAs.[71–74] Similarly, rare, life-threatening tardive syndromes have been reported for FGAs,[75,76] but not for SGA monotherapy. Conversely, a registry study of severe adverse events found similar incidences of uncommon, severe drug-induced movement disorders with SGAs and FGAs, excluding, however, the more common versions of TD.[77]

Prevalence studies are ill-suited to specify antipsychotic-specific TD risks, mostly because the agent causative of TD may well not be the one recorded at the time of TD assessment. However, RCTs, even when designed as large pragmatic trials, represent a highly selected spectrum of the psychiatric population, with exclusion of treatment-resistant subjects and subjects unable or unwilling to consent to a complex and often demanding study schedule or to be followed up. By contrast, prevalence studies specifically aim to capture most comprehensive and complete samples. Nevertheless, the limitations of prevalence studies are ample. First, TD has been described as a waxing-and-waning condition, even under constant treatment conditions.[68] In a study of risperidone, TD emerged or resolved without change in medication in 12% of subjects annually.[32] Second, switching to an SGA is a preferred therapy of TD in subjects who need antipsychotic treatment,[78] distorting the causal relationship in a cross-sectional view. However, in a small cohort included in this meta-analysis,[38] only 8% of those on SGAs were switched due to TD. Third, antipsychotic treatment may mask TD symptoms, and substantial dose or treatment changes may elicit withdrawal dyskinesia. Fourth, and most importantly, selective prescribing of SGAs to subjects with a presumed high-risk profile for TD as well as a survivor bias of subjects tolerating FGA treatment for many years without developing TD may heavily bias prevalence patterns. Importantly, this bias also applies to the studies reporting on > 1 antipsychotic class, as treatment allocation was not randomized. Lastly, class-wide assessments of antipsychotics are clearly oversimplified, and the heterogeneity within each antipsychotic class has likely attenuated between-class comparisons. Conversely, most patients with serious mental illness are typically exposed to a broad variety of antipsychotics during their lifetime, and lifetime risks for TD can be reduced to a single substance in exceptions only.

These considerations underscore the notion that it is impossible to draw causal conclusions from prevalence studies. While this lack of ability to infer causal associations from prevalence studies is a major shortcoming, the major strength of cross-sectional data is the opportunity to include

subjects with varied illness severity and comorbidity who would not be eligible for clinical studies, but who match usual care conditions as closely as possible.[79] Thus, our study reflects a broad overview of real-world patients and clinical practice patterns, with an emphasis on long-term antipsychotic users. Nevertheless, prospective studies, in FGA-naïve subjects and broader cohorts beyond schizophrenia-spectrum disorders, are needed to properly estimate the TD risk of SGAs.[80]

Another aspect of prevalence studies is a contribution to hypothesis-generating considerations of TD etiology. In this regard, the relatively small difference in TD prevalence between SGAs vs FGAs questions the notion that D_2-receptor affinity is the predominant mechanism of TD induction,[81] as SGAs and FGAs substantially differ in this regard.[82,83] Similarly, neurotoxicity, another potential mechanism of TD, has been reported to be lower with SGAs than FGAs.[84–86] In fact, recent concepts imply maladaptive plasticity as a mechanism of TD[87] and importantly suggest an interaction of dopaminergic *and* serotonergic neurons in the modulation of striatal synaptic plasticity.[88] It is possible that either very long-term effects of the receptor profile of SGAs (which were not captured in 1-year studies shortly after SGA introduction) or the frequent combination with selective serotonin reuptake inhibitors in current treatment regimens has prevented TD from vanishing despite lower dopamine receptor blockage.

Moreover, TD quite likely needs to be conceptualized as an etiologically complex syndrome, influenced both by a set of genetic risk factors reflecting the individual liability to TD[89] and by a range of antipsychotic and other treatment characteristics. In this regard, we found geographical differences in TD prevalence, with 31.3% in the United States and, consistent with earlier studies,[90] a significantly lower TD prevalence of 17.3% in Asia. Although this observation is suggestive of differences in genetic susceptibility,[91] other factors including differences in earlier cumulative FGA exposure are equally likely. Specific effects of Asian race could not be calculated across studies, as numbers of Asians in studies outside Asia (and the reverse for Caucasians treated in Asia) were not specified in the included studies. To estimate the effect of race, we used the percentage of Caucasians per study sample, but had to merge all non-Caucasian ethnicities for this purpose. We found near-significantly higher prevalence rates in Caucasians, which is surprising given the fact that African-Americans have repeatedly been reported to carry a higher risk for TD at least during FGA treatment.[80,92,93] However, among the non-Caucasian group, the effect of higher TD rates in African-Americans was likely attenuated by the lower rates in Asians.

The regional differences in TD prevalence are probably also related to differences in prescription patterns, which have yet to be identified more clearly. For example, use of the "atypical" FGA sulpiride is customary in Europe, but not in the United States, representing, for example, 58% of FGAs used in the CUtLASS study.[14] Moreover, slightly higher dosing recommendations exist in the United States compared to Asia and Europe.[94] However, dosing exceeding recommendations and high rates of polypharmacy have been reported in a practice survey from Asia,[95,96] treatment characteristics that would rather be expected to increase TD rates.

Lower SGA- than FGA-related TD rates have been attributed to high-dose FGA treatment, but our results do not support this notion. FGA doses in the 9 studies that provided dosage information ranged around a mean dose of 440 mg/d of chlorpromazine equivalents, which falls in the middle of the range of current dosing recommendations.[63,97] Moreover, TD rates in these studies did not differ from rates in FGA studies with unknown dosing.

Surprisingly, FGA-SGA cotreatment was associated with a lower prevalence of TD (22.7%) than FGA treatment alone (30.0%), and the prevalence was not substantially increased relative to SGA monotherapy (20.7%). A cautious interpretation of this result is warranted, as there were only 9 studies for direct comparison and as it is likely that FGA + SGA treatment was ill-represented in our data since higher rates of dual-class antipsychotic polypharmacy have been reported (ranging from 20%[95] up to 50%[98]). Nevertheless, the possibility that SGAs may attenuate the FGA-inherent TD risk, consistent with the improvement of TD symptoms during randomized SGA trials,[71–74] even when FGA treatment is continued, needs to be investigated further. However, an alternative hypothesis that current FGA + SGA treatment strategies might frequently reflect shorter-term FGA augmentation of SGA management with insufficient treatment response also needs to be examined.

In this vein, the subgroup and regression analyses of the set of data included in our meta-analysis were not designed to determine TD risk profiles, as the information on potential individual risk factors was not complete for a sufficient number of studies. Moreover, the spread of study-level risk factors does not reflect the spread of these factors within each of the studies, and thus meta-regression is limited in the identification of risk factors. Nevertheless, our analyses confirmed the finding of higher TD prevalence rates with FGAs (either compared to SGAs or SGAs + FGAs), as well as in cohorts of older age, with longer illness duration, and with comorbid parkinsonism.[1,90,91]

In addition to the already discussed order effects and selection biases inherent in cross-sectional studies, several additional limitations warrant a cautious interpretation of our results. Most importantly, prior exposure to FGAs was not explicitly recorded in the majority of studies, but with a mean illness duration of 18.7 years across studies, prior FGA exposure *must* be assumed in the majority of subjects. Indeed, TD prevalence was most significantly lower in the 4 studies that included purely SGA-exposed subjects (7.2%[21,49,54,59]) compared with those on SGAs but with unspecified FGA history (23.4%*). This finding further underscores the need for future longitudinal studies in FGA-naïve patients.

Only 4 meta-analyzable studies reported TD rates of individual antipsychotics.[21,42,47,49] Detailed analyses for

*References 13,22–24,26,31,32,34–36,38–40,43,46–48,50,51,53,56–58,60

specific antipsychotics were thus not possible, although SGAs differ widely regarding EPS[99] and may also differ regarding TD. Moreover, neither the effect of antipsychotic polypharmacy within 1 antipsychotic class nor the effect of psychotropic polypharmacy could be analyzed. Indeed, polypharmacy has been suggested as a contributor to TD,[100] as, for example, antidepressants have also been reported to rarely cause tardive syndromes.[5,101] Furthermore, the majority of included prevalence studies included subjects with schizophrenia-spectrum disorders, but due to the increased use of antipsychotics in nonpsychotic disorders, this sample is unlikely to be representative of the overall group of antipsychotic-treated patients. While oversampling of patients with schizophrenia may bias toward subjects with higher rates of prior FGA exposure, mood disorders have been identified as a risk factor for TD[62] and might thus increase prevalence rates, although treatment duration and doses may be lower than in patients with schizophrenia. Indeed, in a recent, longitudinal study of TD from a movement disorders clinic, patients with mood disorders treated with SGAs were far overrepresented (38%) relative to patients with psychotic disorders (7%).[102] Finally, most studies reported "probable" instead of "persistent" TD,[103] as movement examinations were not necessarily repeated after 6 months.

CONCLUSION

In conclusion, this meta-analysis of prevalence studies confirmed an association between increased risk of TD and FGAs, older age, and longer illness (and, thus, treatment) duration, as well as higher EPS frequencies. Additionally, this meta-analysis points toward lower TD rates in studies conducted in Asia, patients treated with SGAs but not previously exposed to FGAs, and, possibly, to an attenuation of the FGA-related TD signal if these are combined with SGAs. However, in order to better and fully understand the impact of SGA-associated TD on patient-related outcomes, current TD prevalence studies need to be complemented by more detailed studies and by prospective studies that are conducted in representative samples of antipsychotic users and that include repeated measurements of dyskinesia severity as well as complete medication history and dose information.

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Drug names: aripiprazole (Abilify), asenapine (Saphris), clozapine (Clozaril, FazaClo, and others), droperidol (Inapsine), iloperidone (Fanapt), lurasidone (Latuda), olanzapine (Zyprexa and others), paliperidone (Invega), pimozide (Orap), prochlorperazine (Procomp and others), quetiapine (Seroquel and others), risperidone (Risperdal and others), thiothixene (Navane and others), ziprasidone (Geodon and others).

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REFERENCES

1. Aquino CC, Lang AE. Tardive dyskinesia syndromes: current concepts. *Parkinsonism Relat Disord*. 2014;20(suppl 1):S113–S117.
2. Chong SA, Remington G, Mahendran R, et al. Awareness of tardive dyskinesia in Asian patients with schizophrenia. *J Clin Psychopharmacol*. 2001;21(2):235–237.
3. Browne S, Roe M, Lane A, et al. Quality of life in schizophrenia: relationship to sociodemographic factors, symptomatology and tardive dyskinesia. *Acta Psychiatr Scand*. 1996;94(2):118–124.
4. Yassa R. Functional impairment in tardive dyskinesia: medical and psychosocial dimensions. *Acta Psychiatr Scand*. 1989;80(1):64–67.
5. Waln O, Jankovic J. An update on tardive dyskinesia: from phenomenology to treatment. *Tremor Other Hyperkinet Mov (N Y)*. 2013;3:tre-03-161-4138-1.
6. Glazer WM, Morgenstern H, Doucette JT. Predicting the long-term risk of tardive dyskinesia in outpatients maintained on neuroleptic medications. *J Clin Psychiatry*. 1993;54(4):133–139.
7. Rascol O, Fabre N. Dyskinesia: L-dopa-induced and tardive dyskinesia. *Clin Neuropharmacol*. 2001;24(6):313–323.
8. Remington G. Tardive dyskinesia: eliminated, forgotten, or overshadowed? *Curr Opin Psychiatry*. 2007;20(2):131–137.
9. Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet*. 2013;382(9896):951–962.
10. Correll CU, Leucht S, Kane JM. Lower risk for tardive dyskinesia associated with second-generation antipsychotics: a systematic review of 1-year studies. *Am J Psychiatry*. 2004;161(3):414–425.
11. Chan HY, Chiang SC, Chang CJ, et al. A randomized controlled trial of risperidone and olanzapine for schizophrenic patients with

neuroleptic-induced tardive dyskinesia. *J Clin Psychiatry*. 2010;71(9):1226–1233.
12. Correll CU, Schenk EM. Tardive dyskinesia and new antipsychotics. *Curr Opin Psychiatry*. 2008;21(2):151–156.
13. Woods SW, Morgenstern H, Saksa JR, et al. Incidence of tardive dyskinesia with atypical versus conventional antipsychotic medications: a prospective cohort study. *J Clin Psychiatry*. 2010;71(4):463–474.
14. Peluso MJ, Lewis SW, Barnes TR, et al. Extrapyramidal motor side-effects of first- and second-generation antipsychotic drugs. *Br J Psychiatry*. 2012;200(5):387–392.
15. Miller DD, Caroff SN, Davis SM, et al; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Extrapyramidal side-effects of antipsychotics in a randomised trial. *Br J Psychiatry*. 2008;193(4):279–288.
16. Hugenholtz GW, Heerdink ER, Stolker JJ, et al. Haloperidol dose when used as active comparator in randomized controlled trials with atypical antipsychotics in schizophrenia: comparison with officially recommended doses. *J Clin Psychiatry*. 2006;67(6):897–903.
17. Parabiaghi A, Tettamanti M, D'Avanzo B, et al; GiSAS study group. Metabolic syndrome and drug discontinuation in schizophrenia: a randomized trial comparing aripiprazole olanzapine and haloperidol. *Acta Psychiatr Scand*. 2016;133(1):63–75.
18. Campbell M. Risperidone-induced tardive dyskinesia in first-episode psychotic patients. *J Clin Psychopharmacol*. 1999;19(3):276–277.
19. Addington DE, Toews JA, Addington JM. Risperidone and tardive dyskinesia: a case report. *J Clin Psychiatry*. 1995;56(10):484–485.
20. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177–188.
21. Achalia RM, Chaturvedi SK, Desai G, et al. Prevalence and risk factors associated with tardive dyskinesia among Indian patients with schizophrenia. *Asian J Psychiatr*. 2014;9:31–35.
22. Adam UU, Husain N, Haddad PM, et al. Tardive dyskinesia in a South Asian population with first episode psychosis treated with antipsychotics. *Neuropsychiatr Dis Treat*. 2014;10:1953–1959.
23. Ascher-Svanum H, Zhu B, Faries D, et al. Tardive dyskinesia and the 3-year course of schizophrenia: results from a large, prospective, naturalistic study. *J Clin Psychiatry*. 2008;69(10):1580–1588.
24. Bakker PR, de Groot IW, van Os J, et al. Long-stay psychiatric patients: a prospective study revealing persistent antipsychotic-induced movement disorder. *PLoS One*. 2011;6(10):e25588.
25. Bhatia T, Sabeeha MR, Shriharsh V, et al. Clinical and familial correlates of tardive dyskinesia in India and Israel. *J Postgrad Med*. 2004;50(3):167–172, discussion 172.
26. Boke O, Gunes S, Kara N, et al. Association of serotonin 2A receptor and lack of association of CYP1A2 gene polymorphism with tardive dyskinesia in a Turkish population. *DNA Cell Biol*. 2007;26(8):527–531.
27. Brar JS, Parepally H, Chalasani L, et al. The impact of olanzapine on tardive dyskinetic symptoms in a state hospital population. *Ann Clin Psychiatry*. 2008;20(3):139–144.
28. Brousse G, Meary A, Mouret J, et al. Tardive dyskinesia and glucid metabolism. *Hum Psychopharmacol*. 2007;22(6):373–380.
29. Chong SA, Mahendran R, Machin D, et al. Tardive dyskinesia among Chinese and Malay patients with schizophrenia. *J Clin Psychopharmacol*. 2002;22(1):26–30.
30. Covell NH, McEvoy JP, Schooler NR, et al; Schizophrenia Trials Network. Effectiveness of switching from long-acting injectable fluphenazine or haloperidol decanoate to long-acting injectable risperidone microspheres: an open-label, randomized controlled trial. *J Clin Psychiatry*. 2012;73(5):669–675.
31. de Leon J. The effect of atypical versus typical antipsychotics on tardive dyskinesia: a naturalistic study. *Eur Arch Psychiatry Clin Neurosci*. 2007;257(3):169–172.
32. Eberhard J, Lindström E, Levander S. Tardive dyskinesia and antipsychotics: a 5-year longitudinal study of frequency, correlates and course. *Int Clin Psychopharmacol*. 2006;21(1):35–42.
33. Ellingrod VL, Schultz SK, Arndt S. Abnormal movements and tardive dyskinesia in smokers and nonsmokers with schizophrenia genotyped for cytochrome P450 2D6. *Pharmacotherapy*. 2002;22(11):1416–1419.
34. Fodstad JC, Bamburg JW, Matson JL, et al. Tardive dyskinesia and intellectual disability: an examination of demographics and topography in adults with dual diagnosis and atypical antipsychotic use. *Res Dev Disabil*. 2010;31(3):750–759.
35. Gebhardt S, Härtling F, Hanke M, et al. Prevalence of movement disorders in adolescent patients with schizophrenia and in relationship to predominantly atypical antipsychotic treatment. *Eur Child Adolesc Psychiatry*. 2006;15(7):371–382.
36. Gharabawi GM, Bossie CA, Zhu Y, et al. An assessment of emergent tardive dyskinesia and existing dyskinesia in patients receiving long-acting, injectable risperidone: results from a long-term study. *Schizophr Res*. 2005;77(2–3):129–139.
37. Güzey C, Scordo MG, Spina E, et al. Antipsychotic-induced extrapyramidal symptoms in patients with schizophrenia: associations with dopamine and serotonin receptor and transporter polymorphisms. *Eur J Clin Pharmacol*. 2007;63(3):233–241.
38. Halliday J, Farrington S, Macdonald S, et al. Nithsdale Schizophrenia Surveys 23: movement disorders: 20-year review. *Br J Psychiatry*. 2002;181(5):422–427.
39. Hansen LK, Nausheen B, Hart D, et al. Movement disorders in patients with schizophrenia and a history of substance abuse. *Hum Psychopharmacol*. 2013;28(2):192–197.
40. Hitzeroth A, Niehaus DJ, Koen L, et al. Association between the MnSOD Ala-9Val polymorphism and development of schizophrenia and abnormal involuntary movements in the Xhosa population. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007;31(3):664–672.
41. Hsieh CJ, Chen YC, Lai MS, et al. Genetic variability in serotonin receptor and transporter genes may influence risk for tardive dyskinesia in chronic schizophrenia. *Psychiatry Res*. 2011;188(1):175–176.
42. Jaanson P, Marandi T, Kiivet RA, et al. Maintenance therapy with zuclopenthixol decanoate: associations between plasma concentrations, neurological side effects and CYP2D6 genotype. *Psychopharmacology (Berl)*. 2002;162(1):67–73.
43. Janno S, Holi M, Tuisku K, et al. Prevalence of neuroleptic-induced movement disorders in chronic schizophrenia inpatients. *Am J Psychiatry*. 2004;161(1):160–163.
44. Kim JH, Byun HJ. Prevalence and characteristics of subjective akathisia, objective akathisia, and mixed akathisia in chronic schizophrenic subjects. *Clin Neuropharmacol*. 2003;26(6):312–316.
45. Koola MM, Tsapakis EM, Wright P, et al. Association of tardive dyskinesia with variation in CYP2D6: is there a role for active metabolites? *J Psychopharmacol*. 2014;28(7):665–670.
46. Lee J, Jiang J, Sim K, et al. The prevalence of tardive dyskinesia in Chinese Singaporean patients with schizophrenia: revisited. *J Clin Psychopharmacol*. 2010;30(3):333–335.
47. Lee JY, Kim SW, Lee YH, et al. Factors associated with self-rated sexual function in Korean patients with schizophrenia receiving risperidone monotherapy. *Hum Psychopharmacol*. 2015;30(6):416–424.
48. Leung SK, Ungvari GS, Ng FS, et al. Tardive dyskinesia in Chinese inpatients with chronic schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2003;27(6):1029–1035.
49. Li CR, Chung YC, Park TW, et al. Clozapine-induced tardive dyskinesia in schizophrenic patients taking clozapine as a first-line antipsychotic drug. *World J Biol Psychiatry*. 2009;10(4 pt 3):919–924.
50. Miller DD, McEvoy JP, Davis SM, et al. Clinical correlates of tardive dyskinesia in schizophrenia: baseline data from the CATIE schizophrenia trial. *Schizophr Res*. 2005;80(1):33–43.
51. Modestin J, Stephan PL, Erni T, et al. Prevalence of extrapyramidal syndromes in psychiatric inpatients and the relationship of clozapine treatment to tardive dyskinesia. *Schizophr Res*. 2000;42(3):223–230.
52. Patterson BD, Swingler D, Willows S. Prevalence of and risk factors for tardive dyskinesia in a Xhosa population in the Eastern Cape of South Africa. *Schizophr Res*. 2005;76(1):89–97.
53. Ross DE, Thomas M, Booth M, et al. Rate of tardive dyskinesia in hospitalized patients. *Am J Psychiatry*. 2005;162(4):816.
54. Ryu S, Yoo JH, Kim JH, et al. Tardive dyskinesia and tardive dystonia with second-generation antipsychotics in non-elderly schizophrenic patients unexposed to first-generation antipsychotics: a cross-sectional and retrospective study. *J Clin Psychopharmacol*. 2015;35(1):13–21.
55. Sejil I, Oumaya A, Bouguerra C, et al. Tardive dyskinesia induced by classical antipsychotic drugs: a Tunisian sample of schizophrenics [in French]. *Encephale*. 2013;39(suppl 1):S36–S41.
56. Souza RP, de Luca V, Remington G, et al. Glial cell line-derived neurotrophic factor receptor alpha 2 (GFRA2) gene is associated with tardive dyskinesia. *Psychopharmacology (Berl)*. 2010;210(3):347–354.
57. Sun H, Wang F, Fan H, et al. The interaction of polymorphisms of IL10 and DBH was associated with general symptoms of PANSS with TD in Chinese Han schizophrenic patients. *PLoS One*. 2013;8(8):e70963.
58. Sundram S, Lambert T, Piskulic D. Acculturation is associated with the prevalence of tardive dyskinesia and akathisia in community-treated patients with schizophrenia. *Acta Psychiatr Scand*. 2008;117(6):474–478.
59. Wonodi I, Reeves G, Carmichael D, et al. Tardive dyskinesia in children treated with atypical antipsychotic medications. *Mov Disord*. 2007;22(12):1777–1782.
60. Yoon JY, Oh DY, Choi JH. Prevalence of tardive dyskinesia in inpatients using antipsychotics. *Korean J Psychopharmacol*. 2004;15(3):305–311.
61. Tenback DE, van Harten PN, Slooff CJ, et al. Incidence and persistence of tardive dyskinesia and extrapyramidal symptoms in schizophrenia. *J Psychopharmacol*. 2010;24(7):1031–1035.

62. Kane JM, Smith JM. Tardive dyskinesia: prevalence and risk factors, 1959 to 1979. *Arch Gen Psychiatry*. 1982;39(4):473–481.
63. Gardner DM, Murphy AL, O'Donnell H, et al. International consensus study of antipsychotic dosing. *Am J Psychiatry*. 2010;167(6):686–693.
64. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand suppl*. 1970;212:11–19.
65. Morgenstern H, Glazer WM, Niedzwiecki D, et al. The impact of neuroleptic medication on tardive dyskinesia: a meta-analysis of published studies. *Am J Public Health*. 1987;77(6):717–724.
66. Chakos MH, Alvir JM, Woerner MG, et al. Incidence and correlates of tardive dyskinesia in first episode of schizophrenia. *Arch Gen Psychiatry*. 1996;53(4):313–319.
67. Tenback DE, van Harten PN, Slooff CJ, et al. Evidence that early extrapyramidal symptoms predict later tardive dyskinesia: a prospective analysis of 10,000 patients in the European Schizophrenia Outpatient Health Outcomes (SOHO) study. *Am J Psychiatry*. 2006;163(8):1438–1440.
68. Rosenheck RA. Evaluating the cost-effectiveness of reduced tardive dyskinesia with second-generation antipsychotics. *Br J Psychiatry*. 2007;191(3):238–245.
69. Woerner MG, Alvir JM, Saltz BL, et al. Prospective study of tardive dyskinesia in the elderly: rates and risk factors. *Am J Psychiatry*. 1998;155(11):1521–1528.
70. Tenback DE, van Harten PN, Slooff CJ, et al; SOHO Study Group. Effects of antipsychotic treatment on tardive dyskinesia: a 6-month evaluation of patients from the European Schizophrenia Outpatient Health Outcomes (SOHO) Study. *J Clin Psychiatry*. 2005;66(9):1130–1133.
71. Bai YM, Yu SC, Lin CC. Risperidone for severe tardive dyskinesia: a 12-week randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2003;64(11):1342–1348.
72. Emsley R, Turner HJ, Schronen J, et al. A single-blind, randomized trial comparing quetiapine and haloperidol in the treatment of tardive dyskinesia. *J Clin Psychiatry*. 2004;65(5):696–701.
73. Jeste DV, Okamoto A, Napolitano J, et al. Low incidence of persistent tardive dyskinesia in elderly patients with dementia treated with risperidone. *Am J Psychiatry*. 2000;157(7):1150–1155.
74. Miller DD, Eudicone JM, Pikalov A, et al. Comparative assessment of the incidence and severity of tardive dyskinesia in patients receiving aripiprazole or haloperidol for the treatment of schizophrenia: a post hoc analysis. *J Clin Psychiatry*. 2007;68(12):1901–1906.
75. Kovacs N, Balas I, Janszky J, et al. Status dystonicus in tardive dystonia successfully treated by bilateral deep brain stimulation. *Clin Neurol Neurosurg*. 2011;113(9):808–809.
76. Lazarus AL, Toglia JU. Fatal myoglobinuric renal failure in a patient with tardive dyskinesia. *Neurology*. 1985;35(7):1055–1057.
77. Stübner S, Rustenbeck E, Grohmann R, et al. Severe and uncommon involuntary movement disorders due to psychotropic drugs. *Pharmacopsychiatry*. 2004;37(suppl 1): S54–S64.
78. Spivak B, Mester R, Abesgaus J, et al. Clozapine treatment for neuroleptic-induced tardive dyskinesia, parkinsonism, and chronic akathisia in schizophrenic patients. *J Clin Psychiatry*. 1997;58(7):318–322.
79. Correll CU. Real-life dosing with second-generation antipsychotics. *J Clin Psychiatry*. 2005;66(12):1610–1611.
80. Woerner MG, Correll CU, Alvir JM, et al. Incidence of tardive dyskinesia with risperidone or olanzapine in the elderly: results from a 2-year, prospective study in antipsychotic-naïve patients. *Neuropsychopharmacology*. 2011;36(8):1738–1746.
81. Margolese HC, Chouinard G, Kolivakis TT, et al. Tardive dyskinesia in the era of typical and atypical antipsychotics, part 1: pathophysiology and mechanisms of induction. *Can J Psychiatry*. 2005;50(9):541–547.
82. Abi-Dargham A, Laruelle M. Mechanisms of action of second generation antipsychotic drugs in schizophrenia: insights from brain imaging studies. *Eur Psychiatry*. 2005;20(1):15–27.
83. Correll CU. From receptor pharmacology to improved outcomes: individualising the selection, dosing, and switching of antipsychotics. *Eur Psychiatry*. 2010;25(suppl 2):S12–S21.
84. Gassó P, Mas S, Molina O, et al. Neurotoxic/neuroprotective activity of haloperidol, risperidone and paliperidone in neuroblastoma cells. *Prog Neuropsychopharmacol Biol Psychiatry*. 2012;36(1):71–77.
85. Marchese G, Casu MA, Bartholini F, et al. Sub-chronic treatment with classical but not atypical antipsychotics produces morphological changes in rat nigro-striatal dopaminergic neurons directly related to "early onset" vacuous chewing. *Eur J Neurosci*. 2002;15(7):1187–1196.
86. Tan QR, Wang XZ, Wang CY, et al. Differential effects of classical and atypical antipsychotic drugs on rotenone-induced neurotoxicity in PC12 cells. *Eur Neuropsychopharmacol*. 2007;17(12):768–773.
87. Cerasa A, Fasano A, Morgante F, et al. Maladaptive plasticity in levodopa-induced dyskinesias and tardive dyskinesias: old and new insights on the effects of dopamine receptor pharmacology. *Front Neurol*. 2014;5:49.
88. Rylander D, Parent M, O'Sullivan SS, et al. Maladaptive plasticity of serotonin axon terminals in levodopa-induced dyskinesia. *Ann Neurol*. 2010;68(5):619–628.
89. Brandl EJ, Kennedy JL, Müller DJ. Pharmacogenetics of antipsychotics. *Can J Psychiatry*. 2014;59(2):76–88.
90. Pandurangi AK, Aderibigbe YA. Tardive dyskinesia in non-western countries: a review. *Eur Arch Psychiatry Clin Neurosci*. 1995;246(1):47–52.
91. Miura I, Zhang JP, Nitta M, et al. BDNF Val66Met polymorphism and antipsychotic-induced tardive dyskinesia occurrence and severity: a meta-analysis. *Schizophr Res*. 2014;152(2–3):365–372.
92. Tenback DE, van Harten PN, van Os J. Non-therapeutic risk factors for onset of tardive dyskinesia in schizophrenia: a meta-analysis. *Mov Disord*. 2009;24(16):2309–2315.
93. Ormerod S, McDowell SE, Coleman JJ, et al. Ethnic differences in the risks of adverse reactions to drugs used in the treatment of psychoses and depression: a systematic review and meta-analysis. *Drug Saf*. 2008;31(7):597–607.
94. Gaebel W, Weinmann S, Sartorius N, et al. Schizophrenia practice guidelines: international survey and comparison. *Br J Psychiatry*. 2005;187(3):248–255.
95. Chong MY, Tan CH, Fujii S, et al. Antipsychotic drug prescription for schizophrenia in East Asia: rationale for change. *Psychiatry Clin Neurosci*. 2004;58(1):61–67.
96. Sim K, Su A, Leong JY, et al. High dose antipsychotic use in schizophrenia: findings of the REAP (Research on East Asia Psychotropic Prescriptions) study. *Pharmacopsychiatry*. 2004;37(4):175–179.
97. Patel MX, Arista IA, Taylor M, et al. How to compare doses of different antipsychotics: a systematic review of methods. *Schizophr Res*. 2013;149(1–3):141–148.
98. Broekema WJ, de Groot IW, van Harten PN. Simultaneous prescribing of atypical antipsychotics, conventional antipsychotics and anticholinergics: a European study. *Pharm World Sci*. 2007;29(3):126–130.
99. Rummel-Kluge C, Komossa K, Schwarz S, et al. Second-generation antipsychotic drugs and extrapyramidal side effects: a systematic review and meta-analysis of head-to-head comparisons. *Schizophr Bull*. 2012;38(1): 167–177.
100. Gallego JA, Nielsen J, De Hert M, et al. Safety and tolerability of antipsychotic polypharmacy. *Expert Opin Drug Saf*. 2012;11(4):527–542.
101. Vandewalle W, Boon E, Sienaert P. Movement disorders due to modern antidepressants and mood stabilizers [in Dutch]. *Tijdschr Psychiatr*. 2015;57(2):132–137.
102. Zutshi D, Cloud LJ, Factor SA. Tardive syndromes are rarely reversible after discontinuing dopamine receptor blocking agents: experience from a university-based movement disorder clinic. *Tremor Other Hyperkinet Mov (N Y)*. 2014;4:266.
103. Schooler NR, Kane JM. Research diagnoses for tardive dyskinesia. *Arch Gen Psychiatry*. 1982;39(4):486–487.