Clozapine Monotherapy as a Treatment for Antipsychotic-Induced Tardive Dyskinesia: A Meta-Analysis

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ABSTRACT

Objective: Tardive dyskinesia (TD) is an antipsychotic-induced movement disorder that typically occurs after long-term exposure to antipsychotic drugs. There is evidence that switching to clozapine reduces TD. This meta-analysis reviews the effect of switching to clozapine on the severity of TD.

Data Sources: The PubMed, PsycINFO, and Embase databases were searched for *clozapine, tardive dyskinesia*, and related keywords. The search was restricted to articles written in English and Dutch, and it was last updated on October 13, 2015.

Study Selection: Sixteen studies were included in the meta-analysis. Inclusion criteria were a diagnosis of schizophrenia or a related disorder, a switch to clozapine monotherapy, and reports of scores on a TD rating scale before and after the switch to clozapine.

Data Extraction: Two independent investigators extracted the data. Data were converted to standardized mean change scores and analyzed in a random-effects model.

Results: A random-effects model showed that the overall effect of switching to clozapine was a significant reduction in TD ($n_{patients}$ = 1,060, d = −0.40, P < .01), especially in the 4 studies that investigated the severity of TD as a primary outcome ($n_{patients}$ = 48, d = −2.56, P = .02).

Conclusions: The overall results show that clozapine treatment can yield a slight reduction in TD. The severity of TD was reduced greatly in patients with moderate to severe TD. In patients with minimal to mild TD, switching to clozapine seldom worsens TD and a trend toward reduction is seen. These results support that a switch to clozapine should be considered for patients with moderate to severe TD and/or patients who experience substantial discomfort due to TD.

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Antipsychotic drugs are used extensively for the treatment of schizophrenia and other mental illnesses, to control mental symptoms[1] and to reduce the risk of relapse in schizophrenia.[2] Unfortunately, many adverse events and side effects have also been associated with antipsychotic treatment.[3]

Tardive dyskinesia (TD) is a long-term side effect of antipsychotic treatment characterized by repetitive, abnormal, persistent, purposeless, and involuntary movements.[4] Typically, it presents as twisting tongue movements (that in severe cases can protrude from the mouth), jaw movements, lip smacking/puckering/pursing, and eye blinking.[5] Several studies have reported that the risk of TD increases with age and preexisting extrapyramidal symptoms.[6] Consequently, TD is quite prevalent in adult and elderly populations with schizophrenia; reports range from 13% to 40%.[7,8] Second-generation antipsychotics are associated with a reduced risk for TD, compared to first-generation antipsychotics. Nevertheless, second-generation antipsychotics also increase the risk for TD; a meta-analysis reported that average yearly incidence of TD, for adult and elderly patients treated with second-generation antipsychotics, is 0.8% and 5.3%, respectively.[9]

TD has been linked to poorer quality of life[10] and increased mortality[11] and is socially stigmatizing for patients. As of 2017, the first 2 treatments for managing TD have been approved by the US Food and Drug Administration, the vesicular monoamine transporter-2 (VMAT-2) inhibitors valbenazine and deutetrabenazine.[12–14] Earlier, the management of TD relied on off-label use of treatments, many of which lack hard evidence. Previous meta-analyses have investigated the effectiveness of adding anticholinergic medication,[15] benzodiazepines,[16] calcium channel blockers,[17] cholinergic medication,[18] γ-aminobutyric acid agonists,[19] reduction/cessation of antipsychotic treatment,[5] vitamin E supplementation,[20] and other miscellaneous treatments[21] for TD. None of these reviews found decisive evidence for the effectiveness of these treatments. However, switching current antipsychotic treatment to clozapine monotherapy has been reported as an effective strategy to reduce TD.[22–24]

In 2001, a meta-analysis investigated the effectiveness of clozapine as a treatment for TD in a secondary analysis.[22] The data in that study suggested that clozapine was associated with a reduction of TD. However, this effect was nonsignificant, most likely because that analysis consisted of only 3 small studies. The aim of the present meta-analysis is to further investigate the effect of a switch to clozapine monotherapy on the severity of TD. TD has been observed in a variety of neurologic and

Clinical Points

- Antipsychotic-induced tardive dyskinesia is a burden for many patients, yet evidence for most treatment options is still inconclusive.
- For patients with antipsychotic-induced tardive dyskinesia, switching to clozapine is a viable consideration.

mental disorders. We elected to narrow our investigation to patients with schizophrenia to maintain a more homogenous group of patients. Moreover, patients with schizophrenia are usually on long-term antipsychotic treatment. Our primary hypothesis is that clozapine effectively reduces the severity of TD in patients with clinical levels of TD (moderate to severe). As studies that report the effect of switching to clozapine in patients with clinical TD are scarce, we extended our search to studies that investigated a switch to clozapine and reported TD as a secondary outcome. However, the majority of the patients in these studies have subclinical levels of TD (mild to none). Therefore, as a secondary hypothesis, we hypothesized that clozapine does not induce nor increase the severity of TD in patients without or with subclinical TD.

METHODS

Data Sources

Two systematic searches were conducted using Embase, MEDLINE, and PsycINFO, in week 41 of 2013 and week 42 of 2015. We searched for the keywords *clozapine* and *tardive dyskinesia* and all related keywords (Table 1 lists all keywords used in the searches). We obtained the related keywords from the databases' respective thesauruses (Emtree, MeSH, and Thesaurus of Index Terms), and we also included the names and abbreviations of rating scales used to assess TD. These keywords were added to prevent the exclusion of studies that have not yet been assigned MeSH/Index terms by the databases. The reference lists of articles fulfilling all criteria were hand-searched for other relevant studies. Authors of articles published after 1995 that measured TD but did not report it were contacted by e-mail. All the authors we contacted were asked if they had unpublished work relevant to this meta-analysis.

Full-text versions of all potentially relevant papers were obtained. References were entered into an EndNote database, and duplicates were removed. Further data entry, storage, and management were done by creating appropriate forms using Microsoft Access (Microsoft; Redmond, Washington).

Study Inclusion

Figure 1 details the inclusion of the studies. The selection of articles in the screening process was restricted to articles written in English or Dutch, without restrictions regarding the year of publication. The inclusion of studies was restricted to studies that investigated patients who (1) were diagnosed with schizophrenia, (2) switched their medication to monotherapy with clozapine, and (3) were assessed for TD on a rating scale (ie, the Abnormal Involuntary Movement Scale, Extrapyramidal Symptom Rating Scale, Simpson Dyskinesia Scale, or Drug-Induced Extrapyramidal Symptoms Scale) at least once prior to switching to clozapine and once after. When studies reported multiple follow-up assessments, the last data point was used to ensure that any effects of prior antipsychotics had worn off. Case reports and retrospective studies that did not assess TD at fixed intervals were excluded. To include more studies, the screening was extended to studies that assessed TD as a secondary outcome, because we expected that there would only be a few studies that investigated TD as a primary outcome in patients with clinical levels of TD.

Two of the authors (T.Q.M. and R.S.) independently inspected titles identified from the search, and 4 of the authors (T.Q.M., R.S., M.O., and R.L.) independently inspected abstracts identified in the title screening. Studies passed the title and abstract screening if at least 1 of the authors accepted it. The remaining full-text articles were reviewed (T.Q.M.) after completion of the screening processes.

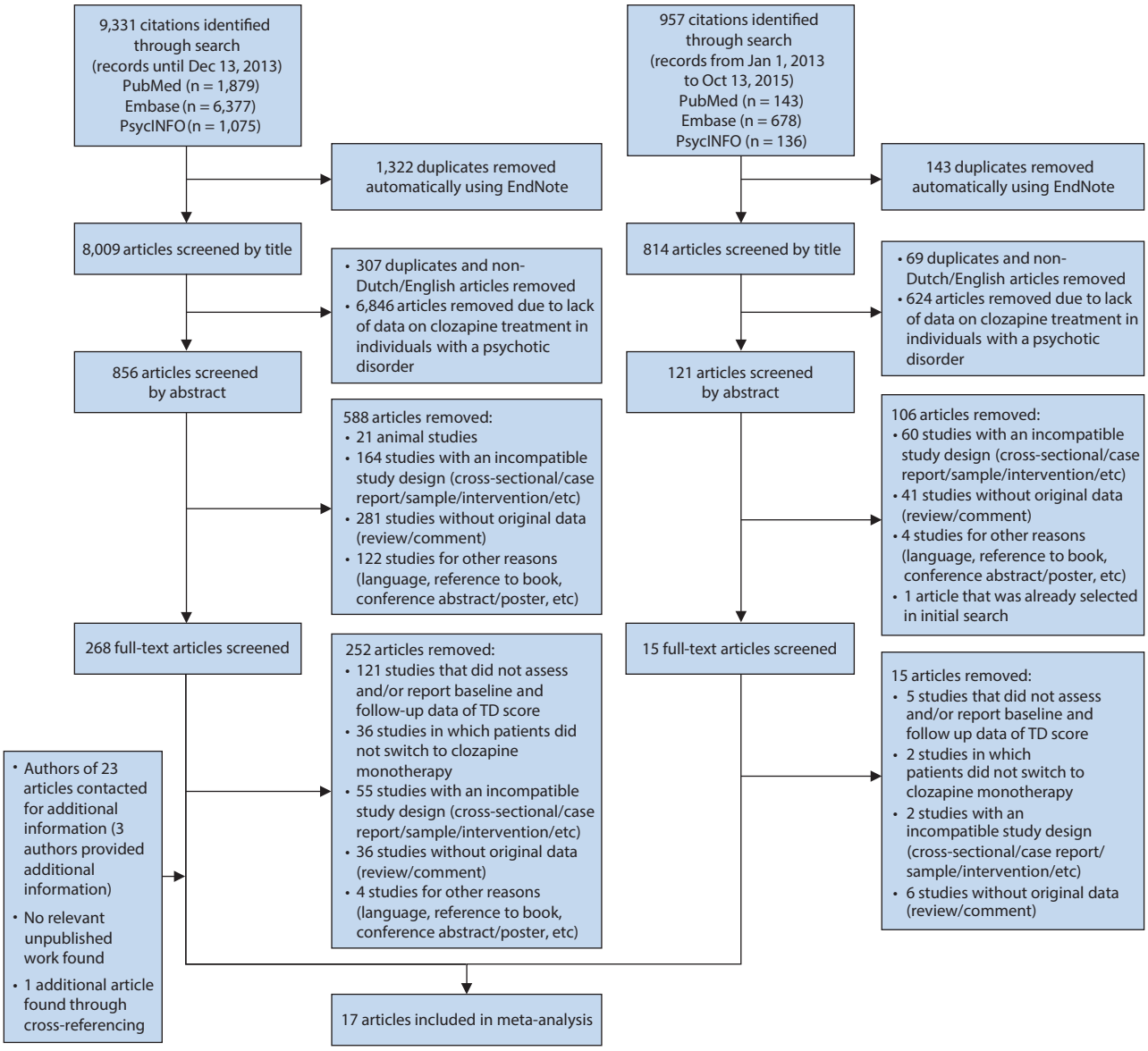
Data Extraction

We documented study details of each full-text paper (year of publication, authors, study duration), TD scores (mean and SD of pre- and post-switch scores), scales used,

Table 1. List of the Keywords Used in the Electronic Search

Keywords related to clozapine
"Clozapine," "Clozaril," "Leponex," "lapenax," "wander compound," "zapen," "lozapin," "lozapine," "sizopin," "versacloz," "zaponex," "alemoxan," "azaleptin," "clopine," "clopsine," "clozapin," "denzapine," "dorval," "dozapine," "elcrit," "fazaclo," "fazaclo odt," "hf 1854," "hf1854"
Keywords related to tardive dyskinesia
"Dyskinesia," "Dyskinesias," "Drug induced Dyskinesia," "Drug induced Dyskinesias," "Medication induced dyskinesia," "Medication induced dyskinesias," "Neuroleptic induced dyskinesia," "Neuroleptic induced dyskinesias," "Antipsychotic induced dyskinesia," "Antipsychotic induced dyskinesias," "Neuromuscular Disorder," "Neuromuscular Disorders," "Movement disorder," "Movement disorders," "Extrapyramidal syndrome," "Extrapyramidal syndromes," "Extrapyramidal symptom," "Extrapyramidal symptoms," "Extrapyramidal side effect," "Extrapyramidal side effects," "Abnormal Movement," "Abnormal Movements," "Involuntary Movement," "Involuntary Movements," "motor dysfunction," "motor dysfunctions," "Hemiballism," "Hemiballismus," "Ballismus," "Asterixis," "Myoclonus," "Bradykinesia," "Hyperkinesia," "Hans Rating Scale," "SHRS," "Simpson Angus extrapyramidal side effects scale," "SAS," "Simpson Angus scale," "mSAS," "Simpson Abbreviated Dyskinesia Rating Scale," "SADRS," "Abnormal Involuntary Movement Scale," "AIMS," "mAIMS," "Extrapyramidal symptom rating scale," "ESRS," "Simpson tardive dyskinesia scale," "STDS," "mSTDS," "Simpson dyskinesia scale," "SDS," "mSDS," "Dyskinesia rating scale," "DRS," "ODRS," "UDysRS," "Tardive dyskinesia rating scale," "TDRS," "mTDRS," "Lang Fahn Activities of Daily Living Dyskinesia scale," "LFADLDS," "Abbreviated Dyskinesia Scale," "ADS," "Bain dyskinesia scale," "BDS," "Abnormal movement scale," "CLAMPS," "Dyskinesia Identification System Condensed User Scale," "DISCUS," "Goetz Dyskinesia Rating Scale," "GDRS," "mGDRS," "Guy's Abnormal Involuntary Movement Scale," "GAIMS," "Modified Webster rating scale," "mWRS," "Obeso Dyskinesia rating scale," "ODRS," "Parkinson Disease Dyskinesia Scale," "PDYS 26," "Rockland Simpson Dyskinesia Rating Scale," "RSDRS," "Rush Dyskinesia Rating Scale," "RDRS," "Clinical Dyskinesia Rating Scale," "CDRS," "Barnes Kidger Scale," "BKS," "Crane rating scale," "CRS," "Paul Ramsey Hospital Scale," "StPRHS," "Smith Tardive Dyskinesia Scale"

Figure 1. Study Selection Flowchart



Abbreviation: TD = tardive dyskinesia.

demographics (gender, age, illness duration), clozapine treatment (mean and SD of doses, washout period), and baseline pathology (mean and SD of Positive and Negative Syndrome Scale [PANSS] or Brief Psychiatric Rating Scale [BPRS] scores). If contacted authors provided missing data, these were coded as well.

Meta-Analytic Procedure

Primary outcome. The primary outcome for TD was the combined score of the TD scale items that specify the severity of TD in different body regions before and after starting clozapine treatment. TD was assessed on the Abnormal Involuntary Movement Scale (AIMS), the Extrapyramidal Symptom Rating Scale TD subscale, the Simpson Dyskinesia Scale, and the Drug-Induced Extrapyramidal Symptoms Scale TD subscale.

Statistical procedures. Statistical analyses were conducted in R[25] (version 3.2.4, R Core Team) using the metafor package[26] (version 1.9–8). Based on the pre- and post-switch means and the pre-switch SD, we computed the standardized mean change using raw score standardization as the effect size measure for the meta-analysis.[27] Negative values indicate a decrease in TD symptoms after the switch. The corresponding standard errors were calculated conservatively, accounting for loss to follow-up by using the sample size at follow-up and assuming a correlation of 0.2 between baseline and follow-up scores, as these data were not reported in any of the articles and a sensitivity analysis indicated that the strength of the correlation did not have an influence on the conclusions obtained from the model.

We opted for a random-effects model as we expected considerable study heterogeneity. Moderators were not

Table 2. Studies Reporting the Effect of Switching to Clozapine on the Severity of Tardive Dyskinesia in Patients With Schizophrenia or a Related Disorder

		Total Study Duration	TD as Inclusion Criterion	Tardive Dyskinesia Scores							Demographics			Clozapine Treatment			Psychopathology			
					Baseline			Follow-Up			Age (y)		Gender	Dose (mg/d)					Baseline		
Year	Authors	(days)		TD Scale	n	Mean	SD	n	Mean	SD	Mean	SD	% Male	Mean	SD	Washout	Scale	n	Mean	SD
2005	Louzã and Bassitt[29]	1,826	Yes	ESRS TD	7	19.9	2.9	7	2	1.3	28.5	10.2	29%	428	269	Yes, 7 days	PANSS total	7	98.6	14.1
1997	Spivak et al[43]	126	Yes	AIMS	20	12.3	10.1	20	3.2	3.9	43.1	7.1	50%	208.7	176.6	Yes, 14 days	PANSS total	20	114.9	24.2
1993	Littrell and Magill[37]	122	Yes	AIMS	12	16.3	3.2	12	1	1.53	28.67	…	75%	…	…	…	…	…	…	…
1992	Moore et al[30]	91	Yes	AIMS	9	19	8.1	9	12.7	6.9	39.9	5.8	33%	500	0	Yes, mean 33.6 days	BPRS total	9	52.5	10.6
2013	Toyooka et al[46]	84	No	DIEPSS TD	10	0	0	10	0	0	28.7	7.1	30%	502.5	97.5	No	…	…	…	…
2010	Meltzer et al[38]	730	No	AIMS	40	1.5	0.4	31	1.8	0.4	25.8	5.8	68%	383.3	159.2	Yes, 5–7 days	BPRS	40	24.8	1.3
2009	Sacchetti et al[41]	129	No	AIMS	73	0.21	0.4	45	0.13	…	38.3	11.2	67%	379	81	Yes, 1–7 days	PANSS general	73	55.3	10.4
2006	Strous et al[44]	84	No	AIMS	55	7.2	7.6	55	4	3.8	39	12.6	53%	…	…	No	PANSS general	55	53.6	14
2006	Jones et al[34]	365	No	AIMS	65	2.77	5.21	57	1.88	3.59	37.2	12.2	73%	333	…	…	PANSS general	67	38.67	8.7
2005	Raguraman et al[39]	609	No	AIMS	22	3.5	7.5	22	2.5	5.6	32.4	10.4	64%	…	…	…	PANSS general	22	45.9	11.1
2004	Bitter et al[32]	126	No	AIMS	70	1.6	3.1	70	0.7	…	37.6	…	…	216.2	107.9	Yes, 2–9 days	PANSS total	70	104.1	13.7
2001	Tollefson et al[45]	126	No	AIMS	86	1.7	3.2	86	1	…	38.6	10.6	60%	303.6	108.7	Yes, 2–9 days	PANSS total	87	104.6	20
2000	Sajatovic et al[42]	184	No	AIMS	252	5.4	7.6	252	3	5.4	44.8	10.2	95%	503	204	…	BPRS total	522	49.6	14.1
1997	Rosenheck et al[40]	365	No	AIMS	205	5.9	5.9	117	3.6	…	43.2	7.7	99%	552	229	…	PANSS total	205	91	14.9
1996	Essock et al[33]	730	No	AIMS	135	7.8	1.8	130	8.5	2.7	42	12	61%	496	…	Yes, mean 20 days	BPRS total	…	24	…
1994	Lieberman et al[36]	84	No	SDS	30	2.8	0.9	21	1.7	1.1	27.8	5.8	73%	597	…	Yes, 14–28 days	BPRS total	84	50.7	14.6
1988	Kane et al[35]	42	No	AIMS	126	8.8	6.8	126	5.1	5.4	35.7	8.87	80%	500	0	Yes, max 7 days	BPRS total	126	61	12

Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BPRS = Brief Psychiatric Rating Scale, DIEPSS = Drug-Induced Extrapyramidal Symptoms Scale, ESRS = Extrapyramidal Symptom Rating Scale, PANSS = Positive and Negative Syndrome Scale, SDS = Simpson Dyskinesia Scale, TD = tardive dyskinesia.
Symbol: … = not reported.

investigated formally (eg, by means of meta-regression models), considering the limited power due to the low number of studies, the small size of most studies, and the amount of heterogeneity between studies. Instead, subanalyses were performed to investigate differences across several subgroups (see below). Study heterogeneity was investigated by means of the I^2 statistic and the Q test.[28] The presence of publication bias was examined by visual inspection of funnel plots.

Subgroup Analyses

To investigate the influence of potential sources of heterogeneity, several subanalyses were performed: (1) TD as an inclusion criterion, (2) the number of days between baseline and follow-up,[29,30] (3) age,[6] and (4) severity of baseline psychopathology.[31]

RESULTS

Description of Studies

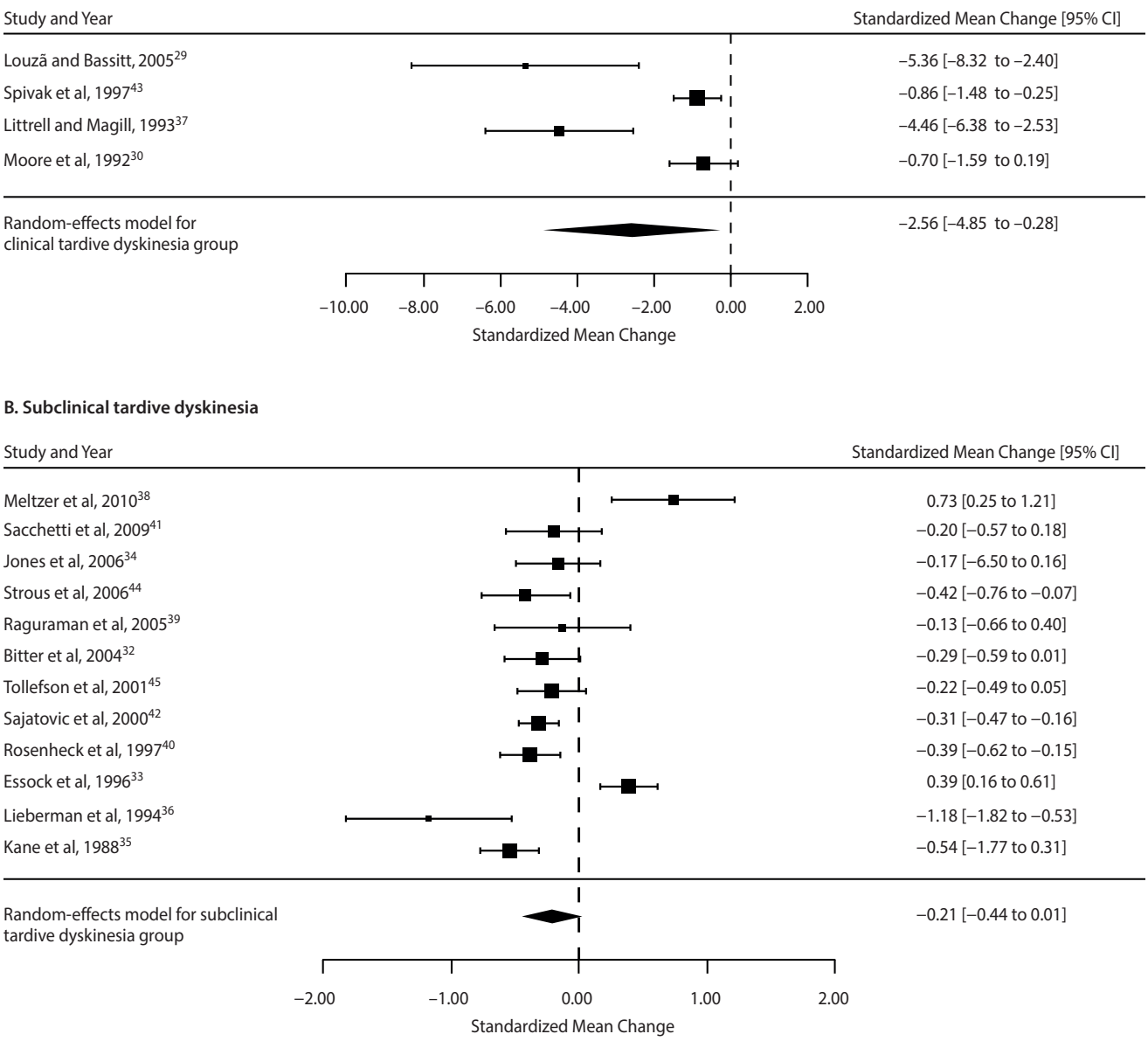
The search strategy identified 283 articles, of which 17 studies met all our inclusion criteria and were investigated in this meta-analysis.[29,30,32–46] More details on the selection of studies are provided in the flowchart in Figure 1.

Table 2 provides an overview of the data we extracted from the included studies. Of the 17 studies, 4 studies investigated switching to clozapine as a treatment for patients with clinical levels of TD (ie, patients with at least 1 moderate (3) to severe (4) TD score or at least mild (2) TD scores in 2 body areas). These studies will be referred to as the clinical TD group.[29,30,37,43] The other 13 studies investigated TD as a secondary outcome, and the majority of the patients in these studies had no to mild TD (ie, patients scoring no [0] to minimal [1] TD). These studies will be referred to as the subclinical TD group.[32–36,38–42,44–46] Fourteen of the 17 studies assessed the severity of TD with the AIMS. The length of the studies varied considerably (ranging from 1 and a half months to 5 years), and other potential sources of study heterogeneity were age and severity of baseline psychopathology.

Effect Size

Figure 2A and 2B detail the outcome of the random-effects models in a forest plot featuring the combined effects of the clinical and the subclinical TD groups. Because the patients in the sample of Toyooka et al[46] did not show any signs of dyskinesia at baseline and follow-up, the effect size could not be calculated and therefore the study was excluded from the analyses. TD decreased significantly in the clinical TD group[29,30,37,43] ($n_{studies} = 4$, $n_{subjects} = 48$, standardized mean change = −2.56, 95% CI = −4.85 to −0.28, $P = .02$). The sample size of these 4 studies is limited, and their mean decrease in TD varied considerably, with 2 studies (Louzã and Bassitt[29] and Littrell and Magill[37]) reporting large and significant decreases while the 2 other studies (Spivak et al[43] and Moore et al[30]) reported more modest decreases, 1 of which was nonsignificant.[30] This

Figure 2. Effect of Switching to Clozapine Treatment on Tardive Dyskinesia[a]



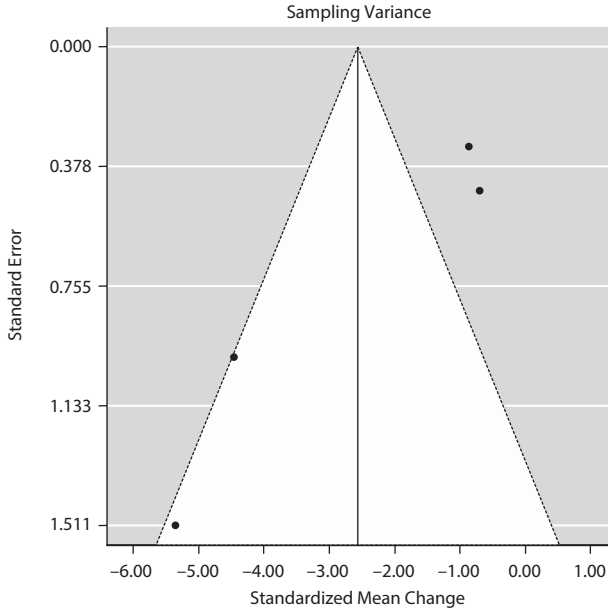
[a]Standardized mean change scores and 95% confidence intervals (CIs) of the random-effects models. Figure 2A shows the effect sizes of the studies that investigated subjects with clinical tardive dyskinesia ($n_{studies}$ = 4, $n_{subjects}$ = 48, standardized mean change = −2.56, 95% CI = −4.85; −0.28, P = .02). Figure 2B shows the studies that reported tardive dyskinesia as a secondary outcome ($n_{studies}$ = 12, $n_{subjects}$ = 1,012, standardized mean change = −0.21, ES 95% CI = −0.44; 0.01, P = .06). The combined effect of all studies was ($n_{studies}$ = 16, $n_{subjects}$ = 1,060, standardized mean change = −0.40, 95% CI = −0.69; −0.11, P < .01).

indicates that there is a high degree of heterogeneity between these studies. To rule out that the overall decrease of TD in the clinical group was only due to the studies of Louzã and Bassitt[29] and Littrell and Magill,[37] another analysis was performed without these 2 studies. The studies of Spivak et al[43] and Moore et al[30] show a smaller, yet significant, overall decrease in TD ($n_{studies}$ = 2, $n_{subjects}$ = 29, standardized mean change = −0.81, ES 95% CI = −1.32 to −0.31, P < .01).

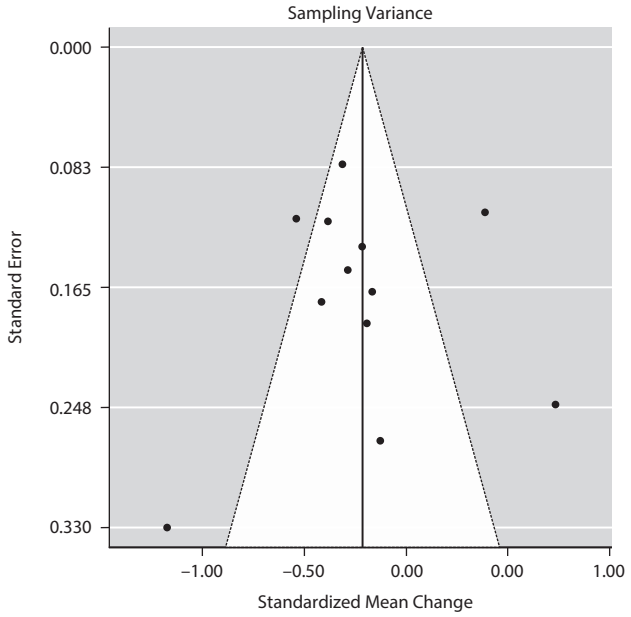
In the subclinical TD group, the difference in the severity of TD after switching to clozapine was nonsignificant[33–36,38–42,44] ($n_{studies}$ = 12, $n_{subjects}$ = 1,012, standardized mean change = −0.21, ES 95% CI = −0.44 to 0.01, P = .06). Three studies (Essock et al,[33] Meltzer et al,[38] and Lieberman et al[36]) are clear outliers and account for a considerable amount of the heterogeneity between the subclinical TD studies. The overall effect of clozapine on TD in the subclinical TD group is likely distorted by these studies. To investigate this, an analysis was performed with just the 9 other subclinical TD studies[32–36,39–42,44,45] ($n_{studies}$ = 9, $n_{subjects}$ = 830, standardized mean change = −0.33, ES 95% CI = −0.42 to −0.24, P < .01). Altogether, the studies in the analyses showed a significant reduction in severity

Figure 3. Studies That Investigated the Effect of Switching to Clozapine on the Severity of Tardive Dyskinesia[a]

A. Clinical tardive dyskinesia



B. Subclinical tardive dyskinesia



[a]Figure 3A shows the funnel plot of the studies that investigated subjects with clinical tardive dyskinesia, and Figure 3B shows the funnel plot of the studies that reported tardive dyskinesia as a secondary outcome.

of TD ($n_{studies}$ = 16, $n_{subjects}$ = 1,060, standardized mean change = −0.40, 95% CI = −0.69 to −0.11, P < .01).

As the majority of the studies assessed TD using the AIMS, we ran a second model using raw mean change scores, which are clinically more interpretable for those familiar with the AIMS, as the amount of change is expressed on the raw scale and not relative to some measure of variability within the group of patients included in each study. On average, switching to clozapine monotherapy reduced the sum of the first 7 items of the AIMS by 10.64 points in the clinical TD group[30,37,43] ($n_{studies}$ = 3, $n_{subjects}$ = 41, raw mean change = −10.64, 95% CI = −16.26 to −5.03, P < .01), by 0.22 point in the subclinical TD group[32–35,38–42,44,45] ($n_{studies}$ = 11, $n_{subjects}$ = 991, raw mean change = −0.22, 95% CI = −0.95 to 0.52, P = .56), and by 3.00 points for all of the studies that reported AIMS scores ($n_{studies}$ = 14, $n_{subjects}$ = 1,032, raw mean change = −3.00, 95% CI = −5.41 to −0.58, P = .01).

Sources of Heterogeneity

According to the Q test for heterogeneity, there is a considerable amount of heterogeneity in the random-effect models of the clinical TD group (I^2 = 93%; Q_3 = 20.95, P < .01) and the subclinical TD group (I^2 = 86%; Q_{11} = 64.37, P < .01). In the clinical TD group, heterogeneity is primarily due to the larger decrease in TD observed by Louzã and Bassitt[29] and Littrell and Magill[37] compared to Spivak et al[43] and Moore et al.[30] In the subclinical TD group, 3 outliers account for most of the heterogeneity between studies: Essock et al,[33] Meltzer et al,[38] and Lieberman et al.[36] As seen in Figure 2A and 2B, the studies in the clinical group have much larger effect sizes compared to those of the subclinical group.

Other characteristics of the study samples that may have contributed to the heterogeneity of the effect sizes between the studies in our models were age, baseline psychopathology, and the number of days between baseline and follow-up.

Differences in the patients' age across studies may explain some of the heterogeneity observed in the studies in the clinical TD group. Of the 4 studies in this group, 2 studies investigated a sample with a mean age above 40 years, and 2 investigated a sample younger than 30. In the younger two samples, switching to clozapine treatment decreased the average severity of TD more (Δ effect size = 4.6). However, age did not appear to have this effect in the subclinical TD group.

To investigate whether baseline psychopathology moderated effect sizes, the PANSS and BPRS scores were rescaled to percentages of their maximum score on the respective scales. The 2 studies in the subclinical TD group that show an increase in TD have a lower baseline psychopathology (2.2 times lower than the other studies in the subclinical TD group). Thus, baseline psychopathology may be a source of study heterogeneity in this meta-analysis.

The time between the pre- and post-clozapine assessments varied considerably between studies (mean = 359 ± 456 days). To account for this, we performed a separate analysis that was limited to the studies that included reports on the severity of TD between 3 to 6 months after the start of clozapine treatment, as most studies reported data in this period and the only studies with data unavailable within this time period were from the subclinical TD group. However, this did not decrease the amount of heterogeneity in the clinical TD group (I^2 = 89%, Q_3 = 17.08, P < .01), subclinical TD group (I^2 = 94%; Q_6 = 40.07, P < .01), or the model including all studies (I^2 = 97%, Q_{11} = 72.18, P < .01).

Publication Bias

Based on the inspection of the funnel plot of the studies in the clinical TD group (Figure 3A), it is clear that the 2 less precise studies (Louzã and Bassitt[29] and Littrell and Magill[37]) report much larger effect sizes, which might be evidence of publication bias. However, as there were only 4 small studies in the TD group, it is not certain whether the difference in effect sizes was due to publication bias. Figure 3B, the funnel plot of the studies in the subclinical TD group, indicated that there is considerable variance in the size of the effect of these studies. However, no particular pattern suggestive of publication bias is immediately discernible in the plot. Therefore, publication bias does not appear to be a significant issue, although the analyses are inconclusive due to the limited number of studies.

DISCUSSION

In line with our hypothesis, there was a large and significant reduction in the severity of TD after switching to clozapine in the 4 studies that specifically investigated patients with clinical levels of TD (ie, moderate to severe). Moreover, when limiting the analysis to the 12 studies of patients with subclinical TD, we found that clozapine seldom worsens TD and the combined effect even suggests a slight reduction in severity of TD. Furthermore, the model including all 16 studies in the analysis reported a significant reduction in severity of TD after the switch to clozapine. Altogether, these findings indicate that switching to clozapine can reduce the severity of TD in many patients.

The effects of many potential treatments for TD have been studied in meta-analyses of the Cochrane collaboration.[5,15–21] None of these meta-analyses found decisive evidence supporting any of these treatments, nor did they investigate the effect of switching to clozapine; however, vitamin E may prevent further deterioration of TD symptoms.[20] The outcomes of their analyses were either negative or inconclusive, partly due to there being too few/small studies. Three recent studies have demonstrated the effectiveness of VMAT-2 inhibitors, valbenazine and deutetrabenazine, for the treatment of TD.[12–14] Compared to the 4 studies that investigated the switch to clozapine in patients with clinical levels of TD, the effects of these VMAT-2 inhibitor studies were smaller. The standardized mean change in severity of TD for switching to clozapine was −2.56, as opposed to −0.88 to −1.10,[12] −0.73,[13] and −0.90[14] for the deutetrabenazine and valbenazine studies. The deutetrabenazine and valbenazine studies investigated patients with a wider range of *DSM* diagnoses than this meta-analysis, and these studies indicate that a portion of the patients with TD showed little to no response to VMAT-2 inhibitors. This stresses the clinical importance of our findings and the need for further investigation of TD treatment options.

The exact underlying pathophysiologic mechanisms of TD and how they are affected by clozapine are still unclear.[24] TD is believed to be the result of hypersensitization of the dopamine system. More specifically, chronic use of antipsychotics is believed to up-regulate the postsynaptic dopamine receptors of the striatum.[24,29] However, studies have indicated that the up-regulation, which occurs gradually, does not coincide with the course of TD symptoms, which occur and stop more abruptly.[24] Another theory is that TD is the result of gradual cell damage resulting from increased dopamine metabolism that subsequently increases the production of free radicals that damage the cells.[24] Speculating why clozapine is such an effective treatment is difficult. The broad range of receptor types targeted by clozapine and its low affinity to striatal dopamine D_2 receptors may explain why clozapine reduces TD in contrast to other antipsychotics. Clozapine's low affinity may affect the hypersensitization of the striatal dopamine system. The antiserotonergic and anticholinergic effect of clozapine could also be involved in reducing the severity of TD.[24] Furthermore, it is also unclear whether clozapine treats TD or merely suppresses its symptoms.[29]

Limitations

A limitation of this meta-analysis is that only 4 studies (with a total of 48 patients) met the inclusion criteria and investigated the switch to clozapine in patients with clinical levels of TD. However, these studies reported such a large effect that it is reasonable to assume that this effect will be similar for other patients with moderate to severe TD. Moreover, there are other studies that have investigated how clozapine affects the severity of TD that did not match our inclusion criteria[23,30,47] (for example, case reports or studies that did not assess TD on a rating scale or report these scores). In line with our findings, these studies reported significant to complete reductions of TD.[30]

To increase the power of the analysis, we also included studies that assessed TD as a secondary outcome. This substantially increased the number of patients in the analysis, but the vast majority of the patients in these studies had no or subclinical levels of TD and little to no room for improvement in TD scores. Thus, the inclusion of these studies decreased the size of the overall effect to a modest and clinically not very relevant improvement in the severity of TD. However, more importantly, with the exceptions of Meltzer et al[38] and Essock et al,[33] these studies demonstrated that clozapine rarely induces or worsens TD.

This meta-analysis was restricted to patients with schizophrenia, which limited the number of studies included in the analyses and the power of these analyses. Patients with other diagnoses (for example, Parkinson's disease or bipolar disorder) also develop TD as a side effect of their medication. However, we opted to limit this meta-analysis to patients with schizophrenia, because the inclusion of studies investigating patients with diagnoses other than schizophrenia would add to the study heterogeneity. In turn, the increase in study heterogeneity would affect the analyses and limit the clinical conclusions that could be drawn from them. The high degree of heterogeneity between studies affected all of our analyses. In the clinical

group, age and baseline severity of TD could have accounted for some of the heterogeneity between the studies, as age has been associated with increased incidence of TD.[6] Louzã and Bassitt[29] and Littrell and Magill[37] investigated younger patients than Spivak et al[43] and Moore et al[30] (respective mean ages of 29 and 29 years compared to 43 and 40 years), and the severity of TD at baseline was also lower in Moore et al.[30] Considering that there are only 4 small studies and that there may be publication bias, the overall decrease in TD after switching to clozapine could have been slightly overestimated in our model. Therefore, we believe that the overall decrease will be closer to that of the studies of Spivak et al[43] and Moore et al,[30] especially in older patients. In the subclinical group, the severity of psychopathology before switching to clozapine appears to account for some of the heterogeneity between studies. Meltzer et al[38] and Essock et al,[33] the 2 studies that found a slight increase in TD after switching to clozapine investigated patients that had markedly lower baseline psychopathology scores than the other subclinical studies before switching to clozapine (respectively, 22% and 19% of the total possible score on the psychopathology scale as opposed to 44% ± 5% on the 10 other subclinical TD studies). Thus, the combined effect of the studies in the subclinical group may have been slightly underestimated. Nevertheless, we do not expect that the average reduction in TD will exceed a 1- or 2-point reduction on the AIMS for patients with minimal to mild symptoms. The heterogeneity in study duration and scales used to assess the severity of TD did not appear to account for a significant amount of heterogeneity in TD scores in either group.

Clinical Implications

Currently, recommendations of the guidelines of the National Institute for Health and Care Excellence[48] and American Psychiatric Association[49] state that switching to clozapine treatment should be considered after a partial or suboptimal response to 2 other antipsychotics (at least 1 being a second-generation antipsychotic). As clozapine can reduce TD so effectively, it may be considered as a separate indication for switching to clozapine. The benefit of switching to TD should nevertheless outweigh the risks associated with clozapine treatment, and there should be substantial room for improvement. Therefore, we recommend adding moderate to severe TD and/or substantial discomfort due to TD as an indication for switching to clozapine to these guidelines.

CONCLUSION

This meta-analysis shows that switching to clozapine results in significant and clinically relevant decreases of TD in patients with at least moderate TD. The evidence could be strengthened by larger studies that investigate switching to clozapine as a treatment for TD. Nevertheless, we propose that there is now sufficient evidence that moderate to severe TD and/or substantial discomfort due to TD may be considered as an indication for switching antipsychotic to clozapine in clinical guidelines.

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